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Die Effekte einer kognitiven Rehabilitation bei Patienten mit Alzheimer-Demenz und die Rolle der funktionellen Konnektivität im Default Mode Network als potentieller Marker

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i. Abkürzungsverzeichnis

AES	Apathy Evaluation Skala (Fragebogen)
AD	Alzheimer-Krankheit
B-ADL	Bayer Activities of Daily Living Skala (Fragebogen)
BL	Baseline
BOLD	Blood Oxygen Level-dependent
CERAD	Consortium to Establish a Registry for Alzheimer's Disease (Testbatterie)
CR	Kognitive Rehabilitation
CT	Kognitives Training
CTP	Boston Cookie Theft Picture Description Test
DEMQOL	Dimensions of Quality of Life (Fragebogen)
DMN	Default Mode Network
EEG	Elektroenzephalographie
FC	Funktionelle Konnektivität
FDG-PET	Fluordesoxyglukose-Positronen-Emissions-Tomographie
fMRT	Funktionelle Magnetresonanztomographie
GDS	Geriatrische Depressionsskala (Fragebogen)
GK	Gruppe gesunder Kontrollprobanden
HOTAP	Handlungsorganisation und Tagesplanung- Planungsfähigkeit im Alltag (Test)
HOTAP-A	Subtest A
HOTAP-C	Subtest C
IG	Interventionsgruppe
KG	Kontrollgruppe
MCI	Leichte kognitive Störung

MMST	Mini-Mental-Status-Untersuchung (Test)
MRT	Magnetresonanztomographie
NPI	Neuropsychiatric Inventory (Fragebogen)
NSL	Nuremberg Aging Observation Skala (Fragebogen)
PET	Positronen-Emissions-Tomographie
PCC	Posteriorer Zingulärer Kortex
RBMT	Rivermead Behavioural Memory Test
Ruhe-fMRT	Funktionelle MRT im Ruhezustand
UMR	Universitätsmedizin Rostock
vMPFC	Ventromedialer präfrontaler Kortex
VU	Verlaufsuntersuchung
ZBI	Zarit Burden Interview

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Die wissenschaftliche Arbeit, die hinter den Publikationen und dieser Schrift steckt, beruht auf der Arbeit vieler Personen. Ich möchte mich an dieser Stelle bedanken.

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iv. Zusammenfassung

Kognitive Interventionen sollen Patienten mit leichter Alzheimer-Demenz (AD) als nicht-medikamentöse Therapieansätze helfen, kognitive Fähigkeiten und Alltagskompetenzen zu erhalten. Die kognitive Rehabilitation (CR) hat zum Ziel, die Selbstständigkeit und Lebensqualität der Betroffenen zu fördern. Die Untersuchung der CR zeigte bislang eine Verbesserung der Depressivität und Lebensqualität, jedoch nicht der Alltagskompetenz.
Um Therapieeffekte in Zukunft besser untersuchen zu können, bedarf es neben der Messung von Verhaltensparametern weiterer Verfahren. So kann die funktionelle Magnetresonanztomographie (fMRT) helfen, die zugrundeliegenden neuronalen Veränderungen darzustellen. Die funktionelle Konnektivität (FC) beschreibt die synchronisierte Aktivität funktionell gekoppelter Gehirnregionen in Form von Netzwerken. Besonders gut untersucht ist das Default Mode Netzwerk (DMN), welches im Ruhezustand mittels fMRT nachweisbar ist (Ruhe-fMRT) und bereits früh im Verlauf einer AD degeneriert.
Ziel meiner Dissertation war die Umsetzbarkeit einer kognitiven Rehabilitation sowie ihre Effekte auf AD-Patienten zu untersuchen. Im Besonderen wollte ich Veränderungen der FC im DMN beschreiben und ihre Rolle als Surrogat-Marker für kognitive Interventionen diskutieren. Zudem werden Möglichkeiten einer Kombination von fMRT und EEG beleuchtet.

Wir führten eine kontrollierte Interventionsstudie mit 16 AD-Patienten durch, die eine gruppenbasierte CR mit einem kognitiven Training als Kontrollbedingung verglich. Primärer Endpunkt war die Alltagskompetenz. Als sekundäre Endpunkte erhoben wir den kognitiven Status und einige nicht-kognitive Parameter, wie Depressivität und Lebensqualität, sowie die FC im DMN. Das dreimonatige, ambulant durchgeführte, modularisierte CR-Programm bestand aus kognitiven und psychotherapeutischen Elementen.
Die prä-post-Analyse ergab einzig für die Lebensqualität eine signifikante Verbesserung in der Interventionsgruppe (IG) im Vergleich mit der Kontrollgruppe (KG). In den Analysen der FC im DMN mittels Korrelations-Karten für einen Saatpunkt im Präcuneus/posterioren zingulären Kortex (PCC) fanden wir einen Anstieg der FC in der IG im Vergleich zur KG im bilateralen zerebellären Cortex.
Insgesamt konnten die praktische Umsetzbarkeit des adaptierten CR-Programms und die Verbesserung der Lebensqualität gezeigt werden. Die fehlende Verbesserung der Alltagskompetenz begründen wir primär mit einem mangelnden Transfer vom Therapiesetting in den Alltag, so dass eine weitere Optimierung der Maßnahme Ziel weiterer Studien sein kann. Aus den Analysen der FC schließen wir, dass Interventionen wie die CR Effekte auf die FC, insbesondere des Cerebellums, im DMN von AD-Patienten haben. Eine lohnende Perspektive bieten innovative Untersuchungsverfahren, wie die simultane fMRT-EEG. So verglichen wir erstmals AD-Patienten und Gesunde (n=28) und fanden verminderte positive Assoziationen zwischen den Alphaband-Signalen und den BOLD-Signalen bei AD-Patienten im DMN.

Die folgende Arbeit bietet einen wichtigen Beitrag für das langfristige Ziel, effektive Interventionen zu konzipieren, die den Prozess der Netzwerkdegeneration verlangsamen und Kompensationsmechanismen fördern.

Einleitung und Fragestellung

1.1 Charakterisierung kognitiver Interventionen für Demenz-Patienten

Die Demenz vom Alzheimer-Typ ist eine neurodegenerative Erkrankung, die kortikal zunächst die Temporal- und Parietallappen betrifft, progredient verläuft und bislang nicht heilbar ist. Sie ist durch eine Einschränkung kognitiver Funktionen gekennzeichnet, welche die Durchführung von Aktivitäten des täglichen Lebens beeinträchtigt. Durch dieses Kriterium grenzt sich die Demenz vom prädementiellen Stadium der leichten kognitiven Störung (MCI) ab [44]. Psychosoziale Interventionen spielen eine wichtige Rolle in der Betreuung von Patienten mit AD und ihrer Angehörigen [95]. Diese Interventionen haben das Ziel, kognitive Funktionen zu verbessern oder zu erhalten, kognitive Reserven zu fördern und somit den Alltag der Patienten zu erleichtern.

Das kognitive Training (CT) zielt auf eine Erhaltung spezifischer Funktionen wie Aufmerksamkeit oder episodisches Gedächtnis. Dafür nutzt dieser Ansatz unter Anleitung durchgeführte, standardisierte Aufgaben, die regelmäßig in Einzel-/Gruppensitzungen oder mit Computerprogrammen wiederholt werden [21]. Hierbei wird die Theorie diskutiert, dass CT nicht nur die spezifische kognitive Domäne verbessert, sondern auch ein indirekter Transfer auf Alltagsfunktionen stattfindet [8]. Weiterhin vermittelt CT auch Lernstrategien, die das implizite bzw. nicht-deklarative Gedächtnis fördern sollen, von dem angenommen wird, dass es bei AD länger erhalten bleibt als das deklarative Gedächtnis [87]. Für die CT ließen sich zum Teil geringe Effekte auf allgemeine kognitive Funktionen nachweisen. Eine Übertragung der kognitiven Verbesserung auf Alltagsfunktionen konnte nicht nachgewiesen werden [30, 59].

Im Gegensatz zur CT versucht die kognitive Rehabilitation (CR) mit multiprofessionellen Maßnahmen das Funktionsniveau im Alltagskontext der Patienten zu fördern oder zu erhalten. Im Vergleich zur CT ist der Hauptunterschied, dass CR Alltagsfähigkeiten, statt einzelner kognitiver Funktionen fördert. Hierbei werden kompensatorische Strategien angewendet und eine direkte Übertragung der beübten Fähigkeiten in den Alltag angestrebt [8]. Erschwerend für die Evidenzbetrachtung kommt hinzu, dass viele Studien nicht zwischen Konzepten von CT und CR differenzieren, beziehungsweise werden Anteile verschiedener Konzepte kombiniert. Aufgrund dieser heterogenen Begriffsverwendung haben wir nach ausgiebiger Literaturrecherche versucht, inhaltliche Kriterien zu identifizieren, welche unabhängig von der jeweiligen Bezeichnung die CR definieren. Unsere Übersichtsarbeit [60] erläutert das Konzept der kognitiven Rehabilitation, aktuelle Studien dazu und die Probleme in der Erforschung der CR.

Wir haben die wesentlichen Merkmale der CR unter folgenden Kriterien zusammengefasst:

1. Individualität: Identifizierung und Verfolgung von Zielen, die für die Patienten und ihren Alltag relevant sind

2. Kompensation: Statt der Restitution einzelner kognitiver Domänen, werden der Erhalt von Fähigkeiten und der Ausgleich von Defiziten angestrebt, z.B. mittels externen Gedächtnishilfen, Biographiearbeit, Psychoedukation
3. Integration: Kombination multimodaler Methoden in einem interdisziplinären multi-professionellem Team, z.B.: Integration von Psychotherapie (Stress- und Angstbewältigung), Ergotherapie, Musiktherapie etc.
4. Interaktion: Adaptation des individuellen Umfelds an das aktuelle Ausmaß der kognitiven Einschränkungen, direkter Transfer in den Alltag: Austausch mit Angehörigen und ihre Einbeziehung bei der Übertragung von beispielsweise Problemlösestrategien in das häusliche Umfeld, Implementierung sozialer Aktivitäten, Konversationstraining, Anpassung der materiellen Umwelt in der Häuslichkeit

Die Evaluation der Studien erfolgte nach den folgenden Dimensionen: Inhalt (Individualität, Kompensation, Interaktion, Integration), Endpunkte (kognitive und nicht-kognitive, Zeitstabilität) und methodische Aspekte (Zielgruppe, Studiendesign, Dauer, Umfang, Setting). Die detaillierten Ergebnisse der Recherche sind in der Übersichtsarbeit umfangreich in Tabellenform dargestellt. In unserer Literaturrecherche berücksichtigten wir Studien zwischen 1/2000 und 9/2014 mit leichter Alzheimer-Demenz und milder kognitiver Einschränkung (MCI) als Zielgruppe. Aus Gründen der Übersichtlichkeit werde ich nur einige wenige beispielhafte Studien mit der Zielgruppe AD aus dieser Übersichtsarbeit vorstellen.

Hinsichtlich der vier Kriterien nutzten Viola et al. 2011 [94] Elemente der Interaktion, wie das Trainieren von Alltagsfähigkeiten, und Elemente der Integration, wie Kunst- oder Physiotherapie. Die Forscher fanden eine Verbesserung der Lebensqualität und eine Verminderung von Angst und Depressivität bei den Angehörigen. In einer Studie von Quayhagen et al. [75] wurden vier verschiedene Interventionen getestet, welche jeweils mehrere wenn auch unterschiedliche Kriterien aufwiesen. So wurde das Konzept der kognitiven Stimulation untersucht, welches als rehabilitative Kriterien Individualität (Stadienspezifität), Kompensation (Problemlösetraining) und Interaktion (Angehörigenpartizipation, Konversationstraining) in das Konzept integrierten. Für die Gruppe dieser Intervention verbesserten sich kognitive Parameter, verbale Flüssigkeit und Depressivität bei Angehörigen.

Als Zeichen einer fortschreitenden Standardisierung von Interventionsstudien gilt die Implementierung manualisierter Konzepte. Schiffczyk et al. evaluierten 2013 in großem Umfang ein (neuro)psychologisches Rehabilitationsprogramm [80], welches als *Selbsterhaltungstherapie* (SET) 2001 von Romero et al. entwickelt wurde [77]. In einem stationären Setting werden mit den Angehörigen (Interaktion) und nach individuellen Gesichtspunkten (Individualität) verschiedene Therapien (Integration), Biographiearbeit (Kompensation) und soziale Aktivitäten zusammengestellt. Schiffczyk et al. konnten zeigen, dass sowohl unmittelbar nach der Intervention als auch nach einem Follow-Up von drei Monaten der kognitive Status bei männlichen und die Depressivität bei weiblichen Patienten eine Verbesserung aufwies [98].

Ebenfalls vier Kriterien erfüllte die *Goal-orientated Cognitive Rehabilitation in early-stage dementia* (GREAT) von Clare et al [29]. Im Zentrum dieses Konzeptes stand die Identifikation und Umsetzung individueller Ziele. Am Ende der dreimonatigen Intervention berichteten die Patienten von subjektiv höherer Kompetenz beim Erreichen ihrer Ziele und im Alltag. Auch fand sich eine Verbesserung der Gedächtnisleistung und der Lebensqualität. Aktuell wird dieses Konzept in einer multizentrischen Studie ausgewertet [28].

Eine weitere manualisierte Studie mit vier erfüllten Kriterien ist die Evaluationsstudie des Konzeptes *Cognitive Rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease* (CORDIAL) von Werheid und Thöne-Otto [98]. Dieser Ansatz hat die Erhaltung der Lebensqualität und Unabhängigkeit im Alltag zum Ziel. Kurz et al. evaluierten dieses Konzept [62] in einer Multicenter-Studie und fanden eine Abnahme der Depressivität bei weiblichen Probanden.
Hinsichtlich der Therapieinhalte und -effekte ist für die CR zusammenzufassen, dass manualisierte, theoriebasierte Konzepte keine größeren Effekte erzielen, als nicht-standardisierte. Ein Schwerpunkt in Interaktion (Angehörigenbeteiligung) und Individualität (Zielsetzung) scheint von Vorteil zu sein, um gezielt relevanten Problemen im Alltag zu begegnen. Zum Teil reflektieren die Ergebnisse, wo die Schwerpunkte des Konzeptes liegen. So fördert eine Integration von Konversationstraining in die CR die verbale Flüssigkeit [75], und ein Fokus auf das Erreichen individueller Ziele die subjektive Kompetenz [29]. Signifikante Ergebnisse sind in allen Studien rar und dann vor allem in nicht-kognitiven Parametern wie Lebensqualität oder Depressivität angesiedelt [62, 75, 80, 94]. Diese Effekte aber blieben auch im Verlauf, sofern die Daten erhoben wurden, stabil [62, 80]. Veränderungen kognitiver Parameter (außer [75, 80]) und der ADL-Kompetenz waren meist ohne Signifikanz.

1.2 Funktionelle Konnektivität und das Default Mode Netzwerk

Um effektive, nichtmedikamentöse Therapiekonzepte wie die CR zu entwickeln, die den kognitiven Abbau verhindern oder vermindern können, ist es essentiell zu verstehen, wie sich solche Interventionen auf die zugrundeliegenden neuronalen Veränderungen auswirken. So stellt sich die Frage, wie genau der kognitive Abbau auf neuronaler Ebene verläuft, um einschätzen zu können, welchen Einfluss eine Intervention im jeweiligen Stadium auf die neuronalen Netzwerke hat. Außerdem kann die Analyse der funktionellen Konnektivität (FC) neben standardisierten Tests und qualitativen Erhebungen die Evaluation von Interventionseffekten erleichtern [24].
In den vergangenen Jahren etablierte sich die Erforschung funktioneller Konnektivität in neuronalen Netzwerken. Die Methode der FC erfasst neuronale Netzwerke als dynamische, synchronisierte Aktivitäten zwischen funktionell gekoppelten Hirnregionen, welche durch den indirekten Nachweis regionaler Fluktuationen in der Blutversorgung gemessen werden [16]. Mittels bildgebender Verfahren können spezifische Netzwerke während einer Aktivierung durch eine Aufgabe nachgewiesen werden, aber auch in Ruhe zeigen sich (wiederum andere) stabile Netzwerke. Mittlerweile vermutet man, dass die progressive Disruption der Konnektivität in-

nerhalb der Ruhenetzwerke einen möglichen Mechanismus im Verlauf der AD-Demenz darstellt [23, 38].
Die Ruhe-fMRT bietet den Vorteil, dass auch eine Untersuchung für Demenzpatienten möglich ist, die von den komplexen Paradigmen einer aufgabenbezogenen MRT-Untersuchung überfordert wären. Das bislang am besten untersuchte Ruhenetzwerk ist das Default Mode Network, welches durch zwei Hauptknotenpunkte im Präcuneus/Posterioren Zingulären Kortex (PCC) und ventromedialen präfrontalen Kortex (vMPFC) charakterisiert ist. Weitere kortikale Komponenten des DMN sind Regionen im lateralen temporalen und parietalen inferioren Kortex, Thalamus und Hippocampus [20, 76]. Die Aufgaben des DMN sind primär unbewusster Natur und umfassen unter anderem Introspektion, die Integration kognitiver und emotionaler Prozesse in die internale Repräsentation und den Abruf episodischer Gedächtnisinhalte [20]. Eine Form der Konnektivitätsanalyse im DMN erfolgt mittels Platzierung eines Saatpunktes in einem Hauptknotenpunkt (PCC oder MPFC), dessen BOLD (blood oxygenation level-dependent) -Signalzeitverlauf mit jedem anderen Voxel im Gehirn verglichen und in einer Korrelationskarte abgebildet wird [45].
Es wurde bereits in vielen Studien gezeigt, dass sich die FC im DMN im Verlauf der AD progressiv verändert und letztendlich vermindert. Diese charakteristischen Veränderungen erlauben eine Unterscheidung zwischen Gesunden, milder kognitiver Einschränkung (MCI) und AD [11, 38]. Aber die FC könnte in Zukunft auch als Marker genutzt werden, um den Verlauf der AD-Krankheit auf neuronaler Ebene nachzuvollziehen und langfristig Diagnostik und Therapien stadiengerecht anzuwenden [55]. Bislang erforschten nur wenige Studien Veränderungen im DMN bei Patienten mit MCI und AD mit longitudinalem Design. Diese Studien legen eine Frakturierung des Netzwerks in verschiedene Subsysteme nahe, die dann selbst nach und nach desintegrieren [2, 35, 65].
Longitudinale Untersuchungen suggerierten eine zeitweilige Zunahme der Konnektivität innerhalb des DMN in frühen Stadien der AD [9, 35, 96]. Auch konnten Veränderungen des DMN eine Konversion von MCI zu AD vorhersagen, wobei sich eine Zunahme der Konnektivität zwischen PCC und Präcuneus in der Gruppe von MCI-Patienten zeigte, die sich zu AD-Patienten entwickelten, während eine solche Zunahme in der Kontrollgruppe, die MCI blieb, nicht nachweisbar war [82]. Diese Zunahme an Konnektivität im DMN wurde von den Autoren als eine Art Kompensationsmechanismus im Rahmen neuronaler Plastizität interpretiert. Es wäre also denkbar, dass sich kognitive Ressourcen in der funktionellen Konnektivität wiederspiegeln und in Zukunft entsprechende interventionelle Therapien, die auf Kompensation abzielen, in ihrer Effektivität abbildbar sind.
Doch bis dahin besteht noch viel Forschungsbedarf, denn nur wenige Studien haben bislang einen Zusammenhang zwischen einer Intervention bei MCI/AD-Patienten und Veränderungen im DMN untersucht [24]. Die meisten nutzten eine aufgabenbezogene fMRT [7, 89, 93], aber es existieren auch Ruhe-fMRT-Studien [26, 63, 97]. Von diesen Studien fanden einige einen signifikanten Effekt der Intervention auf neuropsychologische Parameter [10, 31, 109]. Die Vergleichbarkeit ist jedoch eingeschränkt, da die Studien hinsichtlich der Intervention variierten (CR [92], Meditation [97], CT [63], Multistimulationstherapie [7], physisch-kognitives Training [89], Ausdauertraining [26]). Auch untersuchten sie verschiedene Zielgruppen (AD [7, 93],

AD + MCI [97], MCI [26, 89] und Gesunde [63]).
Trotz der Vielfalt dieser Studien existiert nach meinem Wissen keine weitere Studie neben unserer [73] , die mittels Ruhe-fMRT eine CR bei AD-Patienten untersucht hat. Trotzdem möchte ich zwei ähnliche Studien näher betrachten.
Baglio et al. [7] testeten eine Multistimulationstherapie bei AD-Patienten mittels aufgabenbezogener fMRT (Aufgabe zur verbalen Flüssigkeit) und fanden Verbesserungen neuropsychiatrischer Symptome, der Gedächtnisleistung und der verbalen Flüssigkeit. Eine FC-Zunahme ließ sich in Regionen des Temporallappens, der Inselrinde und des Thalamus nachweisen. Es fanden sich positive Korrelationen von FC und Ergebnissen des ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive Subscale). Die Autoren argumentierten, dass so möglicherweise Ressourcen der neuronalen Plastizität durch positive Stimuli aus der Umwelt mobilisiert werden können.
Van Paasschen et al. [92] untersuchten Patienten mit leichter AD vor und nach achtwöchiger CR im Vergleich zu einer Kontrollgruppe mittels Wiedererkennungs-fMRT-Paradigma. Es fand sich vermehrt Aktivität in frontalen und parietalen Regionen, allerdings ohne Effekt auf Verhaltensendpunkte. Die Autoren vermuteten, dass fMRI sensitiver sein könnte als neuropsychologische Tests.

Um die temporalen Vorgänge in den Netzwerken und entsprechende Daten aus fMRT besser zu verstehen, hilft es multimodal in di- oder sogar trimodalen [83] Ansätzen die Methoden zu kombinieren. Die Kombination aus Ruhe-fMRT und EEG verbindet die hohe räumliche Auflösung des MRT mit der hohen zeitlichen Auflösung der EEG [37]. Das Alpha-Band ist im EEG der dominante Rhythmus während des wachen Ruhezustands mit geschlossenen Augen [13]. Es hat seinen Ursprung in der Verbindung von thalamo-kortikalen Neuronen mit dem okzipitalen Kortex [106]. Von dieser neuronalen Bahn wird angenommen, dass sie im Verlauf einer AD-Demenz disruptiert [105]. Funktionell ist das Alpha-Band mit internalen mentalen Prozessen assoziiert [61].
Simultane Ruhe-fMRT-EEG Studien an gesunden Probanden zeigten eine robuste Assoziation des Signals im Alpha-Band mit dem BOLD-Signal im Thalamus [70, 48] und etwas heterogener auch im DMN [56, 79]. In Bezug auf AD fanden Forscher eine positive Korrelation zwischen der Alpha-Band-Power und dem Volumen der grauen Substanz im Hippocampus [4, 5]. Bislang wurde jedoch noch keine simultane Ruhe-fMRT-EEG Studie mit AD-Patienten durchgeführt. Wir verglichen erstmalig AD-Patienten mit Gesunden mittels fMRT-EEG [19]. Diese Promotionsarbeit soll einen Beitrag zur Beantwortung der Frage leisten, inwiefern bildgebende Verfahren als Marker zur Evaluierung von Interventionen mit Demenz-Patienten beitragen können.

1.3 Untersuchungsziele und Hypothesen

Im Rahmen dieser Promotion zum Thema „Die Effekte einer kognitiven Rehabilitation bei Patienten mit Alzheimer-Demenz und die Rolle der funktionellen Konnektivität im Default Mode Network als potentieller Marker“ möchte ich folgende Ziele I-III formulieren:

Studie 1: Kognitive Rehabilitation (drei Publikationen)

In Vorbereitung auf die Studie 1 haben wir im Rahmen einer Übersichtsarbeit den aktuellen Stand der Forschung zur kognitiven Rehabilitation zusammengetragen. Aufgrund der heterogenen Bezeichnungen vieler Konzepte entwickelten wir Kriterien zur konzeptuellen Beschreibung der kognitiven Rehabilitation. Dies hatte zum Ziel, verschiedenartige Studien zu kognitiven Interventionen übersichtlich vergleichen zu können.

I. *Entwicklung/Adaptation eines integrativen Konzepts der kognitiven Rehabilitation und Evaluation der Durchführbarkeit und Effektivität dieser gruppenbasierten kognitiven Rehabilitation in einer partiell-randomisierten kontrollierten Studie*

   Hypothese: Wir erwarten eine Überlegenheit unseres Konzeptes zur kognitiven Rehabilitation gegenüber einer aktiven Kontrollgruppe bei Patienten mit leichter Demenz vom Alzheimer-Typ. Die Überlegenheit sollte sich in einer Verbesserung oder Erhaltung des alltagsbezogenen kognitiven Funktionsniveaus widerspiegeln, sodass Alltagskompetenz, Lebensqualität und Selbstständigkeit bestehen bleiben.

II. *Untersuchung der Effekte einer dreimonatigen kognitiven Rehabilitation auf die funktionelle Konnektivität im DMN bei Patienten mit AD*

   Hypothese: Die kognitive Rehabilitation, von der wir erwarten, dass sie kognitive Ressourcen mobilisiert, könnte eine vermehrte funktionelle Konnektivität im DMN der AD-Patienten im Vergleich zur Kontrollgruppe zur Folge haben.

Die Ergebnisse der Studie 1 legten nahe, dass funktionelle Endpunkte für die Erfassung von Behandlungseffekten bei AD potentiell relevant sind, zugleich aber neuere kombinierte Verfahren möglicherweise größere Sensitivität aufweisen könnten. Deswegen untersuchten wir in der Studie 2 das Potential einer kombinierten fMRT-EEG bei Alzheimer-Patienten in Hinblick auf den zukünftigen Einsatz des Verfahrens im Rahmen von Interventionsstudien.

Studie 2: Simultane fMRT-EEG (eine Publikation)

III. *Untersuchung der Durchführbarkeit einer fMRT-EEG Studie mit Alzheimer-Patienten im Vergleich zu gesunden Kontrollprobanden und Erforschung der Assoziation des Alpha-Signal-Bandes mit dem BOLD-Signal*

   Hypothese: Wir erwarten eine positive Assoziation zwischen dem Alpha-Signal-Band und dem BOLD-Signal in Regionen des DMN und dem Thalamus in beiden Gruppen mit einer reduzierten Assoziation in der AD-Gruppe.

1.4 Studienkohorte und -Design

1.4.1 Studie 1: Kognitive Rehabilitation

Für unsere Interventionsstudie zur kognitiven Rehabilitation untersuchten wir 44 Patienten in der Gedächtnisambulanz der Universitätsmedizin Rostock (UMR). Nach dieser Screening-Phase schlossen wir n=20 Individuen mit entweder milder AD-Demenz oder Demenz mit AD und begleitender zerebrovaskulärer Erkrankung ein. Alle Probanden hatten jeweils eine klinische Diagnose einer wahrscheinlichen AD nach *NINCDS-ADRDA Kriterien* [67] beziehungsweise nach *NIA-AA-Kriterien* [68] erhalten. Die zerebrovaskuläre Begleiterkrankung wurde gemäß ICD-10 Kriterien diagnostiziert [100]. Die Einstufung des Schweregrades erfolgte mithilfe der *Mini-Mental-Status-Untersuchung* (MMST) [43]. Eine Voraussetzung für die Studie war, dass die Patienten Zuhause lebten und mindestens zwei persönliche Kontakte pro Woche mit einem Angehörigen bzw. einer Angehörigen hatten. Probanden mit einer neurologisch relevanten Medikation mussten diese in stabiler Dosis für mindestens drei Monate eingenommen haben. Fast alle Probanden nahmen Antidementiva.
Alle Patienten wurden einer eingehenden körperlichen und neuropsychiatrischen Untersuchung sowie einer Blutentnahme unterzogen. Ausschlusskriterien waren psychiatrische oder neurologische Erkrankungen (außer AD) und umfangreiche pathologische Veränderungen im MRT wie ein Hirntumor oder Zustand nach Schlaganfall. Ebenfalls Voraussetzung zur Studienteilnahme war die Bereitschaft zur Teilnahme an zwei MRT-Untersuchungen. Die Studie wurde mit Zustimmung der zuständigen Ethikkommission der Universität Rostock, im Einklang mit nationalem Recht, sowie gemäß der Deklaration von Helsinki von 1975 (in der aktuellen, überarbeiteten Fassung) durchgeführt. Von allen beteiligten Patienten liegt eine Einverständniserklärung vor. Die Studie ist in der Datenbank *clinicaltrials.org* unter der Nummer *A 2014-0113* registriert.

Tabelle 1: Demographische Charakterisierung der Studienkohorten

	Studie 1			Studie 2		
	IG (n=8) M (SD)	**KG (n=8) M (SD)**	**p***	**AD (n=14) M (SD)**	**GK (n=14) M (SD)**	**p***
Bildung (Jahre)	14.4 (2.3)	14.4 (2.3)	0.957	14.4 (2.7)	13.6 (2.8)	0.417
Alter (Jahre)	70.4 (8.7)	69.8 (8.8)	0.916	75.3 (5.7)	73.4 (3.1)	0.276
Geschlecht (m/w)	4/4	5/3	0.614	10/4	10/4	-
MMST (Punkte)	21.8 (3.24)	24 (3.55)	0.279	24.6 (3.1)	28.7 (0.8)	<0.001

*Zweistichproben-t-Test für unabhängige Stichproben; IG – Interventionsgruppe; KG – Kontrollgruppe; AD – Patientengruppe mit Alzheimer-Demenz; GK – Gruppe mit gesunden Kontrollprobanden; M – Mittelwert; SD – Standardabweichung; m/w – männlich/ weiblich; MMST – Mini-Mental-Status-Test

Fünf Probanden waren von einer Warteliste aus dem vorangegangen Pilotprojekt zu dieser Studie übernommen worden und so bereits für die Interventionsgruppe vorgesehen. Wir führten daher eine partiell balancierte, computerbasierte Randomisierung durch, um die verbliebenen Probanden (n=15) auf die beiden Gruppen aufzuteilen. Die demographischen Daten sind in der Tabelle 1 angegeben. Die IG und KG unterschieden sich in Hinsicht auf Alter (p=0.916), Geschlecht (p=0.614), Bildung (p=0.957) oder MMST (p=0.279) nicht signifikant.
Die Intervention bestand aus einem CR-Programm, das auf dem manualisierten CORDIAL-Programm basierte (*Cognitive Rehabilitation and cognitive–behavioral treatment for early dementia in Alzheimer disease*, CORDIAL", [98]. Diese ambulante Intervention hatte eine Dauer von zwölf Wochen und beinhaltete sechs Module mit je zwei Sitzungen, wobei eine Sitzung 60 min pro Woche beträgt. Die sechs Module hatten folgende Inhalte:

1) **Identifizierung von Problemen und Definition von Behandlungszielen**
   Sammlung aktueller Probleme, welche die Selbständigkeit (Beispiel: Nutzung von Küchenutensilien) oder Lebensqualität (Beispiel: depressive Gedanken) beeinträchtigen
2) **Einführung externaler Gedächtnishilfen**
   Beispiele: Hauskalender, Merkzettel, Listen
3) **Einführung und Umsetzung von Alltagsroutinen**
   Übungen zu Alltagsaufgaben (Beispiel: Kaffee kochen), Ausarbeitung von Anleitungen und Plänen (Beispiel: eine Liste von gewohnten Morgenroutinen)
4) **Organisation und Umsetzung von bedeutungsvollen Aktivitäten**
   Psychoedukation zur Prävention von Depression/Apathie, Planung sozialer Unternehmungen und Hobbies
5) **Reminiszenz**
   Reflektion wichtiger Lebensmomente und -phasen als Quelle für Ressourcen und zur Stabilisierung der Identität (Beispiel: Biographiearbeit)
6) **Evaluation erreichter Ziele und Planung des weiteren Vorgehens**

Wir adaptierten dieses Programm in folgender Weise:

1) Wir ersetzten das individuelle Format mit Einzeltherapie durch ein Kleingruppenformat, welches von einer Psychotherapeutin und einer Ergotherapeutin betreut wurde. Dies hatte zum Ziel, die soziale Unterstützung als Ressource zu nutzen und die Therapiemaßnahme kostengünstiger zu gestalten.
2) Wir erweiterten die Sitzungsdauer von 60 auf 120 min pro Woche, um individuellen Bedürfnissen trotz des Gruppensettings gerecht zu werden.
3) Wir erlaubten eine Flexibilität bezüglich der Reihenfolge der Module, um besser auf die Bedürfnisse der Teilnehmer eingehen zu können.
4) Wir reduzierten je nach kognitivem Status der Patienten die Komplexität der Arbeitsblätter.
5) Wir reduzierten die Frequenz der Angehörigenteilnahme von sechs Sitzungen auf drei Sitzungen in Abhängigkeit von deren zeitlichen Kapazitäten.

6) Wir ergänzten ein erweitertes Training von Alltagsaufgaben, um eine Übertragung der Strategien in den Alltag zu erleichtern. Zur Verbesserung der zeitlichen Orientierung und Kommunikationsfertigkeiten wurden beispielsweise Zeitungsartikel gelesen und anschließend diskutiert.

Die Kontrollbedingung beinhaltete ein standardisiertes CT [36] in Form von Hausaufgaben, die jeder Teilnehmer selbstständig durchführen sollte und welche spezifische kognitive Funktionen trainierte. Die Gruppe traf sich alle vier Wochen zur Besprechung der Hausaufgaben.

1.4.2 Studie 2: Simultanes fMRT-EEG

Beide Gruppen bestanden aus je n=14 Probanden, die nach Alter und Geschlecht gematcht waren. Die Gruppe der Demenzpatienten (AD) hatten wir im Rahmen der Gedächtnisambulanz der UMR rekrutiert. Die Gruppe der gesunden Kontrollprobanden (GK) hatten wir über eine Datenbank der UMR für gesunde Kontrollprobanden rekrutiert. Die GK mussten einen Punktewert innerhalb der ersten Standardabweichung in jedem Subtest der CERAD Batterie (*Consortium to Establish a Registry for Alzheimer's Disease* [71]) aufweisen. Diagnostik, Untersuchungen und Ausschlusskriterien entsprachen denjenigen der Studie 1. Die demographischen Daten sind in Tabelle 1 abgebildet. Die Studie wurde mit Zustimmung der zuständigen Ethikkommission der Universität Rostock, im Einklang mit nationalem Recht, sowie gemäß der Deklaration von Helsinki von 1975 (in der aktuellen, überarbeiteten Fassung) durchgeführt. Von allen beteiligten Patienten liegt eine Einverständniserklärung vor.

1.5 Datenerhebung

1.5.1 Studie 1: Kognitive Rehabilitation

Die Untersucher waren während der Testungen und Befragungen gegenüber der Gruppenzugehörigkeit verblindet.

1.5.1.1 Primäre Endpunkte: ADL-Kompetenz

Für die Erfassung der ADL-Kompetenz nutzten wir zwei Fragebögen. Zum einen verwendeten wir die Bayer *Activities of Daily Living Skala* (B-ADL) [41], welche 25 Fragen enthält, die vom begleitenden Angehörigen mit einer Ziffer zwischen 1 (keine Einschränkung) bis 10 (ständige Einschränkung) beantwortet werden. Zum anderen setzten wir die *Nuremberg Aging Observation Scale* (NSL, [74]) ein, welche von Patienten (NSL-P) und Angehörigen (NSL-C) ausgefüllt wird. Dieser Fragebogen adressiert 15 Alltagsaktivitäten wie Anziehen oder Einkaufen. Null Punkte bedeuten keine Defizite und 30 Punkte zeigen maximale Einschränkungen.

1.5.1.2 Sekundäre Endpunkte: neuropsychologische Testungen

Für die Erfassung kognitiver Fähigkeiten mit Alltagsbezug nutzten wir drei Tests. Der Erste ist der *Rivermead Behavioural Memory Test* (RBMT) [99], welcher alltagsnahe Fähigkeiten testet, wie zum Beispiel einen Weg durch den Raum oder einen Termin zu erinnern. Als zweiten Test

nutzten wir zwei Teile des *Handlungsorganisation und Tagesplanung — Planungsfähigkeit im Alltag* (HOTAP) - Tests [69]. Im Subtest HOTAP-A müssen Fotos von Alltagstätigkeiten in die richtige Reihenfolge sortiert werden. Im Subtest HOTAP-C sollen einzelne Tätigkeiten nach Vorgabe in einen Tagesplan sortiert werden. Wir nutzten als abhängige Variablen die für den Test benötigte Zeit in HOTAP-A und HOTAP-C, das Verhältnis von Zeit und Punkten für HOTAP-C sowie die Summen der beiden Dimensionen „Logisches Denken“ und „Befolgung der Regeln“ in HOTAP-C. Als Indikator für Kommunikationsfähigkeit nutzten wir den *Boston Cookie Theft* -Bilder-Test [49] bei dem eine gezeichnete Situation beschrieben wird. Den funktionellen kognitiven Status erfassten wir mittels CERAD-Batterie, welche ein standardisiertes Instrument für die Testung von Aufmerksamkeit, Gedächtnis, Exekutivfunktionen, räumliches Denken und Sprache darstellt. Wir erhoben Daten zu folgenden nicht-kognitiven Domänen:

1. Lebensqualität in Form des Fragebogens *Dimensions of Quality of Life* (DEMQOL [85]), der von Patienten und Angehörigen ausgefüllt wird
2. Depressivität in Form des Fragebogens *Geriatrische Depressionsskala* (GDS, [102]) mit 30 Fragen
3. Apathie in Form der *Apathie Evaluation Skala* (AES, [66]) für Patienten und Angehörige
4. Neuropsychiatrische Verhaltensauffälligkeiten in Form des strukturierten *neuropsychiatrischen Interviews* (Neuropsychiatric Inventory, NPI, [34]) mit Angehörigen
5. Angehörigenbelastung in Form des *Zarit Burden Interviews* (ZBI [103])

1.5.1.3 Sekundäre Endpunkte: funktionelle Konnetivität

Die funktionelle Konnektivität untersuchten wir mit einem *3T Siemens Magnetom VERIO Magnetresonanztomographen* (Erlangen, Deutschland) mit einer 32-Kanal Kopfspule. Die Patienten wurden angewiesen, still zu liegen, die Augen geschlossen zu halten und nicht einzuschlafen. Die Bildeinstellung umfasste das ganze Gehirn und war entlang der anterioren-posterioren Kommissur gekippt. Alle funktionellen und anatomischen Scans wurden in Hinsicht auf Messfehler oder Artefakte visuell inspiziert. Die funktionellen Bilder basierten auf einer echo-planaren Sequenz mit folgenden Parametern: Echozeit 30 ms, Repetitionszeit 2600 ms, Anregungswinkel 80°, Sichtfeld 224 × 224 × 165 mm, 64x64 Bilder-Matrix mit 47 axialen Schichten (3,5 mm Dicke; 3,5 mm Abstand), Voxelgröße 3,5 mm^3, Dauer 7 min 54 s. Die T1-gewichteten strukturellen Bilder basierten auf der MPRAGE-Sequenz (*Magnetization Prepared Rapid Gradient Echo Sequenz*). Sie umfasste folgende Parameter: 256 x 256 Bildermatrix mit 192 sagittalen Schichten (Bilddicke 1 mm), Sichtfeld 256 × 256 × 192 mm, Voxelgröße 1 mm^3, Echozeit 4,82 ms, Repetitionszeit 2500 ms, Anregungswinkel 7°, Dauer 9 min 20 s.

1.5.2 Studie 2: Simultanes fMRT-EEG

EEG und fMRT wurden simultan für 7min 30 s in Ruhe bei geschlossenen Augen durchgeführt. Für das EEG nutzten wir 32 MRT-kompatible Elektroden und die Software *Brain Vision Recorder* (Brain Poducts, Gilching, Deutschland). Die Elektroden wurden entsprechend dem internationalen 10-20-System positioniert [57] mit der Referenzelektrode zwischen Fz und Cz und

der Erdung auf AFz. Die Widerstände der relevanten Elektroden (O1, O2 und Oz, da hier die Alpha-Aktivität am höchsten ist [70]) waren unter 8 kΩ, außer für einen AD Patienten (18 kΩ). Eine weiterer Elektrokardiogramm-Kanal wurde zur Erfassung kardialer Störsignale angelegt. EEG-Daten wurden bei 5 kHz erfasst. Der EEG-Verstärker arbeitete phasensynchronisiert mit der MRT-Frequenz über *Syncbox* (Brain Products, Gilching, Germany). Weitere Maßnahmen wurden umgesetzt, um Bewegungen der Geräte und Probanden entgegenzuwirken. Das MRT-Gerät und entsprechende Einstellungen sind den Ausführungen aus Studie 1 zu entnehmen.

1.6 Bilddaten(vor)verarbeitung

1.6.1 Studie 1: Kognitive Rehabilitation

Zur Vorverarbeitung der Bilder verwendeten wir zur Datenprozessierung *Statistical Parametric Mapping* 8 (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK [46]) in MATLAB (R2012a, The Math-Works, Inc., Natick, Massachusetts, USA) zusammen mit der *Voxel-Based Morphometry Toolbox* (VBM8, r4123, Structural Brain Mapping Group, Kliniken für Neurologie und Psychiatrie, Universität Jena [47]) und dem *Daten-Prozessierungs-Assistenten für Resting-State fMRI*, DPARSF (Erweiterte Edition 3.1, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China [101]).
Die anatomischen T1-gewichteten Scans wurden entsprechend dem longitudinalen Protokoll der VBM8-Toolbox präprozessiert. Aus diesen bereinigten, anatomischen, T1-gewichteten Bildern von der Baseline (BL)- und der Verlaufsuntersuchung (VU) errechneten wir für jeden Patienten ein Mittelwertbild aus BL und VU, welche mittels VBM8 in graue Substanz, weiße Substanz und zerebrospinale Flüssigkeit aufgetrennt wurden (Segmentierung). Danach nutzten wir das Verfahren *Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (*DARTEL *[3])*, um ein studienspezifisches Template zu erstellen, welches dazu verwendet wurde, die T1-Bilder in das *Montreal Neurological Institute* (MNI [72]) Referenzkoordinatensystem zu übertragen (Normalisierung). Die Präprozessierung der funktionellen Bilder erfolgte in der DPARSF-Toolbox. Hier entfernten wir zuerst die ersten sechs Bilder, führten eine Korrektur der Aufnahmezeitpunkte durch (Slice Time Correction) und ließen alle Bilder dem Mittelbild der Serie anpassen (Realignment). Anschließend erfolgte in SPM die Ko-Registrierung der funktionellen Bilder auf das anatomische T1-gewichtete Mittelwertbild. Störsignale durch Kopfbewegungen wurden herausgerechnet und Frequenz-Filter zwischen 0,01 und 0,1 Hz angewendet. Für die Normalisierung der funktionellen Bilder auf den MNI-Standardraum verwendeten wir die Deformationsfelder der anatomischen Bilder aus der VBM8-Toolbox auf das funktionelle BL- und VU-Bild eines jeden Patienten. Diese Normalisierung ist nötig, um die Gehirne der Patienten nach Voxeln und mit korrekten anatomischen Proportionen untereinander vergleichen zu können. Als letzten Schritt glätteten wir die Bilder mit einem 8 mm breiten Gaußkernel (Smoothing).

1.6.2 Studie 2: Simultanes fMRT-EEG

Die EEG-Daten wurden mittels *Brain Vision Analyzer Software* (Version 2.0, Brain Products, Gilching, Deutschland) präprozessiert. Bild- und Puls-Artefakte wurden mit der Subtraktions-Methode nach Allen et al. [1] entfernt, welche in der *Brain Vision Analyzer Software* enthalten ist. Die Daten durchliefen einen Hochpassfilter bei 0.5 Hz und einen Tiefpassfilter bei 70 Hz sowie einen Kerbfilter bei 50 Hz. Mittels *Independent Component Analyse (ICA)* wurden weitere Artefakte, zum Beispiel durch Augenbewegungen, entfernt. Die Daten wurden visuell kontrolliert. Es traten keine Schlaf-Muster auf. Die EEG-Daten der AD-Patienten zeigten in der zweiten Messhälfte mehr Artefakte. Zwei AD-Patienten zeigten phasenweise einen Wechsel von Alpha-Wellen zu Theta-Wellen, diese Abschnitte wurden entfernt. Das arithmetische Mittel der elektrophysiologischen Aktivität von *O1*, *O2*, und *Oz* wurde berechnet. Mittels komplexer Demodulation wurden für jeden Probanden die Alpha-Aktivität für die Gesamtfrequenz (8-12 Hz) extrahiert. Die Präprozessierung der fMRT-Daten ist mit den Verfahren und Programmen aus Studie 1 vergleichbar, außer dass keine longitudinalen Mittelwertbilder erstellt wurden. Zusätzlich wurde ein Hochpassfilter mit einem Cut-off von 128 s für den Signalzeitverlauf eines jeden Voxel angewendet. Weiterhin wurde das Hippocampus-Volumen der Grauen Substanz ermittelt, wobei das IXI-Template für den MNI-Raum genutzt wurde, wie es dem Internationalen Harmonisierungsprotokoll für Hippocampussegmentierung entspricht [51]. Verschiedene Regressoren für Ein-Sekunden-Intervalle von Artefakt-freien, durchschnittlichen Aktivitätsmustern der occipitalen Elektroden wurden erstellt sowie ein on/off-Regressor of-no-interest für Artefakte, die länger als eine Sekunde dauern. Ein weiterer Regressor wurde für die Gesamtfrequenz (8-12 Hz) generiert. Dieser Regressor hatte eine vordefinierte Funktion für die Hämodynamische Antwort [31].

1.7 Statistische Analyse

1.7.1 Studie 1: Kognitive Rehabilitation

1.7.1.1 Statistik zur neuropsychologischen Auswertung

Die Analyse der neuropsychologischen Erhebungen erfolgte mittels *IBM SPSS Statistics 21*. Fehlende Antworten (0,38%) wurden durch den gruppeneigenen Mittelwert für diese Frage ersetzt. Wenn ein vollständiger Test fehlte (0,74%) wurde der Proband für die Analyse dieses Tests ausgeschlossen. Für den Gruppenvergleich der demographischen Variablen und die BL-Analyse verwendeten wir Mann-Whitney-U-Tests für zwei unabhängige Stichproben. Der Chi-Quadrat-Test wurde zum Vergleich der Geschlechter genutzt. Die longitudinale Analyse erfolgte mittels Varianzanalyse für wiederholte Messungen, wobei für jeden Endpunkt Haupt- und Interaktionseffekte für die Faktoren Zeit und Gruppe berechnet wurden. Vor der Varianzanalyse wurden die Werte über die zwei Zeitpunkte nach Rang transformiert. Danach wurde eine rang-abhängige *Inverse Normale Transformation* (INT, [10]) durchgeführt um eine annähernd normalverteilte Stichprobe zu erhalten. Die Varianzanalyse erfolgte mit und ohne INT. Als Effektgröße errechneten wir Cohen's d für die Interaktionseffekte. Die Unterschiede zwischen den Gruppen zur BL und zur VU errechneten wir mittels t-Test für abhängige Stichproben aus den Effektgrößen der t-Werte.

1.7.1.2 Statistik zur funktionellen Konnektivität

Zur Analyse der funktionellen Konnektivität im DMN folgten wir einem Saatpunkt-basierten Ansatz, wie er in der DPARSF-Toolbox umgesetzt wird. Hierbei wurde eine Korrelationskarte für den Signalzeitverlauf eines jeden Voxel im Gehirn im Vergleich zu dem Saatpunkt errechnet, den wir im PCC anhand der MNI-Koordinaten (0, -51, 29) mit einem Radius von 6 mm platziert hatten [50, 18]. Es wurde die Fisher-Transformation vom Pearson Korrelationskoeffizienten zur Erstellung der z-Wert-Karten durchgeführt. Die Karten nutzten wir für die folgende Analyse in SPM8: Zuerst verwendeten wir einen Einstichproben-t-Test zur Bestimmung des Konnektivitätsmusters in der gesamten Stichprobe (Schwellenwert für Signifikanz bei $p<0.05$ mit Family-wise-Korrektur bei einer minimalen Clustergröße von 50 Voxeln). Alle folgenden Tests wurden mit einem Schwellenwert für Signifikanz bei $p<0.001$, unkorrigiert, bei einer minimalen Clustergröße von 50 Voxeln durchgeführt. Als zweiten Test verwendeten wir einen Zweistichproben-t-Test, um die Gruppen zum BL- und VU-Zeitpunkt zu vergleichen. Der dritte Test war eine zweifaktorielle Varianzanalyse für wiederholte Messungen, welche wir mit dem flexiblem faktoriellen Modell in SPM umsetzten. Die untersuchten Faktoren waren der Haupteffekt der Gruppe und der Bedingung, in dem Fall die Zeit zwischen BL und VU, und der Interaktionseffekt für Gruppe und Bedingung, womit wir den longitudinalen Vergleich der beiden Gruppen errechneten. Zuletzt erzeugten wir funktionelle Differenzbilder, wobei wir das Bild zur BL von dem Bild zum Zeitpunkt der VU abzogen. Damit berechneten wir mittels Voxel-basierter linearer Regression die longitudinalen Unterschiede zwischen der funktionellen Konnektivität und einer abhängigen neuropsychologischen Variable. Um die Lokalisation der Cluster topographisch zuordnen zu können, nutzten wir die *Automated Anatomical Labeling toolbox* (2008) für SPM8 mit einem Standard-MNI-Template.

1.7.2 Studie 2: Simultanes fMRT-EEG

Zum Vergleich der Alpha-Aktivität der occipitalen Kanäle *O1*, *O2* und *Oz* zwischen den Gruppen wurde die schnelle Fourier-Transformation angewendet. Der t-Test für unabhängige Stichproben wurde genutzt, um die Alpha-Aktivität und das normalisierte Hippocampus-Volumen der grauen Substanz zu vergleichen. Mit Hilfe des allgemeinen linearen Modells wurde in SPM8 die spezifische Aktivität für das totale Alpha-Band berechnet [46]. Es wurden für jedes Individuum parametrische Karten erstellt, wobei die positive Assoziation der Aktivität des Alphabandes mit der BOLD-Aktivität in jedem Voxel dargestellt wird. Diese EEG-Regressor-Karten wurden für den Gruppenvergleich in Ein- und Zweistichproben-t-Tests genutzt. Die statistische Signifikanz wurde auf $p<0.01$ (unkorrigiert) bei einer minimalen Clustergröße von 50 Voxeln festgesetzt. Die Cluster wurden visuell mit einem Atlas für funktionelle Konnektivität des DMN verglichen [84].

1.8 Ergebnisse

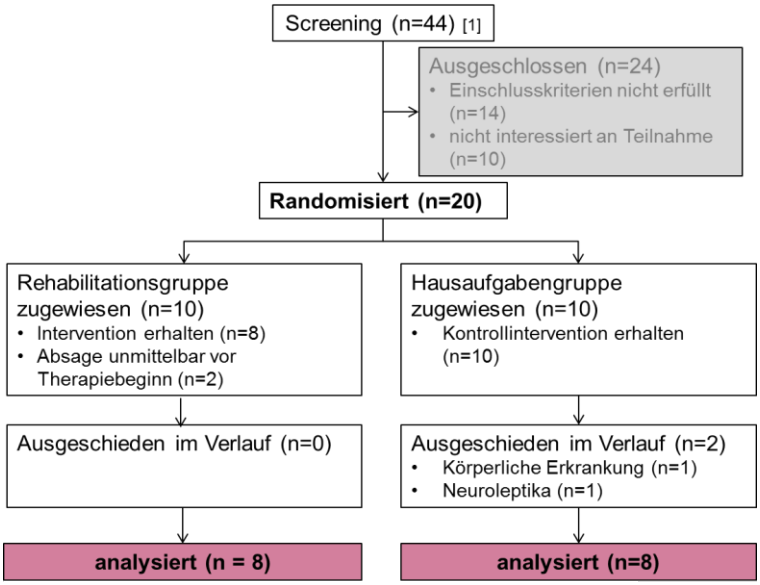
1.8.1 Studie 1: Kognitive Rehabilitation

Der Screenings- und Randomisierungsablauf ist in Abbildung 1 dargestellt. Zwei Patienten sagten bereits vor Interventionsbeginn ab. Während der Intervention erkrankte ein Patient ernstlich und ein anderer entwickelte Psychosen und wurde mit Antipsychotika behandelt. Nach Abschluss der Intervention analysierten wir 16 Patienten. Die Behandlungs-Adhärenz der 16 Patienten betrug 100%.

1.8.1.1 Prä-post-Ergebnisse der neuropsychologischen Auswertung

Die Tabelle 2 zeigt die Interaktionseffekte, welche auf der Varianzanalyse beruhen. Der primäre Endpunkt der ADL-Kompetenz, wie er mittels Angehörigenbeurteilung in der Bayer-ADL ermittelt wurde, verbesserte sich in der IG und verschlechterte sich in der KG. Diese Effekte waren jedoch nicht signifikant (p=0.109). Die c-NSL-Skala zeigte eine Abnahme der ADL-Kompetenz in beiden Gruppen (nicht-signifikant, p=0.900). Die p-NSL-Skala zeigte eine Abnahme in der IG und eine Zunahme in der KG (nicht signifikant, p=0.310). Die sekundären Endpunkte, welche die kognitive Fähigkeiten mit Alltagsbezug erfassen, gemessen durch RBMT, HOTAP und CTP, zeigten keine signifikanten Interaktionseffekte. Gleiches gilt für die longitudinalen Ergebnisse der CERAD-Batterie. Innerhalb der nicht-kognitiven Domänen fanden sich signifikante Interaktionseffekte für die Selbstbeurteilung der Lebensqualität, welche in der IG zunahm und in der KG abnahm (p=0.013). Keine andere Domäne zeigte signifikante Effekte. Die Effektgrößen variierten zwischen mittel und groß (Tabelle 2). Ähnliche Resultate fanden sich in der Varianzanalyse ohne vorheriger INT.

Abbildung 1: Studie 1 - Screenings- und Randomisierungsverlauf



(1) entspricht CONSORT – Kriterien [81]

Tabelle 2 Studie 1 - Ergebnisse: Differenzwerte von Baseline zu Verlaufsuntersuchung und Interaktionseffekte (erfasst mittels Varianzanalyse)

Endpunkte	Tests und Fragebögen	**IG (n=8)**	**KG (n=8)**			
		Mittlere Differenz (SD)	Mittlere Differenz (SD)	F	p	d
Primärer Endpunkt: ADL-Kompetenz	B-ADL-Angehörige*	–0.52 (0.94)	0.26 (1.10)	2.93	0.109	0.86
	NSL-Angehörige*	3.00 (13.93)	0.63 (11.40)	0.02	0.900	0.86
	NSL-Patienten*	0.50 (5.42)	-4.50 (6.19)	1.11	0.310	-0.53
Sekundäre Endpunkte:						
Kognitive Fähigkeiten mit Alltagsbezug: Prospektives Gedächtnis	RBMT	-0.13 (3.52)	-1.88 (3.00)	0.07	0.789	-0.14
Planungs- und Organisationsfähigkeiten	HOTAP-A	1.10 (1.60)	0.82 (1.73)	0.02	0.890	-0.07
	HOTAP-C kombinierter Wert	0.10 (2.34)	0.89 (1.28)	0.71	0.414	0.36
	HOTAP-C logisches Denken	-0.7 (2.56)	-0.38 (1.19)	0.10	0.760	0.16
	HOTAP-C Regelbefolgung	0.00 (2.08)	0.75 (3.88)	0.17	0.688	0.21
Spontane Sprache	CTP	-1.13 (2.36)	-2.75 (2.66)	1.46	0.247	-0.6
Funktioneller kognitiver Status CERAD:	MMST	1.00 (1.51)	0.13 (2.17)	0.21	0.658	-0.23
Aufmerksamkeit	Trail Making Test A*	24.23 (25.71)	15.63 (24.08)	0.00	0.965	-0.02
Gedächtnis	Wortliste Gedächtnis	0.63 (4.03)	1.38 (3.85)	0.44	0.517	0.33
	Wortliste Abrufen	-0.13 (2.03)	0.00 (1.41)	0.03	0.874	-0.08
	Konstruktive Praxis Abrufen	0.00 (2.51)	0.75 (2.76)	0.34	0.569	0.29
Exekutivfunktionen	Trail Making Test B*	26.86 (49.75)	25.57 (45.32)	0.22	0.650	-0.23
Sprache	Phonematische Flüssigkeit	-1.63 (3.11).	-3.38 (3.16)	0.78	0.392	-0.44
	Semantische Flüssigkeit	1.50 (4.17)	-2.38 (2.17)	3.69	0.075	-0.96

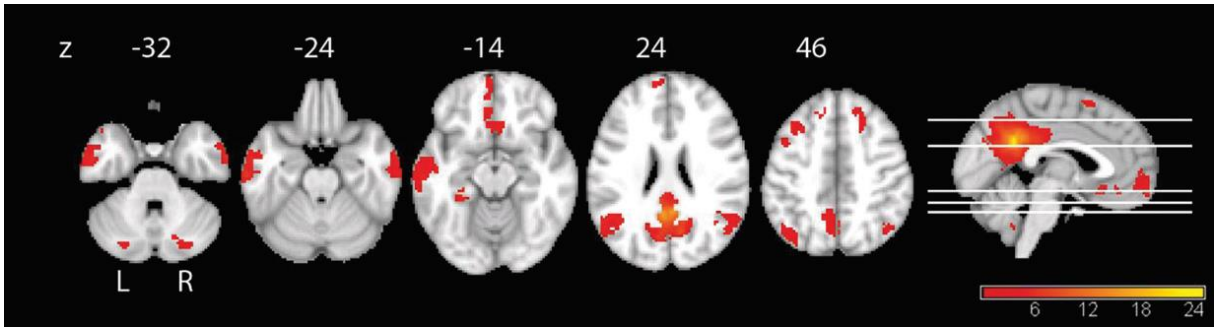
Räumliche Vorstellungskraft	Boston Naming Test	-0.13 (1.25)	-0.88 (1.64)	1.24	0.285	-0.56
	Konstruktive Praxis	0.25 (1.49)	-0.50 (2.20)	2.30	0.152	-0.76
Nicht-kognitive Domänen: Apathie	AES-Angehörige*	3.75 (6.96)	2.13 (5.84)	0.05	0.832	-0.11
	AES-Patienten*	4.75 (6.73)	2.50 (2.51)	0.51	0.487	-0.36
Depressivität	GDS-Patienten*	0.13 (3.09)	0.88 (3.23)	0.05	0.833	0.11
Lebensqualität	DEMQOL-Patienten	3.1 (5.79)	-4.4 (5.40)	8.15	**0.013**	-1.43
Angehörigenbelastung	ZBI-Angehörige	5.3 (5.18)	0.8 (7.25)	1.16	0.300	-0.54

*Positive Werte bedeuten eine Abnahme von der Baseline zur Verrlaufsuntersuchung; Grauhinterlegung zeigt Effekte mit erwarteter Richtung; SD, Standardabweichung; F, Intervention über die Zeit; d, Cohen's d von t-Werten abgeleitet; ADL, Activities of Daily Living; B-ADL, Bayer Activities of Daily Living; NSL, Nuremberg Aging Observation Skala, RBMT, Rivermead Behavioural Memory Test; HOTAP, „Planung und Organisation"; HOTAP–A, das Sortieren von Fotos mit typischen Alltagshandlungen; HOTAP–C, „das Sortieren von Handlungen in einen semistrukturierten Tagesplan; CTP, Boston Cookie Theft Picture Description Test; MMST, Mini-Mental-Status-Test; CERAD, Consortium to establish a registry for Alzheimer's disease; AES, Apathy Evaluation Skala; DEMQOL, Dimensions of Quality of Life; GDS, Geriatrische Depressionsskala; NPI, Neuropsychiatrisches Interview; ZBI, Zarit Burden Interview. Grenzwert: $p < 0.05$

1.8.1.2 Ergebnisse zur funktionellen Konnektivität

Die gesamte Stichprobe zeigte eine signifikante PCC-Konnektivität mit den Arealen Präcuneus, superioren parietaler Kortex, lateraler temporaler Kortex und medialer präfrontaler Kortex (Abbildung 2). Diese Regionen sind typisch für das DMN-Muster [20].

Abbildung 2: Studie 1 - Funktionelle Konnektivität des PCC in der Stichprobe zur Baseline



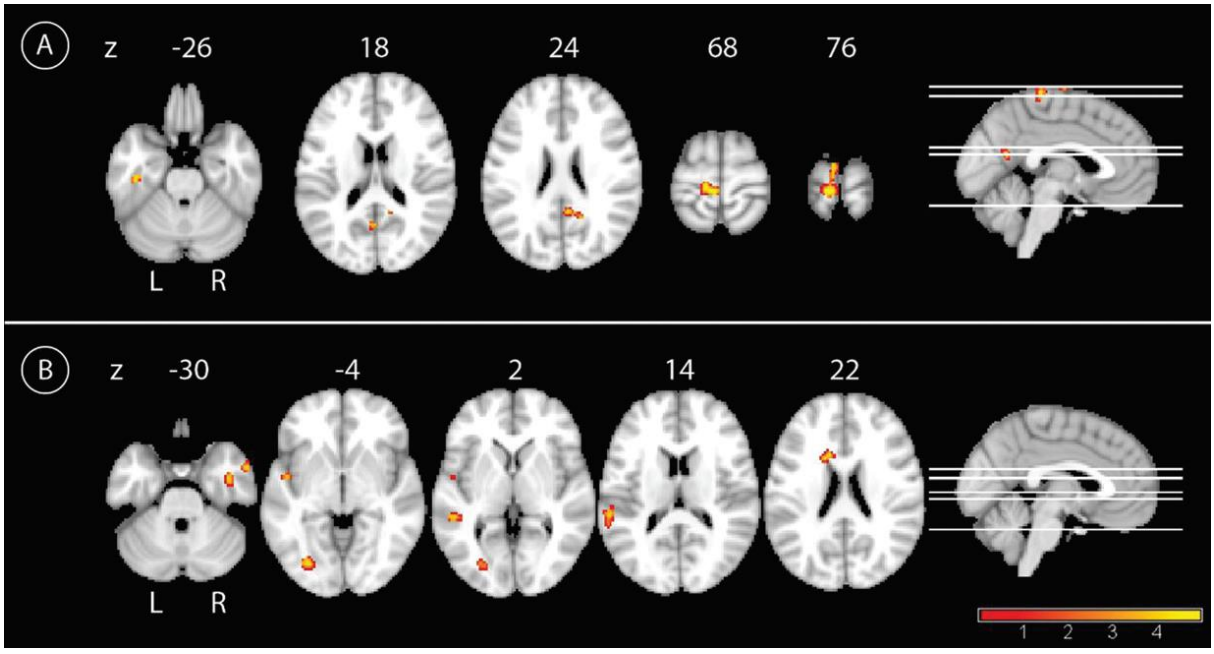
Die Konnektivitätskarten zeigen das typische Muster des Default Mode Netzwerkes. Wir setzten den Schwellenwert für Signifikanz bei $p<0.05$ mit Family-Wise-Korrektur bei einer minimalen Clustergröße von 50 Voxeln. im Horizontalschnitt mit Koordinaten des MNI Referenzsystems. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC

In der longitudinalen Analyse zeigte der Haupteffekt über die Zeit eine Zunahme der Konnektivität von BL zur VU in der gesamten Stichprobe im linken präzentralen Gyrus und in geringerer Ausprägung im bilateralen Präcuneus, im rechten PCC und im rechten inferioren Temporallappen (Abbildung 3). Eine Abnahme der FC von BL zur VU fanden wir zwischen PCC und Regionen im linken Temporallappen und dem rechten temporalen Pol. Kleinere Cluster, die ebenfalls eine Konnektivitätsabnahme über die Zeit anzeigen, waren im linken mittleren okzipitalen Kortex und linken Nucleus caudatus (Abbildung 3, Tabelle 3).

Die Interaktion der Gruppen über die Zeit zeigte für die IG im Vergleich zur KG eine vermehrte FC des PCC vor allem im bilateralen cerebellären Kortex. Kleinere Cluster fanden sich für diesen Kontrast im linken postzentralen Gyrus, im supplementärmotorischen Kortex und im orbitalen frontalen Kortex (Abbildung 4, Tabelle 3). Im Kontrast dazu zeigte die KG im Vergleich mit der IG eine vermehrte Aktivität zwischen PCC und kleinen, weit vereinzelten Regionen wie dem linken lingualen Kortex, dem temporalen inferioren Lappen, dem orbito-frontalen Kortex, dem rechten präzentralen Kortex, dem Pallidum und dem Nucleus Caudatus (Abbildung 4 und Tabelle 3).

Da die Lebensqualität als einziger neuropsychologischer Parameter eine Signifikanz im Interaktionseffekt aufwies, korrelierten wir die Zu- oder Abnahme dieser Variable mit der FC. In der IG war eine Zunahme der Lebensqualität mit einer Konnektivitätszunahme des PCC mit dem bilateralen Präcuneus, inbesondere dessen linker Seite, dem rechten mittleren Temporallappen, dem linken Gyrus calcarinus und dem rechten inferioren Cortex assoziiert (Abbildung 5 und Tabelle 4). In der KG zeigte sich keine signifikante Korrelation von Lebensqualität und FC.

Abbildung 3: Studie 1 - Haupteffekt über die Zeit für die gesamte Stichprobe

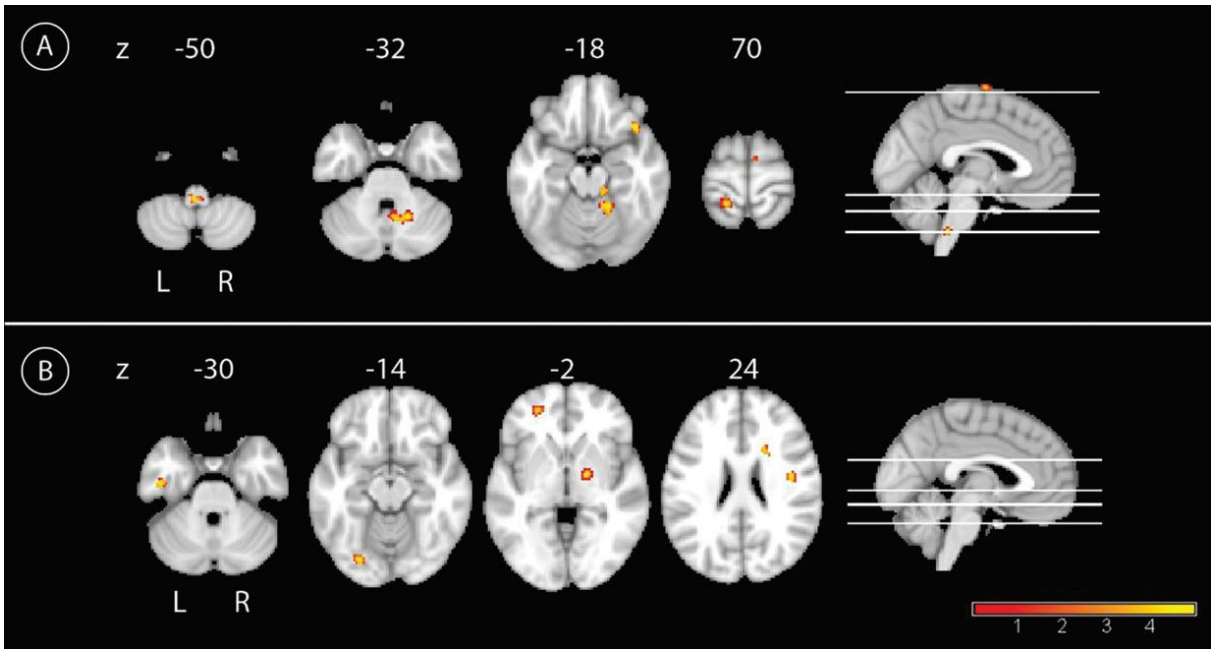


A) Ergebnisse für den Haupteffekt über die Zeit mit dem Kontrast Verlaufsuntersuchung > Baseline für die gesamte Stichprobe. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC zur Verlaufsuntersuchung im Vergleich

zur Baseline, p<0.001, unkorrigiert, mit einer minimalen Clustergröße von 50

B) Ergebnisse für den Haupteffekt über die Zeit mit dem Kontrast Baseline > Verlauf für die gesamte Stichprobe. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC zur Baseline im Vergleich zur Verlaufsuntersuchung, p<0.001, unkorrigiert, mit einer minimalen Clustergröße von 50 Voxeln.

Abbildung 4: Studie 1 - Longitudinaler Interaktionseffekt



A) Vergleich des longitudinalen Effektes der kognitiven Reha zwischen den Gruppen mit dem Kontrast Interventionsgruppe > Kontrollgruppe über die Zeit. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC für die Interventionsgruppe im Vergleich zur Kontrollgruppe, p<0.001, unkorrigiert, mit einer minimalen Clustergröße von 50.

B) Vergleich des longitudinalen Effektes der kognitiven Reha zwischen den Gruppen mit dem Kontrast Kontrollgruppe > Interventionsgruppe über die Zeit. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC für die Kontrollgruppe im Vergleich zur Interventionsgruppe, p<0.001, unkorrigiert, mit minimaler Clustergröße von 50 Voxeln

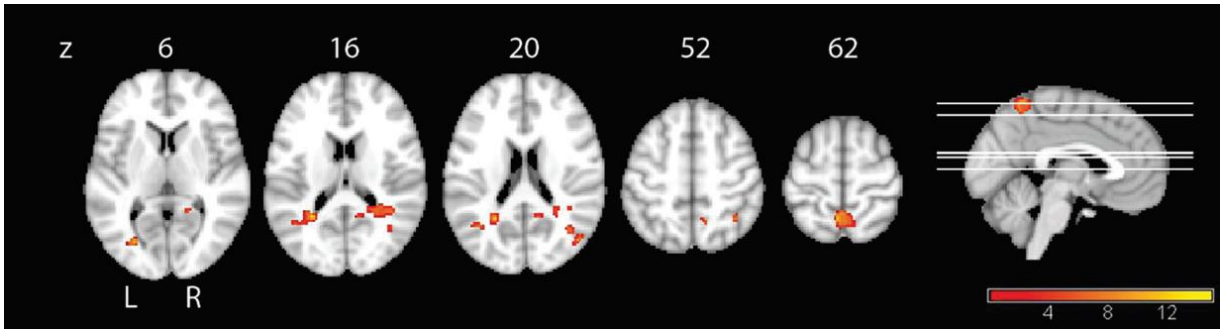
Tabelle 3: Studie 1 - Ergebnisse der longitudinalen Veränderungen der funktionellen Konnektivität

Longitudinale Kontraste		Region, rechts (R) oder links (L)	Cluster-größe (Voxel)	Lokales Maximum MNI Koordinaten (mm) x	y	z	Lokales Maximum T-Statistik
Haupteffekt über die Zeit	VU > BL	Präcuneus, R	124	18	-54	27	5.28
		präzentraler Gyrus, L	594	-6	-31	67	5.07
		temporaler inferiorer Lobus, L	67	-42	-21	-26	4.45
		Präcuneus, R	51	12	-48	13	4.17
		Präcuneus, L	55	-2	-61	19	3.97
		mittlerer occipitaler Lobus, L	175	-28	-76	-2	5.61

	BL > VU	superiorer temporaler Lobus, L	155	-60	-36	12	4.27
		temporaler inferiorer Lobus, R	101	42	-6	-29	4.46
		Korpus Nuclei Caudatus, L	96	-16	14	24	4.83
		mittlerer temporaler Lobus, L	96	-50	-36	4	4.58
		mittlerer temporaler Lobus, R	74	56	6	-32	4.48
Inter-aktionseffekt	IG > KG	Cerebellum, Lobulus IV/V, R	210	18	-45	-15	5.04
		Cerebellum, Lobulus VI, R	175	18	-55	-33	4.82
		postzentraler Kortex, L	109	-18	-43	69	4.40
		inferiorer frontaler Kortex, Pars Orbitalis, R	104	40	22	-18	5.10
		Supplementärmotorischer Kortex, L	91	0	-6	73	4.17
		Cerebellum, Lobulus III, R	50	15	-31	-17	4.77
	KG > IG	lingualer Kortex, L	77	-26	-79	-14	4.93
		inferiorer temporaler Lobus, L	74	-45	-13	-29	4.47
		präzentraler Kortex, R	70	42	-6	27	5.03
		Nucleus Caudatus, R	65	20	15	24	4.06
		Pallidum, R	54	18	-6	-2	5.04
		orbitofrontaler Kortex, L	51	-26	50	-3	3.99

Ergebnisse der Querschnitts- und Longitudinalanalyse, p<0.001, unkorrigiert, mit einer minimalen Clustergröße von 50; IG – Interventionsgruppe; KG – Kontrollgruppe; BL – Baseline, VU – Verlaufsuntersuchung, MNI, Montreal Neurologisches Institut

Abbildung 5: Studie 1 - Lineare Regressionsanalyse der Lebensqualität und funktionellen Konnektivität



Positive Korrelation der Differenzergebnisse des Quality of Life – Tests und den Differenzbildern der funktionellen Konnektivität für die Interventionsgruppe. Gelbe Farbe repräsentiert höhere Konnektivität mit dem PCC für die Interventionsgruppe im Vergleich zur Kontrollgruppe, p<0.001, unkorrigiert, mit einer minimalen Clustergröße von 50

Tabelle 4: Studie 1 – Longitudinale Korrelationsanalyse von Lebensqualität und Konnektivität

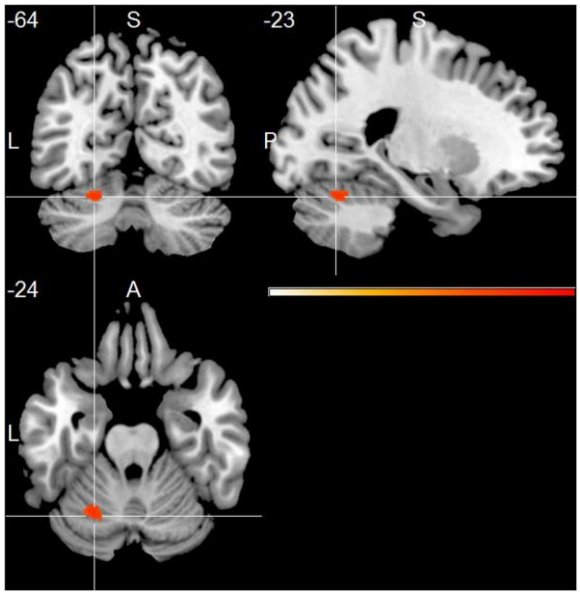
Kontraste		Region, rechts (R) oder links (L)	Clustergröße (Voxel)	Lokales Maximum MNI Koordinaten x	y	z	Lokales Maximum T-Statistik
Lebens-qualität – IG	Positive Korrelation	Präcuneus, L Präcuneus, R	461 295 104	-4 -27 22	-54 -52 -48	63 16 27	4.76 4.77 4.00
		mittlerer temporaler Lobus, R	324 52 50	40 46 40	-48 -72 -63	13 21 18	3.92 4.52 3.98
		Gyrus Calcarinus, L	82	-27	-73	6	4.53
		inferiorer parietaler Kortex, R	65	38	-54	52	4.30

Lineare Regression der funktionellen Differenzbilder als abhängige Variable und die Differenzwerte des Verhaltensparameter Lebensqualität als unabhängige Variable (erfasst mit dem Test DEMQOL), $p<0.001$, unkorrigiert, mit einer minimalen Clustergröße von 50. IG – Interventionsgruppe; KG – Kontrollgruppe; MNI - Montreal Neurologisches Institut

1.8.2 Studie 2: Simultanes fMRT-EEG

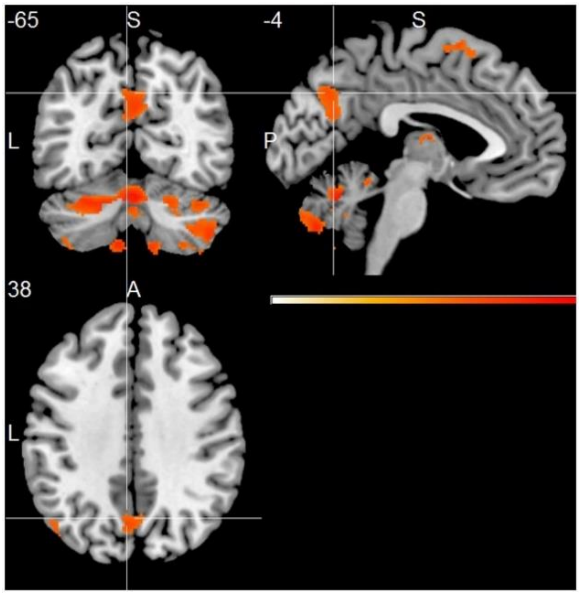
Die AD-Gruppe zeigte positive Assoziationen des Alpha-Power-Bandes mit dem BOLD-Signal im Cerebellum (Einstichproben-t-Test, $p< 0.01$, unkorrigiert, Clustergröße mindestens 50, Abbildung 6). Für die GK-Gruppe fanden wir positive Assoziationen des Alpha-Power-Bandes in folgenden Regionen: superiorer, mittlerer und inferiorer frontaler Kortex, temporaler Pol, parietaler Kortex, Thalamus, Putamen and Cerebellum. (Einstichproben-t-test, $p < 0.01$, unkorrigiert, Abbildung 7). Im Vergleich zur KG zeigte die AD-Gruppe im Zweistichproben-t-Test eine Abnahme positiver Assoziationen des Alpha-Power-Bandes mit dem BOLD-Signal in Clustern des frontalen Kortex (superiorer, mittlerer, inferiorer, präzentraler Gyrus, und ACC), des inferioren temporalen Lobus und des Thalamus ($p < 0.01$, unkorrigiert, Abbildung 8). Auf individueller Ebene zeigte sich in der Erstlevel-Analyse eine positive Assoziation des Alpha-Power-Bandes mit Regionen des DMN [103] in n=6 gesunden Kontrollprobanden und n=3 AD-Patienten und mit Regionen des Thalamus für n=5 GK und für n=3 AD-Patienten ($p<0.01$, unkorrigiert). Das normalisierte Volumen der grauen Substanz des Hippocampus war niedriger in der AD-Gruppe, allerdings nicht signifikant (t-Test für unabhängige Stichproben, $p=0.095$). Die Eingabe als covarianten Regressor im allgemeinen linearen Modell veränderte die Ergebnisse der Ein- und Zweistichprobentests nur unwesentlich.

Abbildung 6: Studie 2 – Positive Assoziationen für den AD-Gruppeneffekt



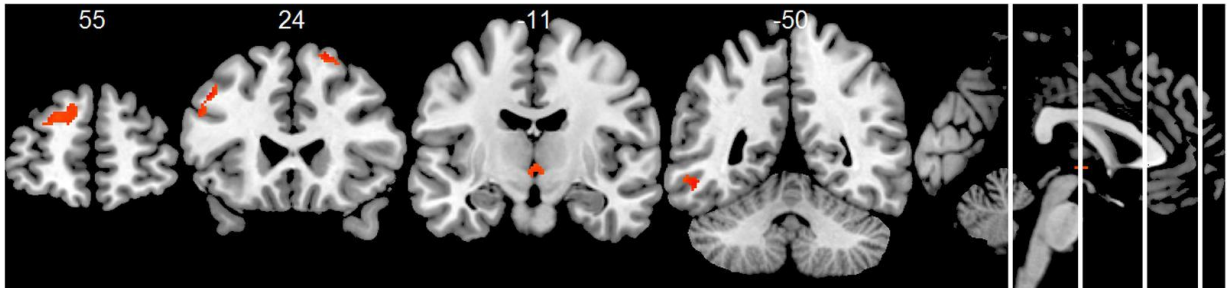
Positive Assoziationen des Alpha-Power-Bandes mit dem BOLD-Signal für die AD-Gruppe (p< 0.01, unkorrigiert, Clustergröße mindestens 50)

Abbildung 7: Studie 2 – Positive Assoziationen für den Gruppeneffekt der gesunden Kontrollen



Positive Assoziationen des Alpha-Power-Bandes mit dem BOLD-Signal für die Gruppe der gesunden Kontrollen (p< 0.01, unkorrigiert, Clustergröße mindestens 50)

Abbildung 8: Studie 2 – Positive Assoziationen im Gruppenvergleich



Positive Assoziationen des Alpha-Power-Bandes mit dem BOLD-Signal für den Kontrast gesunde Kontrollen > AD-Gruppe (p< 0.01, unkorrigiert, Clustergröße mindestens 50)

1.9 Diskussion

1.9.1 Studie 1: Kognitive Rehabilitation

1.9.1.1 Diskussion neuropsychologischer Daten

Die Studie 1 hatte die Entwicklung und Adaptation eines integrativen Konzepts der kognitiven Rehabilitation zum Ziel sowie dessen Evaluation in Hinsicht auf Durchführbarkeit und Effektivität. Die untersuchte CR basierte auf dem manualisierten CORDIAL-Programm [98], welches wir an ein Gruppensetting adaptierten und in verschiedenen Bereichen erweiterten. Es zeigte sich, dass das adaptierte CR-Konzept sehr gut umsetzbar war, allerdings keine Effekte in Hinsicht auf den primären Endpunkt der Alltagskompetenz aufwies. Dieses Ergebnis fügt sich in Erfahrungen aus vorherigen Studien, die ebenfalls keine Veränderungen der ADL-Werte vorweisen konnten [80]. Gleiches gilt auch für die CORDIAL-Evaluationsstudie, welche ebenfalls die BADL-Skala nutzte [62]. Dass eine Verbesserung von ADL-Kompetenzen bei Demenz schwierig zu erfassen ist, wurde bereits diskutiert [39]. Außerdem wurde vermutet, dass die BADL-Skala womöglich eine niedrige Sensitivität bei Demenzpatienten aufweist [98]. Daher verwendeten wir eine weitere ADL-Skala, aber auch hier fanden sich keine signifikanten Interventionseffekte. Die fehlenden Effekte in Tests zur Alltagskompetenz scheinen also nicht allein an fehlender Sensitivität zu liegen, sondern haben noch andere Hintergründe.
Die geringe Stichprobengröße dürfte hierbei eine wichtige Rolle spielen, denn zwei der drei verwendeten ADL-Skalen zeigten mittlere bis große Effektgrößen (Cohen's d > 0.5). Eine größere Stichprobe hätte womöglich Signifikanz erreicht. Wir beobachteten auch einen fehlenden Transfer in den realen Alltag. Die kognitiven Fähigkeiten einiger Patienten lagen bereits auf dem Niveau milder bis moderater Demenz, es benötigt jedoch Gedächtnisfunktionen und die Fähigkeit zur Abstraktion, um gelernte Strategien auf neue Situationen anzuwenden. Möglicherweise wäre bei Patienten mit umfangreicheren Defiziten eine Übertragung der Übungen in die Häuslichkeit von Vorteil gewesen. Zusätzlich ist es von großer Bedeutsamkeit, dass Angehörige in die Therapie eingebunden werden und Verantwortung bei der Umsetzung im Alltag übernehmen. Die Teilnahme der Angehörigen an jeder vierten Sitzung schien hierfür nicht ausreichend zu sein. Gleichzeitig aber bestehen Grenzen hinsichtlich der Verfügbarkeit und Belastbarkeit der Angehörigen. Die Interventionsgruppe (IG) schätzte die eigene ADL-Kompetenz (NSL) im Anschluss an die CR als stabil oder etwas geringer ein, während sich die Kontrollgruppe (KG) im Durchschnitt als verbessert einschätzte. Da die CR eine detaillierte Analyse der Alltagsroutine und -mobilität beinhaltete, könnte nach eventuell bisherigem Mangel an Krankheitseinsicht ein vermehrtes Bewusstsein für die persönlichen Grenzen entstanden sein, sodass eigene Fähigkeiten kritischer beurteilt wurden. Dass dieser Mechanismus für Interventionsstudien relevant ist, wurde bereits mehrfach beschrieben [27, 42].

Hinsichtlich der sekundären Endpunkte fanden wir für die alltagsrelevanten kognitiven Fähigkeiten keine signifikanten Veränderungen. Die Spontansprache (CTP) zeigte jedoch in der IG einen verminderten Abfall zum Zeitpunkt der Verlaufsuntersuchung im Vergleich zur KG (Cohen's d: -0.6), was als Hinweis für den positiven Nutzen von Kommunikationstraining in CR zu

werten ist, wie schon anderweitig berichtet wurde [75, 78]. Aufgrund bisheriger Studien erwarteten wir für den kognitiven Status (CERAD-Batterie) keine Verbesserungen [22, 80, 94]. Studien, die Verbesserungen einzelner Domänen fanden, hatten die CR über einen längeren Zeitraum durchgeführt (5 Monate [17]) oder hatten die Angehörigen mit höherer Frequenz eingebunden [75]. In den nicht-kognitiven Domänen fanden wir einen signifikanten Interaktionseffekt für die Lebensqualität (DEMQOL) mit einem Anstieg in der IG und einer Abnahme in der KG. Andere Studien konnten dies ebenso zeigen [80, 94], die CORDIAL-Studie fand jedoch keinen signifikanten Effekt [62]. Dies scheint hinweisend auf einen Vorteil unserer Adaptation des Programms gegenüber dem ursprünglichen CORDIAL-Programm.

Desweiteren sollte der Einfluss antidementiver bzw. antidepressiver Medikation berücksichtigt werden. Dies gilt auch für die Interpretation der funktionellen Daten. Wir versuchten diesen Faktor zu minimieren, indem wir als Einschlusskriterium eine stabile Dosis über drei Monate voraussetzten und bei der Auswertung nur Differenzwerte und keine absoluten Werte nutzten, um so relative Änderungen untersuchen zu können. Limitationen dieser Studie sind die kleine Stichprobengröße und die Stichprobenheterogenität in Hinsicht auf Alter und Werte des MMST. Außerdem wurde die Zuordnung zu den Gruppen nur in Teilrandomisierung durchgeführt, da fünf Teilnehmer aus einer Warteliste des vorherigen Pilotprojektes stammten und für die IG vorbestimmt waren. Auch ist die kurze Interventionsdauer zu kritisieren, jedoch basierte unser Ansatz auf einem manualisierten Programm, was wiederum den Vorteil der besseren Vergleichbarkeit mit sich bringt.

Es bleibt auch weiterhin offen, welche Endpunkte zur Auswertung einer Intervention wie der CR eine hohe Aussagekraft haben. Aufgrund des individualisierten Ansatzes der CR empfiehlt sich für die Zukunft auch eine systematische qualitative Analyse, zum Beispiel mittels strukturierter Interviews. So konnten die Patienten in der CR-Studie von Clare et al. von einer subjektiv höheren Kompetenz beim Erreichen ihrer Ziele und von einer verbesserten Alltagskompetenz berichten [29]. Unsere qualitative Betrachtung der CR führte zu folgenden Erkenntnissen: 1) Trotz der Heterogenität der Gruppe hinsichtlich der Kognition, teilten die Gruppenteilnehmer ihre Erfahrungen miteinander und profitierten von den Ressourcen und Bewältigungsstrategien des jeweils anderen. Wir beobachteten einen aktiven Ideenaustausch. 2) Wir dehnten die Sitzung von 1 Stunde/Woche auf 2 Stunden/Woche, aber auch das schien noch zu kurz, um relevante Inhalte im Gruppensetting durchzuarbeiten. Es empfiehlt sich eine längere Dauer inklusive Pausen. 3) Die variable Reihenfolge der Module war vorteilhaft, da beispielsweise die Problemidentifikation zu vermehrter Krankheitseinsicht und zu darauffolgenden depressiven Symptomen oder Frustrationen führten. Daher zogen wir das Modul zur Biographiearbeit vor, um individuelle Ressourcen zu aktivieren. Eine qualitative Fallbeschreibung des CORDIAL-Versuchs durch Tonga et al. [88] bestätigte diesen Ansatz der flexiblen Modulsequenz. 4) Das von uns hinzugefügte Problemlösetraining ließ sich gut in die CR einfügen und wurde von den Patienten sehr positiv aufgenommen. Trotzdem schien der Trainingseffekt zu gering, sodass keine Übertragung in den Alltag beobachtet wurde. Wobei in der Theorie implizite Gedächtnisinhalte, wie zum Beispiel Tagesroutinen, im Verlauf der Demenz länger bestehen bleiben, als deklarative Erinnerungen [87]. Interessanterweise zeigte sich dafür in der

Auswertung der funktionellen Daten eine vermehrte Konnektivität zu Arealen des Cerebellums, was einen Zusammenhang zur Implementierung von alltagsrelevanten Routinen denkbar macht.

Zusammenfassung: Für das erste Untersuchungsziel der Studie 1 konnten wir eine Umsetzbarkeit der adaptierten CR zeigen, welche eine verbesserte Lebensqualität in der IG zur Folge hatte. Wir fanden keine Effekte für die ADL-Kompetenz, was wir auf einen mangelnden Transfer vom Therapiesetting in den Alltag zurückführen. Wir empfehlen daher für zukünftige Studien die Interventions- und Einzelsitzungsdauer zu erweitern und die Angehörigen enger einzubinden. Das Gruppensetting sollte beibehalten werden, da es Kommunikation und Bewältigungsprozesse fördert. Nichtsdestotrotz sind Studien mit größeren Stichproben nötig, um die Erkenntnisse verallgemeinern zu können. Dies gilt insbesondere auch für die nun folgenden Ausführungen zu den Daten der Ruhe-fMRT-Bildgebung.

1.9.1.2 Diskussion funktioneller Daten

Die Ruhe-fMRT wird intensiv erforscht, um Veränderungen in den neuronalen Netzwerken über verschiedene AD-Stadien hinweg zu verfolgen [6, 15, 35, 54]. In unserer Studie 1 untersuchten wir den Effekt einer CR auf die funktionelle Konnektivität bei Patienten mit milder AD. Einige Studien zeigten bereits geringe Effekte kognitiver Interventionen mit Hilfe funktioneller Bildgebung [24]. Von diesen Studien fanden einige einen signifikanten Effekt der Intervention auf neuropsychologische Parameter [7, 26, 89]. Die Vergleichbarkeit ist jedoch eingeschränkt, da die Studien in mehreren Dimensionen variierten. Nach meinem Wissensstand existiert bislang keine weitere Studie, die eine CR bei AD-Patienten mit Ruhe-fMRT untersucht.

Zur Baseline (BL) zeigte die gesamte Stichprobe ein für das DMN typische Verteilungsmuster der Konnektivität des PCC, wie es auch bisherige Studien für Stichproben dieser Art gefunden haben [38]. Der Interaktionseffekt über die Zeit offenbarte für die IG im Vergleich zur KG einen Anstieg der Konnektivität mit dem PCC in Regionen des Cerebellums. Es gibt mehr und mehr Hinweise, dass das Cerebellum für eine Vielzahl von Ruhe-Netzwerken inklusive des DMN von Bedeutung ist [53, 25] und die FC des Cerebellums ebenfalls eine Abnahme im AD-Verlauf aufweist [9, 52]. Weiterhin werden dem Cerebellum mittlerweile weitaus mehr als nur motorische Funktionen zugeordnet, wie zum Beispiel Aufmerksamkeits- und Sprachprozesse, Entscheidungsfindung oder Verarbeitung von Emotionen [90]. Vor allem ist das Cerebellum auch an impliziten prozeduralen Gedächtnisleistungen beteiligt [86]. Da unsere CR die Implementierung von Routinen zum Ziel hatte, wäre ein Effekt auf die FC zwischen PCC und Cerebellum denkbar. Auch die Interventionsstudie von Chirles et al. fand eine Zunahme der PCC-Cerebellum-Konnektivität nach zwölfwöchigem aeroben Fitnesstraining [26].

Für die KG beobachteten wir Zunahmen der FC über die Zeit im Vergleich zur IG in mehreren, weitverteilten Regionen, wobei auch die Cluster im Vergleich zum Kontrast IG > KG deutlich kleiner ausfielen. Trotzdem sollte ein Effekt der Kontrollbedingung auf die FC der KG berücksichtigt werden.

Unabhängig von der Gruppenzugehörigkeit fanden wir für die gesamte Stichprobe von BL zur VU eine FC-Zunahme im bilateralen Präcuneus und parazentral. Dies könnte als unspezifischer Trainingseffekt der Interventionen interpretiert werden. Auf der einen Seite würden wir eine Zunahme der PCC-Konnektivität erwarten, da die PCC-Präcuneus-Region einen zentralen Knotenpunkt innerhalb des DMN darstellt [104] und unter anderem einen wichtigen Beitrag zur Kontrolle der Aufmerksamkeit leistet [65]. Auf der anderen Seite widersprechen unsere Ergebnisse der Hypothese zur frühen Desintegration dieser Region in der Diskonnektierungskaskade des DMN von MCI zu AD [58, 35], bei der wir eine FC-Abnahme über die Zeit erwartet hätten. Die hohe Konnektivität der PCC-Präcuneus-Region könnte eine Mobilisierung kognitiver Ressourcen ermöglichen. Solche Kompensationsprozesse werden bereits als Teil der Netzwerkdegeneration diskutiert, da schon mehrere longitudinale Studien eine (zum Teil temporale [35]) Zunahme der Konnektivität des PCC/Präcuneus mit anderen Regionen, wie zum Beispiel frontalen Arealen, beschrieben [96].
Wir fanden auch eine Abnahme der FC für die gesamte Stichprobe über die Zeit insbesondere in temporalen Regionen. Im Allgemeinen stimmt dieses Ergebnis mit der bislang bekannten Progression neuronaler Degeneration bei AD überein, wobei der Temporallappen bereits in frühen Stadien betroffen ist [50, 40].

Der einzige signifikante Effekt der Reha war die Verbesserung der Lebensqualität, weswegen wir diesen Parameter mit den funktionellen Daten der IG und KG korrelierten. Wir fanden eine positive Korrelation zwischen dem Differenzwert der Lebensqualität und einer Zunahme der FC im Präcuneus und dem mittleren temporalen Lobus, allerdings nur in der IG. Dies war ein Post-hoc-Vergleich, daher bedarf es Vorsicht bei der Interpretation. Wie bereits beschrieben kam es zwischen BL und VU zu einer FC-Abnahme im Temporallappen in der gesamten Stichprobe. Nun ist jedoch eine verbesserte Lebensqualität, welche nur für die IG besteht, mit einer höheren Konnektivität zwischen PCC und Temporallappen verbunden, weswegen wir vermuten, dass die CR kompensatorische Prozesse im Temporallappen anstoßen könnte.

Da es sich hier um eine Stichprobe mit AD-Patienten handelt, sollte berücksichtigt werden, dass man einen Effekt der Kopfbewegung während der MRT-Untersuchung nicht ausschließen kann. Wir führten eine Kopfbewegungskorrektur durch, wobei kein Patient eine Bewegung von 1,5 mm überschritt. Zur BL fanden eine Bewegung von 1,0 mm und eine weitere von 0,5 mm in der KG statt. Daher erwarten wir nur wenig Störungen unserer Daten. Die Hauptlimitation stellt die niedrige Stichprobengröße dar, sodass die Replikation der Ergebnisse in größeren Studien erfolgen sollte.

Zusammenfassung: Unsere funktionellen Daten der Studie 1 zeigen einige Effekte der CR auf die funktionelle Konnektivität des DMN, deren weitere Erforschung lohnend ist. Es sollte beispielsweise die Rolle des PCC/Präcuneus in kompensatorischen Prozessen oder die Funktion des Cerebellums im DMN besser untersucht und verstanden werden. So können nach und nach die Regionen identifiziert werden, welche aufgrund ihrer Vulnerabilität oder aber ihrer Fähigkeit zur Kompensation gezielt durch kognitive Interventionen beeinflusst werden können.

Möglicherweise können somit effektiver kognitive Ressourcen mobilisiert und weitere Netzwerkdegeneration gehemmt werden.

1.9.2 Studie 2: Simultanes fMRT-EEG

Die Studie 2 wandte erstmals erfolgreich die Technik der simultanen fMRT-EEG bei einer Stichprobe mit AD-Patienten an und konnte eine verminderte positive Assoziation zwischen den Signalen des Alpha-Bandes und den BOLD-Signalen in der AD-Gruppe im Vergleich zur GK zeigen. In der GK konnte ebenjene positive Assoziation in vielen verschiedenen Regionen nachgewiesen werden, inklusive Regionen des DMN. Die Reduzierung der positiven Assoziationen in der AD-Gruppe kann von verminderten funktionellen Interaktionen der Regionen herrühren [50]. Die funktionellen Assoziationen wurden nicht durch Korrekturen des Hippocampusvolumens verändert, sodass Atrophieprozesse scheinbar eine untergeordnete Rolle spielen.
Basierend auf bisherigen simultanen fMRT-EEG-Studien mit gesunden Probanden, vermuteten wir für die GK eine positive Assoziation zwischen der Alpha-Power und den BOLD-Signalen im Thalamus [48, 70]. Angesichts der gestörten Integrität thalamo-kortikaler Bahnen im AD-Verlauf erwarteten wir eine Abschwächung dieser Assoziationen in der AD-Gruppe [14, 105]. Unsere Ergebnisse bestätigen diese Hypothesen. Interessanterweise zeigten sich auch Assoziationen mit dem Cerebellum bei fast allen Probanden. Das Cerebellum hat in der fMRT-EEG-Foschung bislang wenig Aufmerksamkeit erhalten [79]. Wir konnten nun in beiden Studien zeigen, dass das Cerebellum in der funktionellen Konnektivität des DMN von Bedeutung ist.

Eine allgemeine Limitation von fMRT-Studien im Ruhezustand ist die hohe Variabilität über die Zeit [33]. Die Instruktion, die Augen geschlossen zu halten, aber wach zu bleiben, lässt Raum für spontane kognitive Prozesse mit variierendem Status der Aufmerksamkeit. Uns fiel eine hohe regionale Variabilität der Assoziationen zwischen den Alpha-Band-Signalen und den BOLD-Signalen zwischen den einzelnen Individuen auf, was auch in anderen Studien beschrieben wurde [48, 64]. Die Forscher argumentierten, dass diese Variabilität teilweise eine Folge wechselnder Vigilanz sein könnte. Diese Theorie findet sich insofern in unseren Daten bestätigt, als dass wir eine Zunahme der Artefakte zum Ende der Aufnahmezeit beobachteten, was für einen Ermüdungsprozess sprechen könnte. Möglicherweise wäre die Aktivierung des DMN in einem aufgabenbezogenen fMRT-Paradigma robuster gewesen, bei dem beispielsweise Aufgaben zum selbstbezogenen Denken oder autobiographischen Gedächtnis gestellt würden. Andererseits spricht die vereinfachte Anwendung in der klinischen Praxis für die Ruhe-fMRT-Methode, da gerade AD-Probanden geringere kognitive Kapazitäten aufweisen [24]. In zukünftigen Bildgebungs-Studien sollte die Vigilanz bei AD-Patienten vermehrt berücksichtigt werden.
Eine weitere Limitation ist der relativ liberale statistische Grenzwert, da dies allerdings die erste Studie mit simultanem fMRT-EEG bei AD-Patienten ist, wollten wir die Assoziationen im grö-

ßeren Umfang über das gesamte Gehirn darstellen. Um die inter- und intraindividuelle Variabilität zu reduzieren, sollten in größeren Stichproben Untergruppen definiert werden, sodass sich eine verminderte Heterogenität positiv auf die statistische Signifikanz auswirkt.

Zusammenfassung: Dieses Pilotprojekt konnte eine Umsetzbarkeit simultaner fMRT-EEG bei AD-Patienten zeigen und für diese Gruppe im Vergleich zur GK eine verminderte Assoziation zwischen der Alpha-Band-Power und den BOLD-Signalen unter anderem in Regionen des DMN und Thalamus nachweisen.

1.9.3 Diskussion der funktionellen Konnektivität als Marker für kognitive Interventionen und Ausblick

Kognitive Interventionen stellen eine wichtige Therapiemöglichkeit dar, um Patienten mit AD und ihre Angehörigen in ihrem Alltag zu unterstützen. Verschiedenste Konzepte wurden bereits getestet, doch bislang fehlen sensitive Surrogatmarker zum Nachweis der Effektivität. Es gibt diverse methodische Gründe, warum es in vielen Interventionsstudien an signifikanten Effekten mangelt [24, 60]. Ein wesentliches Problem sind die kleinen Stichproben vieler Untersuchungen. Ein statistisch relevanter Stichprobenumfang ist jedoch Voraussetzung, um signifikante Ergebnisse in vielen neuropsychologischen Parametern zu erreichen, wie es auch die Analyse unserer Daten aus der CR-Studie zeigte. Surrogatmarker mit höherer Power und Sensitivität würden eine Reduzierung des Stichprobenumfangs erlauben. Es hat den Anschein, als könnten bildgebende Verfahren wie fMRT in dieser Hinsicht zukünftig einen wesentlichen Beitrag leisten [55, 91]. Die Analyse der FC in Korrelation mit neuropsychologischen Markern könnte helfen, die Veränderungen kognitiver Prozesse zu verstehen, wie es in unserer Arbeit mit dem Endpunkt zur Lebensqualität erfolgte. Andere Interventionsstudien konnten ebenfalls eine Korrelation der FC im DMN mit Veränderungen klinischer Parameter nachweisen [12, 24].
Nachdem wir in beiden Studien als relevante Region überraschend das Cerebellum fanden, sollte in zukünftigen Interventionsstudien dessen Rolle im DMN vermehrt Berücksichtigung finden, insbesondere dessen Funktion in prozeduralen Gedächtnisleistungen. Außerdem wäre es bedeutsam, neben dem DMN weitere Netzwerke zu untersuchen. Das DMN ist zwar früh im AD-Progress betroffen, doch gerade deshalb sollten andere, resilientere Netzwerke untersucht werden, um neuronale Regionen mit Kompensationskapazitäten zu identifizieren [25, 32]. Um die Aussagekraft der fMRT zu erhöhen, bietet die Kombination mit der EEG die Möglichkeit, Nachteile der MRT-Technik auszugleichen und auf anderer Ebene einen Informationsgewinn zu erreichen [37].

Zusammenfassung: Mittelfristig könnte die Analyse der FC die Interpretation der Effekte kognitiver Interventionen erleichtern und eine wichtige Rolle in der Identifikation neuronaler Kompensationsmechanismen einnehmen. Das langfristige Ziel kognitiver Interventionen sollte sein, AD-Patienten nicht nur in ihrem Alltag zu unterstützen, sondern durch die Mobilisierung kognitiver Reserven den Degenerationsprozess auf neuronaler Ebene zu verlangsamen.

Publikationen

Die folgenden Publikationen sind Bestandteil dieser Dissertation und im Anhang abgedruckt.

Studie 1: Kognitive Rehabilitation

Kasper E, Ochmann S, Hoffmann W, Schneider W., Cavedo E., Hampel H., Teipel S. (2015) *Cognitive Rehabilitation in Alzheimer's Disease – A Conceptual and Methodological Review*. Journal of Prevention of Alzheimer's Disease 2:142–152

Brüggen K, Kasper E, Ochmann S, Pfaff H, Webel S, Schneider W, Teipel S (2017) Cogntive *Rehabilitation in Alzheimer's Disease. A Controlled Intervention Trial*. Journal of Alzheimer's disease: JAD 57(4):1315–1324 (IF: 3;7)

Ochmann S, Dyrba M, Grothe MJ, Kasper E, Webel S, Hauenstein K, Teipel S (2017) Does *Functional Connectivity Provide a Marker for Cognitive Rehabilitation Effects in Alzheimer's Disease? An Interventional Study. Journal of Alzheimer's disease*: JAD 57(4):1303–1313 (IF: 3,7)

Studie 2: Simultanes fMRT-EEG

Brüggen K, Fiala C, Berger C, Ochmann S, Babiloni C, Teipel S (2017) *Early Changes in Alpha Band Power and DMN BOLD Activity in Alzheimer's Disease. A Simultaneous Resting State EEG-fMRI Study*. Frontiers in aging neuroscience 9:319 (IF: 4,5)

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Anhang

Publikationen

Studie 1: Kognitive Rehabilitation

Kasper E, Ochmann S, Hoffmann W, Schneider W., Cavedo E., Hampel H., Teipel S. (2015) *Cognitive Rehabilitation in Alzheimer's Disease – A Conceptual and Methodological Review*. Journal of Prevention of Alzheimer's Disease 2:142–152

Brüggen K, Kasper E, Ochmann S, Pfaff H, Webel S, Schneider W, Teipel S (2017) Cogntive *Rehabilitation in Alzheimer's Disease. A Controlled Intervention Trial*. Journal of Alzheimer's disease: JAD 57(4):1315–1324 (IF: 3;7)

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Studie 2: Simultanes fMRT-EEG

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Cognitive Rehabilitation in Alzheimer's Disease – A Conceptual and Methodological Review

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Abstract

Within the last 20 years, several standardized cognitive trainings have been developed aiming at the delay of cognitive decline in older people who are at risk of Alzheimer's Disease (AD) or in mild stages of dementia. The transfer of cognitive training effects into activities of daily living was very limited in most previous studies. Therefore, multimodal Cognitive Rehabilitation approaches have been designed that aim to improve the activities of daily living. These approaches also attempt to integrate the patient's psychopathological and behavioral status as well as social relationships into the treatment plan. Contrary to other approaches, CR mainly focuses on compensation rather than restoration of impaired functionality.

In this review, we define CR conceptually, and derive specific criteria to evaluate current CR approaches for individuals with mild cognitive impairment (MCI) and AD dementia. In addition, we perform a critical, methodical analysis of available CR studies, reviewing their short- and long-term treatment effects.

Findings suggest that CR approaches improve memory performance and competence of activity of daily living (ADL) in mildly cognitively impaired subjects (MCI), when compensatory, integrative, as well as interactive elements and domain specificity are taken into account. Interactive and individual aspects also appear to be relevant to sustain long-term effects. In AD dementia, similar results emerged, although with smaller effect sizes. The efficacy of individualized CR approaches was comparable with theory-based, manual-guided concepts as long as promoting interaction was part of the treatment.

So far, only few randomized controlled studies of sufficient sample size are available. Future systematic efficacy studies need to consider precisely defined outcome variables. This is necessary before one can draw conclusions of how CR can be used for secondary prevention of AD dementia as well as AD treatment.

Key words: Cognitive rehabilitation, cognitive training, dementia, mild cognitive impairment, Alzheimer's disease.

Background

Cognitive interventions such as Cognitive Stimulation (CS), Cognitive Training (CT) or Cognitive Rehabilitation (CR) play an important role as part of multimodal interventions for individuals with mild cognitive impairment (MCI) or mild dementia (MD) in Alzheimer's disease (AD) (1). This is demonstrated by empirical findings showing that approaches, aimed at promoting cognitive capacities in AD patients, can enhance the patient's cognitive reserve (2). In recent years, researchers have developed and applied various approaches of cognitive interventions for individuals with MCI or dementia in AD.

Cognitive Stimulation (CS) attempts to improve cognitive and social functioning using general mental activation (3). Such methods include all forms of mental stimulation (e.g., conversation, games, and quizzes) and are usually carried out in a group setting. These are often complemented by reality orientation therapy or biographical work (4, 5). Thus, CS comprises rather unspecific mental stimulation.

In contrast, Cognitive Training (CT) aims to maintain or improve specific cognitive functions, e.g., attention, episodic memory, and problem solving skills (6), with the help of guided execution and repetition of standardized tasks. The underlying idea is that the effects, obtained by training specific cognitive functions in a controlled environment, i.e., the task setting, can be transferred automatically to patient's everyday life activities, i.e., the real world setting (6).

Furthermore, CT often involves specific learning strategies such as "Errorless learning" (7) and the "Spaced Retrieval" (8) approaches. Such strategies are based on the assumption that implicit or non-declarative memory is better preserved than declarative memory in AD (9).

The concept of Cognitive Rehabilitation (CR) combines different behavioral and cognitive therapy approaches, aiming to maintain or improve everyday skills. In contrast to CS and unspecific activation, CR

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trains individual skills. In contrast, however, to CT, which focuses on specific cognitive functions, CR aims at specific everyday skills. The key difference between CR and CT is that CR aims to improve skills that are directly relevant to daily living rather than to a single cognitive function. Another difference between CT and CR is the use of compensatory strategies, which range from an adaption of the environment to the use of external memory aids in CR, whereas CT uses mainly restitute exercises.

In the following sections, first we provide a short summary of efficacy studies on CT, followed by an overview on CR in individuals with MCI and mild AD dementia. To this end, we derive a conceptual framework to interpret the findings from CR studies. This may lead to guidance for future concept development and the design of empirical studies.

Please note that studies on CS will not be considered in this review as firstly, comprehensive reviews are already available (3) and secondly, we focus on the description of CR in comparison to CT.

Efficacy of standardized Cognitive Training in MCI subjects and dementia patients

Descriptive as well as systematic reviews on CT in subjects with MCI suggest positive short-term effects on general cognitive functioning and single cognitive abilities. Findings are particularly positive regarding prospective memory performance, as measured by objective neuropsychological tests (10-12). Contrary to these results, the few studies that have investigated long-term effects (10, 12), or implications for activities of daily life (13, 14), are rather inconsistent, suggesting that the positive effects obtained from CT are not stable over time (15) and cannot achieve an improvement of cognitive abilities for everyday life demands.

Bahar-Fuchs et al. (6) conducted a meta-analysis of post-interventional effects of CT in dementia. This was based on 10 randomized controlled studies, including patients with mild to moderate AD dementia, or vascular dementia. All interventions focused on the enhancement of cognitive functions, either directly or in combination with secondary objectives, e.g., reduction of depression or anxiety. Only a subset of studies allowed the comparison of treatment and control conditions. Compared to a control condition, 6 studies, using restorative and/or compensatory elements showed no significant improvements in global cognitive function at the end of the CT intervention. Moreover, in a further subset of 4 studies, subjective quality of life and activities of daily living (ADL) skills showed no significant improvements. The authors emphasized that the interpretation of the results was hampered by the lack of comparable outcome variables across the studies.

A further meta-analysis of 4 controlled CT trials by Alves and colleagues (2013) (16) revealed only an improvement in global cognition measured by the Mini Mental State Examination, with no improvement in any other specific cognitive domain, e.g., memory. In summary, in dementia patients, standardized cognitive training lacks sufficient evidence of efficacy, in particular regarding the stability of therapeutic effects over time (15).

Cognitive Rehabilitation in MCI subjects and patients with mild AD dementia

Conceptual aspects

The main aim of rehabilitation is the support of persons to achieve or to maintain an optimal level of physical, psychological, and social functioning in the presence of specific risks and impairments which arise from an illness or an injury (17).

CR is an individualized approach which supports people by identifying personally relevant goals and defining individual strategies to achieve these goals despite their cognitive impairments (18). The main objective is the preservation of the patient's ability to participate in meaningful everyday life activities.

CR integrates different therapeutic approaches and can be realized in inpatient, outpatient, or day care settings. Treatment elements include, for example, CS, CT, and teaching of compensation strategies. In CR, the compensation of impairments is more important than restoration. Huckans and colleagues (15) compared these distinct concepts in a meta-analysis on 14 controlled trials in AD. Cognitive interventions that focus on the enhancement or restoration of cognitive abilities, use highly structured and repeated practice of specific cognitive tasks. In contrast, cognitive interventions that focus on compensation, include the development of individual strategies to reduce the impact of cognitive impairments on the patient's life. Huckan's analysis showed that compensatory methods seem to be associated with higher long-term effects on memory performance compared to restorative approaches.

CR, however, is not limited to cognitive functions, but also considers current behavior and social disabilities, as well as the interaction between function and environment (19). For example, Schecker et al. 2013 (20) compared a standardized CT and a systemic-oriented client-centered intervention in 42 patients with mild AD dementia. The CT focused on working memory, and the client-centered intervention used communication training relevant to patient's daily routine. Interestingly, the client-centered intervention correlated with an improvement of linguistic skills, while the standardized CT did not improve working memory. These results indicate that cognitive tasks that are relevant to a patient's life on a day to day basis may facilitate the improvement of abilities in patient's home.

Table 1. Cognitive Training versus Cognitive Rehabilitation (based on Bahar-Fuchs, 2013 (6))

	Cognitive Training	Cognitive Rehabilitation
Aim	Improvement or maintenance of specific cognitive functions	Improvement or maintenance of functioning within everyday context
Focus on	Impairment	Resources as basis of compensation
Assumption	Improvement of specific cognitive functions supports an improvement of everyday abilities ↓ Indirect ADL-transfer	Improvement of cognitive state needs an individual setting ↓ Direct ADL-transfer
Preconditions of patients	Sufficient cognitive resources for therapy	none
Methods	• restorative • standardised • quasi-experimental setting	• compensatory and restorative individual, multi-professional • "real-world" setting
Contents	•Practice of specific cognitive functions (memory, concentration, attention, problem solving, etc.)	• Identification of individual goals • Practice of strategies • Psychoeducation • Participation of caregivers

Table 1 presents characteristics and aims that distinguish between CR and CT. Based on this comparison we derive the following criteria and objectives:

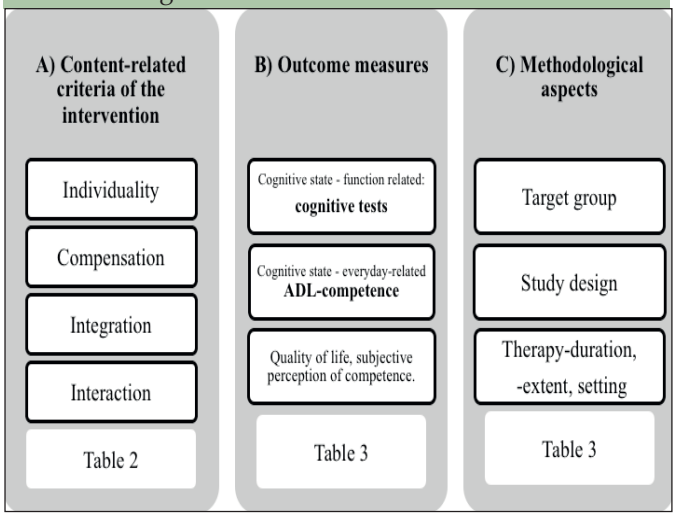
- Individuality: Goals that are relevant for the patients and their everyday life are identified and pursued.
- Compensation: Maintaining skills and compensating impairments is more important than recovery or improvement of single cognitive skills.
- Integration: Multimodal methods are combined in an interdisciplinary multi-professional team, e.g., integration of psychotherapy, ergo-therapy, psychoeducation, biographical work, metacognitive training etc..
- Interaction: The individual's environment has to be adapted to the level of their cognitive impairments. This requires direct interaction with the caregiver and everyday practical exercises to achieve a sustainable transfer from rehabilitation to daily life.

Cognitive Rehabilitation - Contents and efficacy

Unfortunately, many studies do not clearly separate between concepts of CR and CT. For example, many interventions that are labelled as CT, include compensatory approaches such as the implementation of external memory aids, and thus represent CR.

For the present review, rather than relying on author's use of CT or CR to characterize the treatment approach, we selected studies that consider at least two of the features: individuality, compensation, integration, and interaction. In addition to this content-related dimension (dimension A) we considered two further dimensions: (B) the outcomes stratified according to cognitive test results, everyday skills, and subjective perception, and (C) the methodological aspects (see Figure 1).

Figure 1. Dimensions of evaluation for effectiveness of studies on Cognitive Rehabilitation



The number of fulfilled criteria (A) and their operationalization in different CR studies are illustrated in Table 2, for MCI and mild AD separately. The corresponding outcomes (B) and methods (C) are shown in Table 3.

Interventions of Cognitive Rehabilitation with the use of various active components – fulfilling two or three dimension A criteria

Most studies of CT integrate single therapeutic components and therefore fulfil two or three of the outlined criteria (table 2).

Focusing on MCI, Troyer et al. 2008 (18) used compensatory, i.e., external memory aids, and integrative, i.e., psychoeducation: imparting metacognitive knowledge, elements (table 2). They found an increase of the knowledge of external

Table 2. Dimension A: Criteria for interventions of Cognitive Rehabilitation

Number of criteria fulfilled	Criterion / Study	Individuality	Compensation	Integration	Interaction
Mild cognitive Impairment (MCI)					
2	Troyer et al. 2008 (18)		• external memory aids	• psychoeducation: life style	
	Buschert et al. 2011 (22) STACOG	• stage-specific in regard to MCI		• psychoeducation: metacognitive knowledge	
3	Kinsalla et al. 2009 (17)		• external memory aids	• psychoeducation: life style	• training of everyday skills (organization)
	Kurz et al. 2009 (21)		• external memory aids	• psychomotoric • psychotherapy: stress management, relaxation techniques • psychoeducation: life style	• planning of activities, practical problem solving • caregiver-group
4	Moro et al. 2014 (30)	• problem identification	• external memory aids	• psychoeducation: metacognitive knowledge	• participation of caregivers • problem solving strategies for activities of daily living
Mild Dementia					
2	Bottino et al. 2005 (24)		• external memory aids		• training of everyday skills
	Viola et al. 2011 (25)			• art therapy, physiotherapy • participation of caregivers	• participation of caregivers • training of everyday skills • social activities
3	Quayhagen et al. 2000 (26)	• problem identification		• psychotherapy: problem identification, stress management	• participation of caregivers • training of conversation
	Buschert et al. 2011 (22) STACOG	• stage specific in regard to mild dementia		• establishing of pleasant activities	• establishing of activities • social behavior
	Romero 2001 (29) SET	• individual compilation of single therapeutic components		• art therapy, ,music therapy, movement therapy • psychoeducation: metacognitive knowledge • biography work	• participation of caregivers • social activities
4	Clare et al. 2010 (33) GREAT	• analysis of individual goals	• external memory aids • mediation of strategies for the improvement of attention and concentration • mediation of strategies for the improvement of attention and concentration	• psychotherapy: overcoming fears and stress management	• establishing of activities • participation of caregivers
	Werheid et al. 2010 (32) CORDIAL	• analysis of individual goals	external memory aids	• psychotherapy: coping strategies and establishing of pleasant activities • biography work	• use of a diary • establishing of activities • participation of caregivers

memory aids, which applies for the objectively measured as well as for the self-perceived knowledge. This learning, however, did not transfer to everyday performance as measured by standardized ADL scales. They found no significant improvement of single cognitive parameters, such as prospective memory performance, neither immediately after the intervention nor after the follow-up of three months.

Similar to Troyer et al. 2008 (18), two studies involving MCI subjects (Kurz et al. 2009 (21) and Kinsella et al. 2009 (17)) used strategies of compensation, i.e., external memory aids and integration, i.e., psychoeducation and/or psychotherapeutic elements like stress management (21). Additionally, both groups considered the criterion of interaction, i.e., planning of everyday activities, practical problem solving training, and the participation of caregivers. Despite using different treatment designs, both studies found an improvement of prospective memory performance, and everyday competence (21) or metacognitive knowledge about memory strategies (17). In Kinsella's study, these effects remained consistent at four months post-intervention (Kurz et al. did no follow-up investigation). Interestingly, both studies found no increase of subjectively perceived competence. However, Kurz et al. additionally observed a decrease of depression immediately after the intervention.

In contrast to the aforementioned studies, Buschert et al. 2011 and 2012 (22, 23) explicitly focused on the criterion of individuality by implementing a stage-specific concept. For this they used specific CT strategies adapted to MCI subjects and patients with mild dementia respectively. This intervention which also comprised elements of integration, i.e., imparting metacognitive knowledge, resulted in an improvement of general cognitive performance (MMSE) and a reduction of depression-related symptoms in MCI. In addition, considering an early and a delayed onset of the intervention (6 months delay), authors found long-term effects of improvement only in the group of patients that started the intervention at the early time (23).

Focusing on patients with dementia, Bottino et al. 2005 (24) and Viola et al. 2011 (25) took two of the outlined criteria into account and both employed interactive elements, i.e., training of everyday skills (table 2). But, Bottino et al. taught external memory aids as compensatory element, whereas Viola et al. offered art therapy, physiotherapy, and psychoeducation as integrative elements. Both studies, performed as a day patient setting, found a decrease of fear and depression in caregivers. Regarding the patients, Viola et al. 2011 (25) showed only an improvement of quality of life. Bottino et al. 2005 (24) also reported few improved cognitive test scores , but no improvement of the ADL competence.

Similar to Buschert et al. (22), Quayhagen et al. 2000 (26) considered individuality with emphasis on problem identification (26) and implementation of a stage-specific concept. However, Quayhagen et al. (26) also combined integration, i.e., psychotherapy, and interaction, i.e., caregiver's participation and conversation training in different therapeutic settings: problem solving training, individual meeting, and dual supportive seminars with the caregiver. The authors reported a significant decrease in depressive symptoms of caregivers (26). In all of the different settings, patients with dementia improved in cognitive performance, and showed enhanced compensation strategies.

In contrast to these aforementioned studies, Schiffczyk et al. 2013 (27) evaluated a manual-guided intervention "Self-maintenance therapy (SMT)", fulfilling three of the four outlined criteria. SMT is a (neuro-) psychological rehabilitation program for individuals with AD dementia that is based on a systemic view of one's "self". The "self" is viewed as a dynamic system; it provides the basis for identity and the continuity of a person. Experiences with deficits in the course of dementia have a profoundly destabilizing impact on this self-system. Therefore, according to SMT, preserving one's self in its coherence is the most important objective of rehabilitation (28, 29). To achieve the stabilization of the self-system, different therapeutic strategies are selected for each patient individually. SMT integrates psychotherapy, art-, music-, physio- and relaxation therapy, social activities, and biographical work. SMT requires close interaction with the caregivers and develops individualized recommendations for further meaningful activities that the patient can perform at home.

In an efficacy study on SMT (27) with patients with mild to moderate dementia, only male patients showed a significant improvement of the cognitive status, both immediately after the intervention and at a three-month follow-up. Female patients just showed a decrease in depression. Considering both sexes, ADL skills did not improve. However, the low Mini Mental State Examination scores of these patients (mean = 18.5, SD = 6.5) indicate a relatively high proportion of patients who are in a moderate clinical stage of dementia already. This may have reduced the effect size and comparability to other studies.

Interventions of Cognitive Rehabilitation with the use of all active components - fulfilling all dimension A criteria

Geared towards MCI, a recent study by Moro et al 2014 (30) considered all outlined criteria. The authors realized individual aspects by personal problem identification; integration included both CT and psychoeducation, i.e., metacognitive knowledge; compensatory strategies included the use of external memory aids. Finally, interaction was achieved, involving caregivers into each session and including problem solving training for activities of daily living. The authors used a design with different start points, yielding a 6 months

Table 3. Dimensions B: Outcome measures and C: methodological aspects of studies of Cognitive Rehabilitation in MCI and mild dementia in AD

Number of fulfilled criteria	Study	Study design		Sample			Outcome-Variables	Results	
		Intervention duration/ extent / setting	Control condition	N (IG/CG)	Mean of age (IG/CG)	MMSE (IG/CG)		Post-Intervention	Follow-up
Mild Cognitive Impairment (MCI)									
2	Troyer et al. 2008 (18)	13 Weeks / 8 x/ day patient - group	• waitlist without intervention	24/24	76/75	27.2/ 28.5	Primary • knowledge of memory strategies and use of external memory aids • quality of life Secondary • prospective memory	• improved knowledge about strategies and their use • no improvement of cognitive scores	after 3 months • improved knowledge about strategies and their use • no improvement of cognitive scores
	Buschert et al. 2011 und 2012 (22, 23) State specific cognitive training (STACOG)	• months 1-6: STACOG, 20 x a 120 min./ day patient - group • month 7-12: without intervention	• month 1-6: cognitive stimulation in domesticity, 1x a month • month 7-12: STACOG	12/12	72/71	27.7/27.2	Primary • prospective memory Secondary • depressiveness • quality of Life	• improved cognitive state • reduction of depressiveness	after 12 months • improved cognitive state only in the case of early intervention
3	Kurz et al. 2009 (21)	4 Weeks / 6 h a day/ out patient	• waitlist without intervention	18/12	70/71	27.8/ 28	Primary • prospective memory Secondary • everyday competence: • depressiveness	• improvement of prospective memory • improved everyday competence • reduction of depressiveness	
	Kinsella et al. 2009 (17)	5 Weeks / 5 x a 90 min. /	• waitlist without intervention	22/22	79/75	25.9/ 26.8	Primary • prospective memory Secondary • perception of memory skills in everyday life • knowledge of memory strategies and use of external memory aids • quality of life	• improvement of prospective memory in relation to everyday life • improved knowledge about strategies and their use • no increase of subjective percept competence	after four months • improvement of prospective memory in relation to everyday life • improved knowledge about strategies and their use • no increase of subjective percept competence
4	Moro et al. 2014 (30)	2 + 4 months / 2 x a week + 1 x a week/ day patient - group	• waitlist without intervention for the first 6 months	15/15	76/74	MOCA: 25.3/23.5	• executive functions • language skills • prospective memory	for patients with early start of intervention: • improvement of prospective memory in relation to everyday life • improvement of executive functions	for patients with early start of intervention: • improvement of prospective memory in relation to everyday life • improvement of executive functions
Mild Dementia									
2	Bottino et al. 2005 (24)	5 months / 1x a week a 90 min. / day patient - group	• 1 consultation a month	6/7	75/73	23.5/21.9	Primary • prospective memory • executive functions • language skills Secondary: • caregivers: Depressiveness • everyday competence	• improvement of single cognitive scores • slightly increase of fear and depressiveness in caregivers	
	Viola et al. 2011 (25)	12 Weeks / 2x a week a 6 h / inpatient group	• waitlist without intervention	25/16	75/75	22.6/23.3	Patient: • cognitive state • behavior • depressiveness • depressiveness Caregiver: • depressiveness • Quality of Life	• no improvement if cognitive state • improvement of quality of life • reduction of depressiveness in patients and caregivers	

Table 3. (continued)

Number of fulfilled criteria	Study	Study design		Sample			Outcome-Variables	Results	
		Intervention duration/ extent / setting	Control condition	N (IG/CG)	Mean of age (IG/CG)	MMSE (IG/CG)		Post-Intervention	Follow-up
3	Buschert et al. 2011 (22) STACOG	6 months/ 20 x a 120 min./ day patient - group	• cognitive stimulation (domesticity, one group meeting a month)	8/7	77/74	24.5/25.3	Primary • prospective memory Secondary • depressiveness • quality of life	• reduction of depressiveness	
	Quayhagen 2000 (26)	1. training in memory and problem solving with caregiver in the next view (N=52) 2. individual meeting (N = 29) 3. dual supportive seminars (N = 22)	• cognitive stimulation + caregiver meeting 1x a month (N=16)	103/ 15			Primary: • cognitive state • prospective memory • verbal fluency • problem solving Secondary: • behavior • quality of life • caregiver: Quality of Life	• improvement of cognitive scores • reduction of depressiveness in caregivers • reduction of aggressive behavior and insufficient coping strategies in the group of dual support seminars	
	Schiffczyk et al. 2013 (27) SMT	3-4 weeks/ 20 h a week/ inpatient group	• no intervention	87/101	73/73	18.5/16	• prospective memory • verbal fluency • behavior • depressiveness • everyday competence • quality of life	• improvement of cognitive state in male patients • reduction of depressiveness in female patients	after 3 months • no improvement of cognitive state in male patients • reduction of depressiveness in female patients • decrease of subjectively experienced stressors in male
4	Clare 2010/ 2013 (33) GREAT	8 weeks/ 1x a week	• without cognitive intervention relaxation therapy	23/22/24			Primary: • analysis of goals Secondary (patient): • quality of life • perception of self-efficacy • depressiveness • prospective memory • executive functions Secondary (caregiver): • subjectively experienced stressors • quality of life	• improvement of expectation of self-efficacy and of satisfaction	• ongoing multicenter study
	Kurz et al. 2012 (31) CORDIAL	12 weeks/ 12 x a 60 min/ day patient	• no intervention	100/101	72/75	25.0/25.1	Primary • everyday competence Secondary - patient • prospective memory • executive functions • general cognitive state • quality of life • depressiveness • behavior Secondary- Caregiver • depressiveness • subjectively experienced stressors	• no effects on everyday competence or cognitive state • reduction of depressiveness in female patients	

IG = Intervention group; CG = control group; N = Number of subjects; MMSE = Mini Mental State Examination; MOCA= Montreal cognitive assessment

intervention. Following the intervention, executive functions, memory and general cognition of patients, as examined by standardized neuropsychological tests, improved over the treatment period. The improvements remained preserved over 6 months follow-up post intervention's end. Similar to Buschert et al. 2012 (23), these improvements were significant for patients who participated in the early start version only. The authors postulated that an intervention is more successful, if it starts at an early stage of cognitive decline. However, the study did not record the effect of the program on activities of daily living.

For patients with mild dementia, a study fulfilling all four criteria was published by Kurz et al. 2012 (32) using a manual-guided concept: "Cognitive Rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease (CORDIAL)" as presented by Werheid and Thöne-Otto in 2010 (32). This approach aims at maintaining quality of life and independence in everyday life by integrating neuropsychological and psychotherapeutic elements. At the beginning, the therapist and the patient identify individual problems and define treatment goals (individuality). Compensation is realized through external memory aids such as a calendar. Integration is established with the help of psychotherapeutic interventions like development of coping strategies and promotion of meaningful and pleasant activities, and additionally biographical work and communication training. This aims at a supportive interaction between patient and caregiver. Effective interaction firstly relies on a training of daily routines. Based on the assumption that procedural learning is relatively preserved in early stages of dementia it serves as a resource to develop such routines. Secondly, the caregiver has to be integrated as «therapeutic» partner, supervising the use of external memory aids and supporting adaptive communication strategies. Consequently, psycho-education of the caregivers is part of the treatment program.

The study of Kurz et al 2012 (31) investigated the effect of CORDIAL in a multicenter sample of 100 patients with mild AD. They found no significant effects on the primary outcome of ADL skills. The authors attributed this to the short duration of the intervention (12 weeks). In addition, they speculated that the extent of individualization and adaptation to the context of everyday life was not high enough. Alternatively, this null finding might have resulted from the need to follow a strict manual within the study setting, illustrating the conflict between possibly higher efficacy of individualized treatment strategies and the wish to keep intervention strategies comparable across studies. Regarding to further outcomes, the study detected a decrease in depressive symptoms in female, but not in male patients.

Clare and colleagues (2010) also used a manual-guided multi-professional rehabilitation concept fulfilling all four criteria: "Goal-oriented Cognitive Rehabilitation in early-stage dementia (GREAT)" (6). The main aim of this approach is the identification of individual treatment goals which are defined, operationalized, pursued and regularly followed-up with the therapists. External memory aids are used as compensatory strategies. Integrative elements involve anxiety coping strategies for patients and caregivers. The monitoring of activity levels, which lead to plans for increasing engagement in meaningful and enjoyable activity, and training in situation-specific problem solving, are the interactive parts of this concept.

Compared to untreated patients, participants in this intervention reported higher levels of subjectively experienced expertise in achieving individual goals at the end of three months intervention (6). Moreover, they showed increased ADL compared to the patients in the control group. 6 months after the end of intervention the patients in the treatment group presented significantly higher memory performances and quality of life than the patients in the control group. Currently, this approach is ongoing and assessed in a multicenter study design (33).

Summary of the current stand of the field

Considering the content-related dimension (A: criteria of individuality, interaction, compensation, and integration, (see table 2), in MCI, approaches appear to be efficient, that use interactive elements (17, 21, 30) in addition to compensatory and integrative components. They demonstrated a significant improvement of everyday related prospective memory performances and activities of daily living, especially, if the practice task in the therapy setting is similar to an everyday task (30).

Furthermore, individuality may be associated with significant treatment effects. Research groups, providing individuality (stage specificity (22), or individual problem identification (30)), observed an improvement of cognitive state, even though only Moro et al. realized an interaction with everyday life. Both interactive and individual components appear important for long-term effects (17, 22, 30).

In mild dementia, qualitatively similar effects to MCI could be observed, though to a much lesser extent. Interestingly, based on the limited amount of currently available empirical data, theory-based, manual-guided concepts do not yield better results than unstandardized interventions, which use either at least interactive or individual components.

Considering the outcome (dimension B, see table 3) across all trials, positive treatment effects were observed for metacognitive knowledge and non-cognitive symptoms such as depression or quality of life (21-27, 32, 34). In MCI, particularly in an early stage of cognitive decline, standardized cognitive parameters like general cognitive state or prospective memory improved. In mild AD dementia, this rarely was the case. To date, there is

no empirical evidence for a sustainable improvement in cognitive functions in mild dementia. Evidence of efficacy is much stronger for increase in quality of life and decrease in depression symptoms.

There was no evidence for an improvement of everyday competence (ADL skills) in both MCI and mild dementia. However, as everyday competence in MCI patients is relatively preserved, a highly increase is less likely.

Comparing short- and long term results, effects regarding non-cognitive symptoms, remained stable over follow-up periods varying from three to six months across different studies (27, 32). The long-term stability of cognitive improvement in MCI seems to be dependent on the start of the intervention. A treatment has the most pronounced effect when it begins at an early stage of cognitive decline.

From a methodological perspective (dimension C, see table 3), unfortunately, only few randomized and controlled efficacy studies with larger sample sizes (n>30) are available. Furthermore, the comparability between different studies is hard to achieve as firstly the outcome variables differ largely between studies. Secondly, there is a wide variety regarding frequency, duration and setting of the interventions across the studies (from 6 h a day for 4 weeks (21) to 1 session a week over six months (22)). We might assume that a shorter treatment period hinders patients with memory deficits in learning and internalizing new strategies. But, empirical data suggest that studies with short duration but high frequency of intervention (e.g., (17, 21)) yield larger effects on prospective memory performance and activities of daily living than long-term interventions with low frequency (18, 22, 24). Thirdly, only few theory-based and manual-guided therapy concepts are available. Although high standardized concepts facilitate an objective analysis of effects, CR is characterized by an individual adaptation of interventions. This conflict should be in the focus of further discussions.

Besides the low level of comparability, most studies lack a long-term follow-up to assess sustainability of effects. Lastly, in MCI, diagnostic criteria differ between studies or existing diagnostic concepts are not stringently used. Thus, the interpretation of the Peterson criteria (34) may be based on either psychometric tests or clinical assessment in different studies. The conversion of MCI to dementia, as a clinically important endpoint, received only little attention in the majority of studies.

In summary, the reviewed data indicate that

1) CR seems to be effective, if approaches are highly individualized with a focus on patient relevant goals. Interventions have to be interactive regarding a patient's environment in order to facilitate the transfer of the trained skills from the treatment setting into a patient's daily life. Training the everyday task itself minimizes requirements on transfer capabilities.

2) For patients with mild dementia, there was no evidence of significant effects of CR on cognitive functions or the ADL skills. Such effects have been demonstrated only for subjects with MCI.

3) Interventions revealed greater effects if implemented at earlier stages of cognitive decline.

4) Methodological shortcomings, such as small sample sizes, lack of controlled and randomized studies, heterogeneous outcome variables, and a wide range of intervention characteristics (e.g., in respect to frequency and duration of the intervention) do not allow for valid conclusions on the effectiveness of such interventions.

Recommendations for future research

Considering that greater effects were observed in earlier stages of cognitive decline (23, 30) recent diagnostic concepts such as biomarkers should be implemented. They might be particularly useful in this context since they allow a more precise risk stratification and classification of MCI (35). The incorporation of these diagnostic markers would help to evaluate non-pharmacological interventions such s CR in a precisely defined sample of individuals. This could happen at a much earlier stage of dementia than currently possible.

Moreover, future efficacy studies should integrate larger sample sizes and standardized outcomes, to ensure not only the power to detect treatment effects, but also comparability across studies. Endpoints need to be geared towards a sensitive detection of competence in activities of daily living, as these are most relevant to the health care system, patients and caregivers. In addition, more empirical evidence for sustainable effects of individual therapeutic components is required.

Interventions should balance the degree of manual guidance and individualization, possibly, using post hoc descriptions of interventions that are realized in each single case. This would require to integrate methods from qualitative research into the evaluation of such studies. It addresses a field that remains underdeveloped in the context of efficacy studies. More than in standardized CT, the therapist constitutes an important treatment factor. This poses an issue that deserves more attention in future studies and can benefit from the experience in other areas of research, such as efficacy studies in psychotherapy.

Furthermore, the benefit from interventions might depend on the patient's awareness of their deficits (19), particularly in the case of dementia. For example, in a multi-component cognitive intervention for patients with mild AD, Fernandez-Calvo (36) and colleagues showed that awareness was a significant predictor of the effect of the intervention on all observed cognitive domains. Patients who are not aware of their deficits, only had benefits in non-cognitive domains, e.g., extent of depression symptoms. For this reasons, an assessment of awareness for deficits, associated with the disease, should be part of a cognitive intervention in patients with mild AD dementia. In order to allow treatments also for

unaware patients, the intervention should be open to an adaptation of patient goals and a closer involvement of caregivers.

Lastly, from a health care perspective, evidence-based interventions of CR need to be integrated into an already existing health care system. For example, in a geriatric setting, accountability and funding are important factors with regard to cognitive interventions (37). Wide availability of an interventions requires efficiency and effectiveness; therefore, the conceptual design of CR has to consider cost-effectiveness and practicability. This could be realized in a variety of ways, for instance through group-oriented programs, the integration of non-academic professionals in such programs, or the integration of CR into multimodal treatment strategies. Interventions should ideally combine offers for both caregivers and patients to make use of synergy effects across different interventions. However, currently, there is not sufficient empirical evidence on CR efficacy that would support an implementation of CR into the health care system. To resolve this question, we need more studies providing a higher level of evidence, i.e., clinical phase II or III trials.

Data Sources: For this review, we searched the databases PubMed, PsychINFO, and clinical trials.gov from 2000 to September 2014 with the following key words: Cognitive rehabilitation, cognitive training, cognitive intervention, and cognitive stimulation in Alzheimer's disease and Mild Cognitive Impairment.

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Cognitive Rehabilitation in Alzheimer's Disease: A Controlled Intervention Trial

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Abstract.
Background: Cognitive Rehabilitation for Alzheimer's disease (AD) is an integrative multimodal intervention. It aims to maintain autonomy and quality of life by enhancing the patients' abilities to compensate for decreased cognitive functioning.
Objective: We evaluated the feasibility of a group–based Cognitive Rehabilitation approach in mild AD dementia and assessed its effect on activities of daily living (ADL).
Methods: We included 16 patients with AD dementia in a controlled partial–randomized design. We adapted the manual–guided Cognitive Rehabilitation program (CORDIAL) to a group setting. Over the course of three months, one group received the Cognitive Rehabilitation intervention ($n = 8$), while the other group received a standardized Cognitive Training as an active control condition ($n = 8$). ADL–competence was measured as primary outcome. The secondary outcome parameters included cognitive abilities related to daily living, functional cognitive state, and non–cognitive domains, e.g., quality of life. For each scale, we assessed the interaction effect 'intervention by time', i.e., from pre– to post–intervention.
Results: We found no significant interaction effect of intervention by time on the primary outcome ADL–competence. The interaction effect was significant for quality of life (Cohen's d: –1.43), showing an increase in the intervention group compared with the control group.
Conclusions: Our study demonstrates the feasibility of a group–based Cognitive Rehabilitation program for patients with mild AD dementia. The Cognitive Rehabilitation showed no significant effect on ADL, possibly reflecting a lack of transfer between the therapy setting and real life. However, the group setting enhanced communication skills and coping mechanisms. Effects on ADL may not have reached statistical significance due to a limited sample size. Furthermore, future studies might use an extended duration of the intervention and integrate caregivers to a greater extent to increase transfer to activities of daily living.

Keywords: Alzheimer's disease, cognitive rehabilitation, cognitive training, dementia, mild cognitive impairment

INTRODUCTION

In recent years, researchers developed and evaluated a wide range of cognitive interventions for patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia. Almost all of these interventions addressed specific cognitive functions (for reviews, see [1–3]). For example, Cognitive Training aims to maintain or improve specific cognitive functions, such as attention, episodic memory, and problem solving skills, using guided training and repetitions of standardized tasks. Cognitive Training showed positive effects on general cognitive functioning and selected cognitive abilities in MCI patients [4–6], but not in patients with dementia [2, 3, 7]. However, even in MCI, evidence for long–term effects [4, 5] and a transfer of the trained cognitive abilities to activities of daily living is sparse [5, 6]. For this reason, cognitive interventions for

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AD dementia have adopted the concept of *Cognitive Rehabilitation* [8]. Rehabilitation in general aims to support individuals to achieve and maintain their optimal level of physical, psychological, and social functioning despite specific impairments [9]. Its main goal is to preserve the patient's ability to engage in meaningful everyday activities. Cognitive Rehabilitation in particular aims to develop individualized strategies to deal with cognitive impairments [8]. It is characterized by 1) an individualized approach that identifies and pursues goals that are relevant to the patients and their everyday life; 2) the priority of maintenance of cognitive abilities and compensation of impairments over improvements of single cognitive skills; 3) the integration of multimodal methods by an interdisciplinary multi–professional team; and 4) the interaction with the individual's environment to facilitate transfer from the rehabilitation program to daily life [7].

So far, only few studies have investigated the efficacy of Cognitive Rehabilitation approaches in dementia. Cognitive Rehabilitation proved to be more effective if the approach was highly individualized, focused on goals relevant to the patient [7], and if it was interactive [9–11]. In addition, training a specific everyday task required less residual transfer capabilities [11]. Furthermore, Cognitive Rehabilitation was shown to increase quality of life and to reduce depressive symptoms [12–14]. To date, however, empirical evidence that Cognitive Rehabilitation sustainably improves skills for activities of daily living (ADL) in mild AD dementia is lacking.

In the present study, we aimed to determine the feasibility and efficacy of a group–based Cognitive Rehabilitation program in a partial–randomized controlled trial with an active control condition. Additionally, we aimed at deriving effect size estimates on ADL–related cognitive skills to inform the design of future large–scale multicenter trials. We used a manual–guided Cognitive Rehabilitation approach [15] and adapted it to a group setting, allowing for social interaction effects. Furthermore, aiming to optimize the transfer of strategies, we added a problem–solving training related to everyday life.

METHODS

Subjects and design

Following a screening phase ($n = 44$), we included $n = 20$ individuals with either mild AD dementia or AD with a concomitant cerebrovascular disease (mixed dementia), recruited from the memory clinic of the University Hospital Rostock. All patients were diagnosed with probable or possible AD according to the NINCDS–ADRDA criteria [16], corresponding to a diagnosis of "probable or possible AD dementia based on clinical criteria" according to NIA–AA criteria [17], and characterized using the Mini–Mental State Examination (MMSE) [18]. Cerebrovascular comorbidity was diagnosed according to the ICD–10 criteria [19]. Patients were required to be living at home and to experience at least two face–to–face contacts with a caregiver per week. Subjects taking medication with neurological effects, such as antidementive, antidepressant, or antipsychotic medication, needed to have taken a stable dose during the past 3 months. Subjects were excluded if they had a history of epilepsy or psychiatric illness. Additionally, subjects were not included if they were unable to undergo an MRI examination. MRI data were described in an accompanying manuscript [20]. A radiologist visually inspected all MRI scans to rule out other neurological pathologies, such as tumors or acute stroke events. All participants received a neurological and psychiatric examination and blood testing to determine routine clinical parameters. The study was conducted according to the Declaration of Helsinki and had been approved by the local medical ethics committee of University Hospital Rostock, with all participants providing written informed consent. The study was registered in the database of clinicaltrials.gov ("A 2014–0113").

Five subjects originated from a pilot trial waiting group and were already predetermined for the intervention group. We conducted a partial–randomization to assign the remaining subjects ($n = 15$), using a computer–based balanced randomization.

Outcome measures

All outcome measures were assessed at baseline and at follow–up, i.e., within 14 days after completion of the intervention/control program.

Primary outcome: ADL–competence

Activities of daily living (ADL–competence) were measured on two scales. Firstly, we used the Bayer Activities of Daily Living Scale (B–ADL) [21], consisting of 25 items to be answered by the caregiver, with the mean ranging from 1 (no impairment) to 10 (permanent impairment). Secondly, we employed

the Nuremberg Aging Observation Scale (NSL) [22], completed by both the patients (NSL–P) and the caregivers (NSL–C). This questionnaire consists of 15 items, e.g., dressing, washing, and shopping. A score of 0 indicates no deficits; a score of 30 indicates maximum disability.

Secondary outcomes

Cognitive abilities related to daily living. We administered three tests to assess skills that are especially relevant to everyday life. Everyday memory abilities were assessed using the Rivermead Behavioural Memory Test (RBMT) [23]. This test includes practical demands such as replicating a route across the room, but also prospective memory demands such as remembering a future appointment. To assess planning and organizational skills, we used two subtests of the HOTAP (Handlungsorganisation und Tagesplanung) test [24], which differed in complexity: The subtest HOTAP–A ("individual actions") requires the correct sorting of photos, showing sequences of typical everyday actions, e.g., making coffee or doing laundry. The HOTAP–C ("semi–structured daily schedule") subtest requires fitting single actions into a pre–structured daily schedule, relying on logical reasoning, considering time points and rules. The ratio of the correct items and the invested time, as well as the combined sum scores across HOTAP–C dimensions were used as dependent variables. As an indicator for communication competence, spontaneous speech was measured using the Boston Cookie Theft picture description task, in which a drawn scene has to be described [25].

Functional cognitive state. To assess functional cognitive state, we used the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery [26], a standardized and reliable instrument to assess cognitive functions, including attention, memory, executive functioning, visuo–spatial skills, and language.

Non–cognitive domains. Non–cognitive domains comprised quality of life (measured by the Dimensions of Quality Of Life, DEMQOL [27], which is a questionnaire including patient and caregiver rating), presence and severity of depression (Geriatric Depression Scale, GDS [28], long version with 30 items), the level of consciousness (Apathy Evaluation Scale, AES – patient and caregiver rating), neurobehavioral disturbances (Neuropsychiatric Inventory, NPI, caregiver rating [29]), and the caregiver's burden (Zarit Burden Inventory, ZBI [30]).

Intervention

Our study examined the effects of a Cognitive Rehabilitation program. This intervention was based on the CORDIAL program, a manual–guided approach combining neuropsychological and psychotherapeutic elements, presented by Werheid and Thöne–Otto in 2010 ("Cognitive Rehabilitation and cognitive–behavioral treatment for early dementia in Alzheimer disease, CORDIAL") [15]. This outpatient intervention spans a period of 12 weeks and consists of six modules with 2 sessions each, with one session (60 min) per week. The six modules are described below:

1) *Identification of problems and definition of treatment goals.* This includes determining obstacles to independent living, e.g., the inability to utilize cooking devices, and aspects that reduce the quality of life (e.g., the perception of one's impairments, or depressive thoughts).
2) *Use of external memory aids*, e.g., signposts, lists, or calendars.
3) *Introduction and implementation of daily routines and a structured framework for the day.* This includes exercising daily activities (e.g., making coffee) and repeating these tasks at home, using a written instruction or a schedule, for example one listing the morning routines.
4) *Organization and implementation of pleasurable and meaningful activities.* This includes activities ranging from psychoeducation (in order to prevent depression or apathy) to planning activities like social events and hobbies, etc., to enhance the perception of self–efficacy.
5) *Reminiscence, i.e., biographical work*. This includes dealing with important life events or phases, such as work experience, to retain the temporal structure of life and the use of resources.
6) *Evaluation of achieved goals and planning of future procedures.*

We adapted this program in the following way:

1) We replaced the individual format with a single therapist by a small group program, guided by a psychologist and an occupational therapist. This aimed at increasing social cohesion and support among the group members, as well as rendering the program more cost–effective in a routine care setting.

2) We extended the sessions from a one–hour session per week to one two–hour session per week, allowing sufficient time to address individual needs despite the group setting.
3) We allowed the order of the modules to vary flexibly in response to the participants' needs.
4) We reduced the complexity of the worksheets according to the cognitive state of the participants.
5) We reduced the frequency of the caregiver participation from 6 sessions to 3 sessions, according to caregiver availability.
6) We added advanced training of everyday tasks to facilitate the transfer of strategies to daily life, such as reading and discussing newspaper articles using the "PQRST" method [31] to improve temporal orientation and communication skills, or training basic financial transactions, etc.

During the sessions, we first set goals for the week. For example, we established possibilities to improve compensation of memory deficits (e.g., using external memory aids, or simplifying requirements, etc.). Secondly, explicit tasks were discussed, for example the individual use of a specific memory aid or performing one specific activity a day, and memory aids were created (e.g., calendar, day plan). All discussed items and the tasks were written in a diary. To monitor the activities at home, we called the caregivers once a week.

Active control condition

As an active control condition, we used a standardized Cognitive Training in the form of homework that each participant had to do on his or her own. The tasks originated from a Cognitive Training program [12] aimed at training specific cognitive functions, such as memory, attention, executive functions, and psycho–motor abilities. Patients were asked to perform one task per day; this was not monitored explicitly. The control group met every four weeks to evaluate the homework in order to maintain adherence to the study.

Statistical analysis

All data were analyzed using SPSS V.21. Missing questionnaire items (0.38%) were replaced by the respective item score, averaged over the respective group. In case of missing test data (0.74%), the subject was excluded from the respective analysis. Normally distributed dependent variables were analyzed using parametric tests, while non–parametric tests were used for non–normally distributed dependent variables. For group comparisons of demographic variables and baseline neuropsychological scores, we conducted Mann Whitney U–tests for two independent samples. Chi–square tests were used to compare gender frequency.

To assess the change from baseline to post–intervention, univariate analyses of variance (ANOVA) with repeated measures were conducted for each outcome measure, testing for the main and the interaction effects of the two–level factors intervention (intervention group or control group) and time (baseline or post–intervention). All tests were performed two–tailed, with a significance level of $p < 0.05$. Before entering the repeated–measures ANOVA, scores were rank–transformed across the two time points. Secondly, a rank–based inverse normal transformation (INT) [32] was used to achieve an approximately normal distribution of residuals. ANOVA analyses were conducted using data with and without INT.

As effect size, Cohen's d was calculated for the interaction effects. Between–group differences at baseline and post–intervention, respectively, were assessed using a dependent–samples *t*–test, calculating effect sizes from the *t*–values.

RESULTS

Subjects and baseline characteristics

The screening and randomization procedure is illustrated in Fig. 1. Two patients cancelled their participation before the intervention started. During the intervention one participant became seriously ill and another patient developed paranoid delusions and was treated with antipsychotics. These participants were excluded from the analysis. The final sample included in the analysis consisted of 16 patients, of which thirteen fulfilled the criteria for probable AD and one patient the criteria for possible AD. Two patients (one in the intervention, the other in the control group) had a history of a vascular comorbidity and were diagnosed with mixed dementia. All patients had a CDR score of 1.0. 13 subjects received antidementive medication. In the control group, three subjects took donepezil, two subjects took rivastigmine, and three subjects did not take any

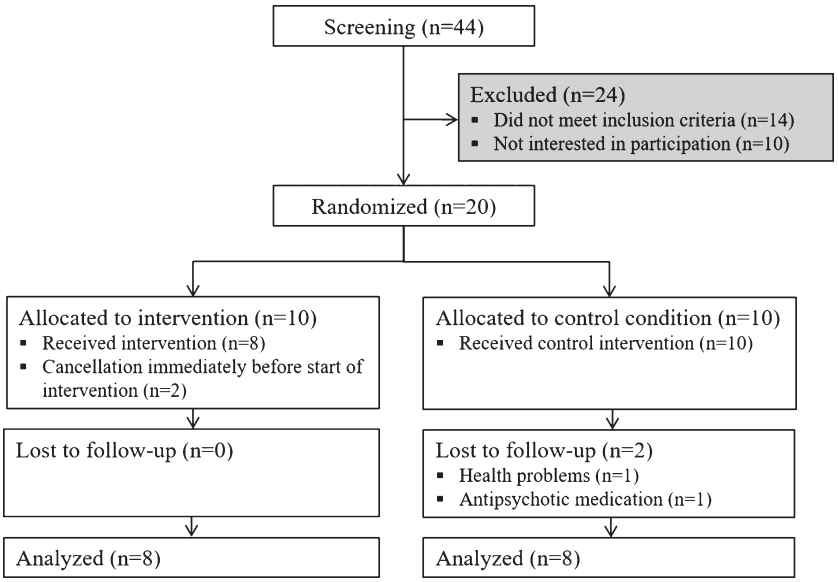

Fig. 1. Flowchart of randomization and procedure according to the CONSORT criteria [43].

antidementive medication. In the intervention group, three subjects took rivastigmine, four subjects took donepezil, and one subject took memantine. Regarding antidepressant medication, in the intervention group, five subjects took serotonin reuptake inhibitors (SSRI). In the control group, one patient took SSRI. All subjects treated with antidementive or antidepressive medication had a stable dose of medication at least for 6 months before the intervention started. A detailed clinical characterization of the subjects is presented in Table 1.

The control group and the intervention group did not differ significantly in age ($p = 0.916$), gender ($p = 0.614$), education ($p = 0.957$), or any of the outcome variables at baseline (shown in Table 2).

Outcome measures: Changes from baseline to post–intervention

The adherence to the treatment of the 16 patients was 100%. Table 3 shows the interaction effects based on the ANOVAs.

Primary outcome

ADL–competence, as measured by caregiver–rating on the Bayer–ADL, increased in the intervention group over time, and decreased in the control group. However, this interaction was not significant ($p = 0.109$). The NSL scale showed a caregiver–rated decline of ADL–competence in both groups over time (interaction effect non–significant, $p = 0.900$). The NSL patient–rating scale showed a decrease in the intervention group and an increase in the control group (interaction effect non–significant, $p = 0.310$).

Secondary outcomes

Cognitive abilities related to daily living, as assessed by the RBMT, CTP, and HOTAP, showed no significant interaction effects (Table 3). In addition, CERAD battery scores showed no significant interactions of intervention by time. Within the non–cognitive domains, a significant interaction effect was found for the self–rated quality of life, with an increase in the intervention group and a decrease in the control group ($p = 0.013$). No other domains revealed significant effects. Effect sizes ranged from medium to large (Table 3). Similar results were obtained by ANOVA analyses without previous INT (data not shown).

DISCUSSION

The present study aimed to evaluate the feasibility and efficacy of a multimodal Cognitive Rehabilitation approach based on the manual–guided CORDIAL program [15], that was adapted to a group setting and expanded to include contents intended to facilitate a transfer to everyday life functioning.

We found that the adapted Cognitive Rehabilitation program was highly feasible but showed no

Table 1
Demographic and clinical data at baseline

Subject number	Group	Age	Gender	Education (years)	Diagnosis	MMSE	GDS
1	CG	76	0	17	Mixed dementia (AD+VaD)	24	4
2	CG	68	1	15	AD	24	1
3	CG	78	1	15	AD	26	5
4	CG	71	0	13	AD	24	14
5	CG	53	0	15	AD	19	14
6	CG	69	0	17	AD	19	5
7	CG	63	0	13	AD	27	12
8	CG	80	1	10	AD	29	10
9	IG	59	0	17	AD	17	4
10	IG	71	1	17	AD	23	10
11	IG	74	1	12	AD	25	15
12	IG	83	0	11	AD	25	8
13	IG	68	1	13	AD	18	12
14	IG	80	0	14	AD	20	13
15	IG	59	1	15	AD	25	10
16	CR	69	0	16	Mixed dementia (AD+VaD)	21	12

CG, control group; IG, intervention group; AD, Alzheimer's dementia; VaD, vascular dementia; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

effect on the primary outcome ADL–competence. This is in line with previous studies using short–term interventions in dementia patients (e.g., [13]). Moreover, the original CORDIAL evaluation study did not find significant changes in ADL scores, as measured by the BADL scale [33]. It has to be noted that ADL scores are difficult to assess in dementia [34], and that the BADL has been suggested to have low sensitivity in dementia [15]. Yet, when using a different ADL–scale, we did not observe a significant intervention effect either, suggesting that effects were not eliminated by a potential lack of sensitivity. Therefore, other factors may have contributed to the absence of significant improvements in ADL. Notably, the sample size was rather small. As two out of three ADL scales showed moderate to large effect size estimates (Cohen's $d > 0.5$), the effects might have reached statistical significance in a larger sample.

Cognitive Rehabilitation effects need to be transferred from the therapy setting to real life. At first, transfer requires a minimum amount of preserved cognitive abilities, especially memory and the ability of abstraction, to be able to apply a strategy in different situations. The cognitive level of our patients, however, ranged from mild to mild–moderate dementia, suggesting that some participants may not have had the required cognitive resources for successful transfer. It can be speculated that Cognitive Rehabilitation benefits ADL skills especially at a mild dementia stage. Consequently, the transfer should have been increasingly supported by the therapist or the caregivers, for example by transferring the exercises to the domestic setting for patients at more advanced disease stages. To successfully achieve transfer, caregivers need to take over responsibilities in the daily setting. The frequency of caregiver's direct participation once in four weeks was too low to achieve adequate involvement. Thus, there is a noticeable conflict of goals: on the one hand, frequent caregiver involvement is required for the Cognitive Rehabilitation to be effective; on the other hand, a higher involvement of caregivers is restricted by their limited availability and already high burden of care. A targeted program at less advanced disease stages involving caregivers may be evaluated in future Cognitive Rehabilitation studies. Additionally, successful transfer depends on well–defined personal goals. The definition of individual goals turned out to be challenging and time–consuming in our treatment group. For example, the participants tended to express global goals, such as "to feel better", rather than specific goals. Furthermore, the intervention group rated their ADL–competence as being stable or slightly decreased (NSL) at follow–up, while the control group rated their ADL–competence as increased at follow–up. As the Cognitive Rehabilitation included a detailed analysis of the daily routine and mobility, it might have led to an increased awareness of challenges, possibly eliciting a more critical evaluation of skills.

Considering secondary outcomes, we found no effects of Cognitive Rehabilitation on cognitive abilities related to daily living. For example, we conducted the RBMT, based on its assessment of explicit daily functions. However, the RBMT includes the

Table 2
Scores of outcome variables at baseline

		Control Group (N = 8)	Intervention Group (N = 8)	
		Mean ± SD	Mean ± SD	*p*
BASELINE SCORES OF PRIMARY OUTCOME				
ADL – competence				
	B–ADL–Caregiver rating*	4.30 ± 1.85	4.75 ± 2.55	0.916
	NSL–Caregiver rating*	57.13 ± 15.38	53.75 ± 16.47	0.494
	NSL–Patient rating*	51.75 ± 13.83	54.75 ± 15.63	0.752
BASELINE SCORES OF SECONDARY OUTCOME				
Cognitive abilities related to daily living				
Prospective memory	RBMT	10.25 ± 4.98	9.75 ± 6.36	0.752
Planning and organizational skills	HOTAP–A	4.39 ± 3.16	3.05 ± 2.24	0.487
	HOTAP–C Combined Score	4.46 ± 3.07	3.84 ± 2.20	0.599
	HOTAP–C Logical thinking	4.75 ± 1.75	3.88 ± 1.73	0.306
	HOTAP–C Rule compliance	7.88 ± 3.09	7.88 ± 3.80	0.874
Spontaneous speech	CTP	11.75 ± 3.92	9.34 ± 4.07	0.328
Functional cognitive state (CERAD)				
Global cognitive state	MMSE	24.00 ± 3.55	21.75 ± 3.24	0.279
Attention	Trail Making Test A*	90.75 ± 51.80	101.14 ± 55.64	0.642
Memory	Word List Memory	12.63 ± 3.54	12.00 ± 5.88	0.874
	Word List Recall	2.38 ± 1.92	2.75 ± 2.82	1.000
	Constructional Praxis Recall	3.75 ± 3.33	4.25 ± 2.92	0.633
Executive functions	Trail Making Test B*	233.29 ± 65.55	240.57 ± 76.40	0.838
	Phonemic fluency	10.88 ± 4.76	11.75 ± 4.59	0.916
Language	Boston Naming Test	13.75 ± 1.28	13.50 ± 0.93	0.406
	Semantic Word fluency	14.13 ± 5.38	12.50 ± 3.38	0.266
Visuo–spatial skills	Constructional Praxis	9.13 ± 1.89	8.88 ± 2.23	0.788
Non–cognitive domains				
Motivation, level of consciousness	AES – caregiver rating*	23.63 ± 10.88	19.25 ± 11.21	0.372
	AES – patient rating*	12.75 ± 10.21	15.63 ± 11.41	0.563
Depression	GDS – patient rating*	8.13 ± 5.00	10.50 ± 3.38	0.427
Quality of life	DEMQOL – patient rating	34.75 ± 6.16	30.00 ± 7.76	0.155
Caregiver's burden	ZBI – caregiver rating*	27.25 ± 14.45	22.75 ± 11.11	0.528

*Higher scores indicate decreased performance, or a higher abnormality of questionnaire statements. SD, standard deviation; ADL, Activities of Daily Living; B–ADL, Bayer Activities of Daily Living Scale; NSL, Nuremberg Aging Observation Scale; RBMT, Rivermead Behavioural Memory Test; HOTAP, "Planning and organization"; HOTAP–A, "individual actions" (sorting of photos showing sequences of typical everyday actions); HOTAP–C, "semi–structured daily schedule" (fitting single actions into a pre–structured daily schedule); CTP, Boston Cookie Theft Picture Description Task; MMSE, Mini-Mental State Examination; CERAD, Consortium to establish a registry for Alzheimer's disease; AES, Apathy Evaluation Scale; DEMQOL, Dimensions of Quality of Life; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; ZBI, Zarit Burden Inventory.

assessment of prospective aspects, including prospective memory [35], which deteriorate at an early stage of the disease [36]. Regarding spontaneous speech, the lower decrease in CTP scores at follow–up in the intervention group compared to the control group supports the use of communication training in future Cognitive Rehabilitation studies (Cohen's d: –0.6, non–significant). With respect to the cognitive state measured by psychometric testing (CERAD battery), we did not expect an improvement, based on previous studies [12–14]. Studies that did find improvements in single cognitive domains [37, 38] had conducted Cognitive Rehabilitation over a longer period of time (5 months) [37], or managed to involve the caregivers to a greater extend [38]. These findings highlight the relevance of a prolonged duration of the program and of social interaction for successful transfer.

A relevant aspect to consider is the possibility of the control group benefitting more than expected from the active control condition. However, as an indirect transfer of improved cognitive functions to improved activities of daily living may not be present in dementia [3, 39], it is unlikely that this should explain the lack of effects.

In the non–cognitive domains, we found a significant interaction for quality of life with an increase in the intervention group and a decrease in the control group. This agrees with several previous studies (for a review, see [7]), but it is in contrast to the original evaluation study of the CORDIAL program [33], which

Table 3
Baseline to post–intervention differences and interaction effects (assessed using ANOVA)

		Control group (N = 8)	Intervention Group (N = 8)			
		Mean difference ± SD	Mean difference ± SD	F	*p*	d
PRIMARY OUTCOME						
ADL–competence						
	B–ADL–Caregiver rating*	0.26 ± 1.10	–0.52 ± 0.94	2.93	0.109	0.86
	NSL–Caregiver rating*	0.63 ± 11.40	3.00 ± 13.93	0.02	0.900	0.06
	NSL–Patient rating*	–4.50 ± 6.19	0.50 ± 5.42	1.11	0.310	–0.53
SECONDARY OUTCOME						
Cognitive abilities related to daily living						
Prospective memory	RBMT	–1.88 ± 3.00	–0.13 ± 3.52	0.07	0.789	–0.14
Planning and organizational skills	HOTAP–A	0.82 ± 1.73	1.10 ± 1.60	0.02	0.890	–0.07
	HOTAP–C– Combined Score	0.89 ± 1.28	0.10 ± 2.34	0.71	0.414	0.36
	HOTAP–C– logic thinking	–0.38 ± 1.19	–0.7 ± 2.56	0.10	0.760	0.16
	HOTAP–C– rule compliance	0.75 ± 3.88	0.00 ± 2.08	0.17	0.688	0.21
Spontaneous speech	CTP	–2.75 ± 2.66	–1.13 ± 2.36	1.46	0.247	–0.6
Functional cognitive state (CERAD)						
Global cognitive state	MMSE	0.13 ± 2.17	1.00 ± 1.51	0.21	0.658	–0.23
Attention	Trail Making Test A*	15.63 ± 24.08	24.23 ± 25.71	0.00	0.965	–0.02
Memory	Word List Memory	1.38 ± 3.85	0.63 ± 4.03	0.44	0.517	0.33
	Word List Recall	0.00 ± 1.41	–0.13 ± 2.03	0.03	0.874	–0.08
	Constructional Praxis Recall	0.75 ± 2.76	0.00 ± 2.51	0.34	0.569	0.29
Executive functions	Trail Making Test B*	25.57 ± 45.32	26.86 ± 49.75	0.22	0.650	–0.23
	Phonemic fluency	–3.38 ± 3.16	–1.63 ± 3.11	0.78	0.392	–0.44
Language	Semantic fluency	–2.38 ± 2.17	1.50 ± 4.17	3.69	0.075	–0.96
	Boston Naming Test	–0.88 ± 1.64	–0.13 ± 1.25	1.24	0.285	–0.56
Visual–spatial skills	Constructional Praxis	–0.50 ± 2.20	0.25 ± 1.49	2.30	0.152	–0.76
Non–cognitive domains						
Motivation level of consciousness	AES – caregiver rating*	2.13 ± 5.84	3.75 ± 6.96	0.05	0.832	–0.11
	AES – patient rating*	2.50 ± 5.21	4.75 ± 6.73	0.51	0.487	–0.36
Depression	GDS – patient rating*	0.88 ± 3.23	0.13 ± 3.09	0.05	0.833	0.11
Quality of life	DEMQOL – patient rating	–4.4 ± 5.40	3.1 ± 5.79	8.15	**0.013**	–1.43
Caregiver's burden	ZBI – caregiver rating*	0.8 ± 7.25	5.3 ± 5.18	1.16	0.300	–0.54

*Positive scores indicate decline from baseline to post–intervention; grey shading indicates a direction of effects as expected. SD, standard deviation; F, intervention by time; d, Cohen's d, derived from *t*–values; ADL, Activities of Daily Living; B–ADL, Bayer Activities of Daily Living Scale; NSL, Nuremberg Aging Observation Scale, RBMT, Rivermead Behavioural Memory Test; HOTAP, "Planning and organization"; HOTAP–A, "individual actions" (sorting of photos showing sequences of typical everyday actions); HOTAP–C, "semi–structured daily schedule" (fitting single actions into a pre–structured daily schedule); CTP, Boston Cookie Theft Picture Description Task; MMSE, Mini-Mental State Examination; CERAD, Consortium to establish a registry for Alzheimer's disease; AES, Apathy Evaluation Scale; DEMQOL, Dimensions of Quality of Life; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; ZBI, Zarit Burden Inventory. Bold: $p < 0.05$.

found no significant effect. One could speculate that this difference reflects the advantage of a group setting over an individual setting, as other group–based interventions also found a positive impact on the quality of life [40].

Furthermore, the influence of antidementive or antidepressant medication has to be considered. We attempted to minimize this factor by only including subjects with a stable dose, and by using the differences between the two time points to assess relative change, rather than using absolute values.

Limitations of the study included a small sample size and the sample heterogeneity with respect to age and MMSE scores. Although this increases the relevance of the sample for the population of people with dementia, the high variability limits the power to detect intervention effects in addition to the small sample size. Furthermore, the assignment to the groups was only partially randomized, since five subjects stemmed from the waiting list of a previous pilot study and had been preassigned to the intervention group. Also, the duration of the intervention of only three months may have been too short for the consolidation of new strategies, however, our approach was based on an existing manual–guided program. In future studies, however, the duration could be extended.

We did not conduct interviews for a detailed qualitative data analysis. We suggest that qualitative research methods should be integrated into the evaluation of efficacy studies of Cognitive Rehabilitation approaches. However, we had the following

impressions: 1) Despite a heterogeneous age range and variability in cognitive functioning, the group members shared their experiences with each other. Participants benefitted from each other's resources and supported each other, e.g., by suggesting different coping strategies. We observed an active process of collecting and sharing ideas. 2) We extended the sessions' durations from 1 h a week in the original CORDIAL program to 2 hours a week. However, even this period proved to be too short to address all contents in the group setting. A longer duration, including breaks, would be more favorable. 3) A variable order of modules was beneficial. For example, the analyses of problems and the resulting awareness of deficits provoked depressive symptoms and frustration in some participants, so that we chose to follow up with the biographical work (originally placed at the end of therapy) to activate individual resources. A qualitative case report of a CORDIAL trial by Tonga et al. [41] confirms the benefit of a flexible module sequence. 4) As adaptation, a problem–solving training related to daily life was included in the program. The tasks could be adjusted individually and were well accepted by the participants. However, the frequency of one session per week seemed to be too low, and no transfer effect to daily living could be observed. Thus, although implicit memory such as learning routines is better preserved than declarative memory in patients with AD dementia, a higher training frequency seems to be necessary [42]. Interestingly, however, the implementation of routines in the Cognitive Rehabilitation may be reflected in an increased functional connectivity between the posterior cingulate cortex and the cerebellum at post-intervention, as reported in an accompanying MRI study [20].

In conclusion, in our study we demonstrated the feasibility of a group–based Cognitive Rehabilitation program, adapted from the CORDIAL program for patients with mild AD [15]. As a result, we found an increased quality of life, but no improvement of ADL skills. This was mainly due to a lack of transfer between the therapy setting and daily life. We therefore recommend increased active involvement of the caregivers in future programs. Aside from that, the group context seemed to promote communicative capabilities and coping processes. However, future studies with larger sample sizes are needed for generalizing the results. Furthermore, our findings demonstrate the variety of challenges when developing Cognitive Rehabilitation approaches and contribute to the urgently required development and refinement of cognitive interventions for dementia.

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Does Functional Connectivity Provide a Marker for Cognitive Rehabilitation Effects in Alzheimer's Disease? An Interventional Study

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Abstract.
Background: Cognitive rehabilitation (CR) is a cognitive intervention for patients with Alzheimer's disease (AD) that aims to maintain everyday competences. The analysis of functional connectivity (FC) in resting-state functional MRI has been used to investigate the effects of cognitive interventions.
Objectives: We evaluated the effect of CR on the default mode network FC in a group of patients with mild AD, compared to an active control group.
Methods: We performed a three-month interventional study including 16 patients with a diagnosis of AD. The intervention group (IG) consisted of eight patients, performing twelve sessions of CR. The active control group (CG) performed a standardized cognitive training. We used a seed region placed in the posterior cingulate cortex (PCC) for FC analysis, comparing scans acquired before and after the intervention. Effects were thresholded at a significance of $p < 0.001$ (uncorrected) and a minimal cluster size of 50 voxels.
Results: The interaction of group by time showed a higher increase of PCC connectivity in IG compared to CG in the bilateral cerebellar cortex. CG revealed widespread, smaller clusters of higher FC increase compared with IG. Across all participants, an increase in quality of life was associated with connectivity increase over time in the bilateral precuneus.
Conclusions: CR showed an effect on the FC of the DMN in the IG. These effects need further study in larger samples to confirm if FC analysis may suit as a surrogate marker for the effect of cognitive interventions in AD.

Keywords: Alzheimer's disease, cognitive rehabilitation, default mode network, dementia, functional connectivity, functional MRI

INTRODUCTION

Cognitive interventions may be useful to reduce rates of cognitive decline in people with Alzheimer's disease (AD) dementia or at risk for AD [1]. Cognitive rehabilitation (CR) is a multimodal cognitive intervention that aims to preserve a patient's everyday activities, independent living, and quality of life [2]. CR combines the dimensions of individuality (e.g., pursuing personal goals with relevance to the patient's everyday life), compensation (e.g., maintaining skills and compensating deficits), integration (e.g., applying multimodal methods), and interaction

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(including the patient's environment) [3]. Several studies integrating key concepts of CR have shown an improvement of quality of life and a decrease in depressive symptoms in people with dementia, but no significant effects on everyday competence (activities of daily living, ADL) or cognitive functions [3–6].

To develop effective therapies, it is essential to better understand the effects of an intervention on underlying neuronal dysfunction in dementia. Functional connectivity networks comprise a dynamic synchronized activity between functionally coupled brain regions [7]. Researchers have employed imaging techniques [8–10] to study progressive disruption of functional connectivity networks as a possible mechanism underlying the clinical course of AD [11–13]. The most widely studied network so far is the default mode network (DMN), which is characterized by a task-related deactivation in functional magnetic resonance imaging (fMRI). Typically, it shows highest activity in a wakeful resting-state in the precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), lateral temporal and parietal cortex, thalamus, and hippocampus [14]. Resting-state fMRI (rs-fMRI) [15] allows the study of patients who are not able to follow complex activation paradigms during fMRI, and the DMN can be readily reconstructed from rs-fMRI by seed-based connectivity analysis of its principle network nodes, most typically the PCC [16, 17]. The progressive decrease of functional connectivity in the DMN facilitates the differentiation between healthy controls, mild cognitive impairment (MCI), and AD dementia [13, 18, 19] but may also provide a marker to track the disease's progress. So far, only a few studies have investigated longitudinal changes in the DMN in patients with MCI and AD. Studies indicate a fractionation of the DMN in several subsystems which disintegrate consecutively [20–22]. Longitudinal studies also suggested an increase of connectivity between the PCC and frontal regions in early stages of AD [20, 23], and an increase of connectivity between PCC and precuneus in a group of MCI patients having converted to AD compared to non-converters [24]. These connectivity increases have typically been interpreted in the context of compensatory mechanisms. Even fewer studies have investigated effects of cognitive interventions on rs-fMRI connectivity. Cognitive training in healthy older people led to initial small increases in functional connectivity between the hippocampus and superior temporal gyrus regions after three weeks, which were lost after the complete training of 12 weeks [25]. In people with MCI an eight weeks meditation-intervention resulted in increased connectivity between PCC and MPFC/hippocampus without changes in behavioral parameters [26]. Functional imaging techniques other than rs-fMRI revealed effects of CR in AD and MCI. Using a recognition-task fMRI paradigm, Van Paasschen found that eight weeks of CR in patients with early-stage AD resulted in an increase of activation in the intervention compared to the control group in frontal and parietal regions, but had no significant effects on behavioral performances. The authors suggested that fMRI may be more sensitive to intervention effects than neuropsychological tests [27]. In an [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) study, six months CR in patients with MCI and AD led to attenuated metabolic decline in both intervention groups compared to the active control group, but the authors found only non-significant correlations between FDG-uptake and cognitive parameters [28]. In summary, functional imaging provides promising endpoints for CR interventions that deserve further study.

The aim of our study was to assess the effect of 12 weeks CR on functional connectivity within the DMN in patients with mild AD compared to an active control group.

We hypothesized that CR, which is thought to mobilize cognitive resources, may alter functional connectivity in the DMN.

METHODS

Subjects

We screened 44 patients in the memory clinic of the University Medical Center Rostock and included 20 subjects with a diagnosis of clinically probable AD or possible AD with concomitant cerebrovascular disease (mixed dementia), according to NINCDS-ADRDA criteria [29]. Cerebrovascular comorbidity was diagnosed according to ICD 10 criteria [30]. Subjects who were taking psychotropic drugs needed to be under stable doses for at least three months. Almost all subjects were taking antidementive medication. In the control group, three subjects took donepezil, two subjects took rivastigmine, and three subjects did not take any antidementive medication. In the intervention group, three subjects took rivastigmine, four subjects took donepezil, and one subject took memantine. All patients received a comprehensive neurological and psychiatric examination.

Table 1
Demographical measures at baseline

Parameters	Intervention group (IG) $n = 8$			Control group (CG) $n = 8$			
	Mean	SD	Range	Mean	SD	Range	p^*
Age (years)*	70.4	8.72	59–83	69.8	8.81	53–80	0.916
Sex (male/female)+	4/4			5/3			0.614
Education (years)*	14.4	2.26	11–17	14.4	2.33	10–17	0.957
MMSE (points)*	21.8	3.24	17–25	24	3.55	19–29	0.297

*Measured by U-test; +measured by chi-square-test; SD, standard deviation; MMSE, Mini-Mental Status Examination.

Exclusion criteria consisted of a history of neurological or psychiatric illness (other than AD), or extensive pathological changes in the MRI scan, such as a tumor or evidence of stroke. The study was approved by the ethics committee of the University Medical Center Rostock and registered in the database of clinicaltrials.gov (A 2014–0113). All subjects and their representatives provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki of 1964, last amended by 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Study design

Our study examined the effects of a three-month cognitive rehabilitation program in a semi-controlled design. Details on the design are described in detail in our companion paper [31]. After screening, 20 patients were partially randomized to either an intervention group (IG) or control group (CG). We conducted an adaptive and partially balanced randomization. As five subjects originated from a pilot trial waiting group and were already predetermined for the intervention group, we were forced to conduct an adaptive randomization at baseline. The remaining subjects ($n = 15$) passed a computer-based balanced randomization. At baseline, the two groups did not differ significantly with respect to age, sex, education, and MMSE (Table 1). Moreover, they did not differ with respect to severity of AD according to MMSE (Table 1) and CERAD-scores (here not reported in detail). Eight subjects per group completed the study. For details on design and dropouts, please see Fig. 1. The intervention group received a cognitive rehabilitation intervention based on the CORDIAL-program [32], as described in detail in our companion paper [31]. In short, this program includes 6 modules in 12 weekly sessions over three months with contents such as identifying

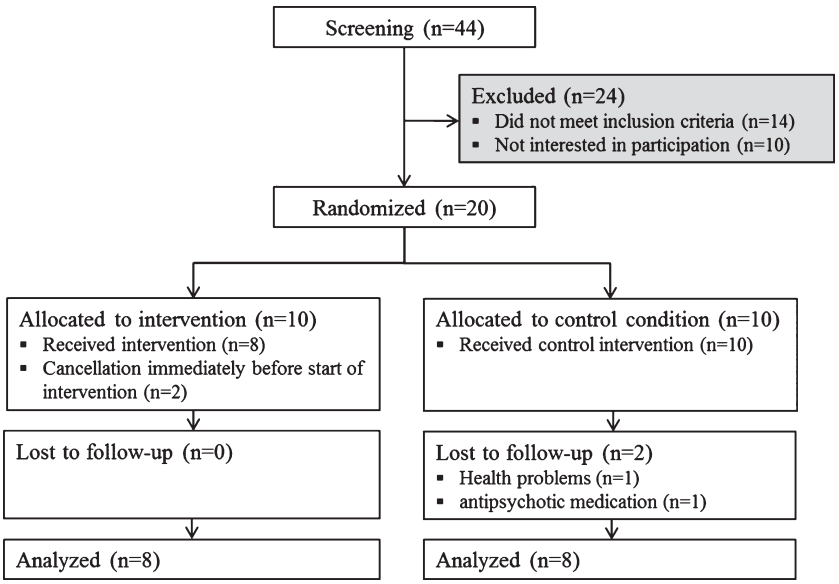

Fig. 1. Flowchart of randomization and procedure according to CONSORT criteria [58].

individual problems, defining personal goals, biographical work, implementation of pleasant activities and external memory aids, concluded by an evaluation session with individual plans for the future. The control group received standardized cognitive training [33] with worksheets for homework and monthly meetings.

Neuropsychological outcome

As primary outcome, we used two scales, measuring Activities of daily living (ADL-competence). Firstly, we used the Bayer's Activities of Daily Living Scale: Bayer-ADL [34], addressing everyday competence. Secondly, we employed the Nuremberg Aging Observation Scale (NSL) [35], completed by both the patients (NSL-P) and the caregivers (NSL-C). Secondary outcomes were the cognitive status, measured with the Consortium to establish a registry for AD (CERAD) [36], and non-cognitive domains, for example depression, measured with the Geriatric Depression Scale (GDS) [37], and quality of life, measured by the Health-related quality of life for people with dementia (DEMQOL) [38]. The neuropsychological testing was conducted blinded to the participants' intervention condition.

Image data acquisition

We used a 3T Siemens Magnetom VERIO scanner (Erlangen, Germany) with a 32-channel head coil. The patients were instructed to lie still, keep their eyes closed and not to fall asleep. The field-of-view (FOV) spanned the whole brain and was aligned along the anterior-to-posterior commissure line. The functional MRI was based on echo-planar imaging using a 64×64 image matrix with 47 axial slices (spacing 3.5 mm, thickness 3.5 mm, no gap, interleaved acquisition). The FOV was $224 \times 224 \times 165$ mm, voxel size $3.5 \times 3.5 \times 3.5$ mm^3, echo time 30 ms, repetition time 2,580 ms, flip angle 80°, and parallel imaging acceleration factor 2. We obtained 180 volumes within 7 min 54 s. During the same session, a high-resolution T1-weighted anatomical image was acquired, applying the magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: 256×256 image matrix with 192 sagittal slices, FOV $256 \times 256 \times 192$ mm, voxel size $1 \times 1 \times 1$ mm^3, echo time 4.82 ms, repetition time 2,500 ms, flip angle 7° and parallel imaging acceleration factor 2. The duration of the sequence was 9 min 20 s.

Image processing

All functional and anatomical scans were visually inspected to ensure data quality. We used SPM8 (Wellcome Trust Centre for Neuroimaging) implemented in MATLAB R2103a (The MathWorks, Inc.) in conjunction with the Voxel-Based Morphometry toolbox (VBM8, r413 [39]) and the Data Processing Assistant for Resting-State fMRI (DPARSF advanced edition, Version 3.1 [40]) for data processing. The anatomical T_1-weighted scans were processed following the longitudinal pipeline of the VBM8 toolbox. Bias-corrected mean images were calculated from the realigned anatomical images of the baseline (BL) and follow-up (FU) time points. The anatomical images were segmented into grey matter, white matter, and cerebrospinal fluid partitions using VBM8. The Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm [41] was used to create a standardized template and to normalize the T_1-weighted images to the Montreal Neurological Institute (MNI) reference coordinate system [42]. We removed the first six volumes from the functional images to ensure scanner gradient field stabilization; the data underwent slice-time correction and were realigned to the mean functional image of the time series. Then, we co-registered the fMRI images to the anatomical T_1-weighted mean image using the temporal mean as reference. We regressed out nuisance signals due to head motion (6 movement parameters + first-order derivatives), as well as the mean time courses for the global signal, white matter signal, and cerebrospinal fluid signal derived from the anatomically segmented maps. We applied temporal band-pass filtering in the frequency range 0.01 to 0.1 Hz. For spatial normalization, we applied the deformation fields, obtained from the anatomical data, to transform the functional data to MNI standard space. As a final step, we smoothed the warped functional images with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Statistical analysis

We followed a seed-based approach to evaluate the functional connectivity of the DMN. As implemented in the DPARSF advanced edition toolbox (State Key Laboratory of Cognitive Neuroscience and Learning, Beijing, http://www.rfmri.org [40]), we calculated whole brain correlation maps of the signal time course

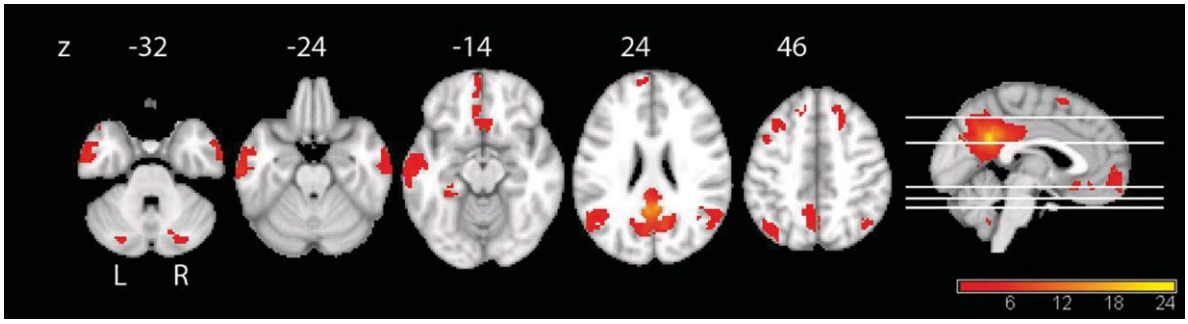

Fig. 2. Functional connectivity of the PCC in the full sample at baseline. The connectivity maps reveal the typical pattern of the DMN. We applied threshold of $p < 0.05$, FWE-corrected with a minimal cluster size of 50.

using a seed sphere placed in the PCC at MNI-coordinates (0, –51, 29) with a radius of 6 mm [16, 17, 43]. In the same step, we applied the Fisher transform to calculate z-score maps from the Pearson correlation coefficients. Using these maps, we conducted the following analyses in SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk):

First, we performed a one-sample *t*-test to determine the functional connectivity pattern within the whole sample ($p < 0.05$ corrected for family-wise error, minimal cluster size of 50 voxels). Second, we performed a two-sample *t*-test to compare the groups at baseline and at follow-up. Third, we conducted a two-way repeated-measures ANOVA, using the flexible factorial design in SPM, on the main effect of group and condition, i.e., time between BL and FU, and the interaction effect for group and condition. Fourth, we performed a paired *t*-test to assess the main effect of time for each group separately. In addition, we calculated functional difference images, subtracting the BL-image from the FU-image, and assessed associations between the longitudinal differences in functional connectivity and the differences of a significant neuropsychological variable using voxel-wise linear regressions. All voxel-wise effects were assessed at a statistical threshold of $p < 0.001$, uncorrected, and a minimal cluster size of 50 contiguous voxels. To identify the clusters' locations, we used the Automated Anatomical Labeling toolbox (2008) for SPM8 with a standard MNI-template.

RESULTS

From the initially included twenty patients, sixteen completed the study. Two subjects in each group dropped out due to various reasons (Fig. 1).

Neuropsychological outcome

There were no significant changes in the primary outcome of ADL-competence after intervention (Bayer-ADL: $F = 2.93$, $p = 0.109$; NSL-Caregivers rating: $F = 0.02$, $p = 0.900$; NSL-patients-rating: $F = 1.11$, $p = 0.310$). Regarding the secondary outcome, we found a significant group × time interaction effect only for the quality of life index ($F = 8.15$, $p = 0.013$), with an effect size of Cohen's $d = –1.43$. Further details regarding all neuropsychological outcomes can be found in our companion paper [31].

Functional connectivity outcome

The whole sample showed significant PCC functional connectivity in the precuneus, superior parietal cortex, lateral temporal cortex, and medial prefrontal cortex (Fig. 2), representing a typical DMN pattern [44]. A comparison of groups at baseline revealed for the IG, compared to the CG, higher connectivity in the right angular cortex and superior frontal cortex, whereas the CG showed higher connectivity in the left supplementary motor cortex. At follow-up, the IG revealed higher connectivity again in the right angular cortex and the CG showed higher connectivity than the IG in the left superior temporal cortex. Details are shown in Supplementary Table 1.

In the longitudinal analyses, the main effect of time showed an increase of PCC connectivity from BL to FU for the whole group in the left precentral gyrus, and to a lower extent in the precuneus bilaterally, the right PCC, and in the right inferior temporal lobe (Fig. 3). Connectivity decreased from BL to FU between the PCC and left temporal regions and the right middle temporal pole. Smaller clusters

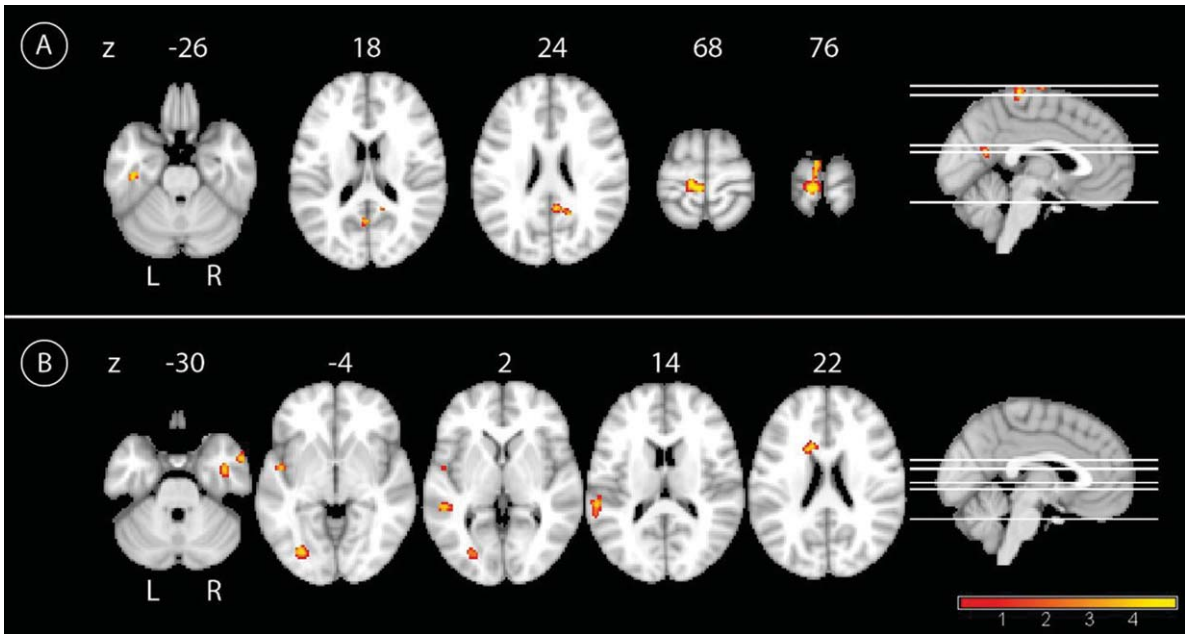

Fig. 3. Main effect of time in the whole sample. A) Results for the main effect of time with the contrast follow-up > baseline in the whole sample. Yellow color represents higher connectivity with the PCC at FU compared to BL, $p < 0.001$, uncorrected, and a minimal cluster size of 50. B) Results for the main effect of time with the contrast baseline > follow-up in the whole sample. Yellow color represents higher connectivity with the PCC at BL compared to FU, $p < 0.001$, uncorrected, and a minimal cluster size of 50.

of connectivity decrease were located in the left middle occipital cortex and the left caudate nucleus (Fig. 3 and Table 2). The interaction of group by time showed a higher increase of PCC connectivity in IG compared to CG over time primarily in the bilateral cerebellar cortex, with smaller clusters in the left postcentral gyrus, supplementary motor cortex, and orbital frontal cortex (Fig. 4). By contrast, CG showed a higher increase of PCC connectivity over time compared with IG in more widespread areas, including peaks in the left lingual cortex, temporal inferior lobe, orbito-frontal cortex, right precentral cortex, pallidum, and caudate nucleus (Fig. 4 and Table 2). The results of the paired *t*-test showed an increase of connectivity over time for IG in the following regions: left supplementary motor cortex, left postcentral gyrus, left precuneus, right insula, and left paracentral lobule. The opposite contrast showed a decrease of connectivity over time in IG in the left fusiform gyrus. In the CG, we found an increase of connectivity over time in the left temporal inferior lobe, right crus II of the cerebellum, and the right middle frontal lobe. Also for the CG, we found a decrease of connectivity over time in the regions left middle temporal lobe, left fusiform gyrus, and lobule VI of the right cerebellum (Table 3).

As quality of life revealed the only significant interaction effect in the behavioral analysis, we correlated this variable with the functional connectivity to reduce the number of comparisons. In the IG group, QoL increase was associated with connectivity increase over time in the bilateral precuneus, particularly on the left side, in the right middle temporal lobe, in the left gyrus calcarinus and in the right inferior parietal cortex (Fig. 5 and Table 4). In the CG group, QoL was not significantly associated with changes in connectivity.

DISCUSSION

Rs-fMRI has been proposed as a promising marker to track changes in functional connectivity throughout different stages of AD [20]. In our study, we assessed effects of CR on functional connectivity in patients with mild AD. Some studies reported small effects of cognitive interventions in functional imaging, such as rs-fMRI [25, 26], task fMRI [45], and FDG-PET [28]. These studies found no significant correlations between functional brain changes and cognitive endpoints. Studies varied in the type of intervention (meditation, cognitive training, CR), design aspects, i.e., duration of intervention (twelve

Table 2
Longitudinal functional connectivity results

Contrast		Brain Region, right (R) or left (L)	Cluster size (voxel)	Peak MNI coordinates (mm)			peak-level T-Statistic
				x	y	z	
Longitudinal: Main effect of time	FU > BL	Precuneus, R	124	18	–54	27	5.28
		Precentral gyrus, L	594	–6	–31	67	5.07
		Temporal Inferior Lobe, L	67	–42	–21	–26	4.45
		Precuneus, R	51	12	–48	13	4.17
		Precuneus, L	55	–2	–61	19	3.97
	BL > FU	Middle Occipital Lobe, L	175	–28	–76	–2	5.61
		Superior Temporal Lobe, L	155	–60	–36	12	4.27
		Temporal Inferior Lobe, R	101	42	–6	–29	4.46
		Corpus Nuclei Caudate, L	96	–16	14	24	4.83
		Middle Temporal Lobe, L	96	–50	–36	4	4.58
		Middle Temporal Pole, R	74	56	6	–32	4.48
Longitudinal: Interaction effect	IG > CG	Cerebellum, Lobule IV/V, R	210	18	–45	–15	5.04
		Cerebellum, Lobule VI, R	175	18	–55	–33	4.82
		Postcentral Cortex, L	109	–18	–43	69	4.40
		Inferior Frontal Cortex, Pars Orbitalis, R	104	40	22	–18	5.10
		Supplementary Motor Cortex, L	91	0	–6	73	4.17
		Cerebellum, Lobule III, R	50	15	–31	–17	4.77
	CG > IG	Lingual Cortex, L	77	–26	–79	–14	4.93
		Inferior Temporal Lobe, L	74	–45	–13	–29	4.47
		Precentral Cortex, R	70	42	–6	27	5.03
		Nucleus Caudate, R	65	20	15	24	4.06
		Pallidum, R	54	18	–6	–2	5.04
		Orbitofrontal Cortex, L	51	–26	50	–3	3.99

Results of functional data from cross-sectional and longitudinal analysis, thresholded at $p < 0.001$, uncorrected for multiple comparisons and a minimal cluster size of 50 voxel; IG- intervention group; CG, control group; MNI, Montreal Neurological Institute.

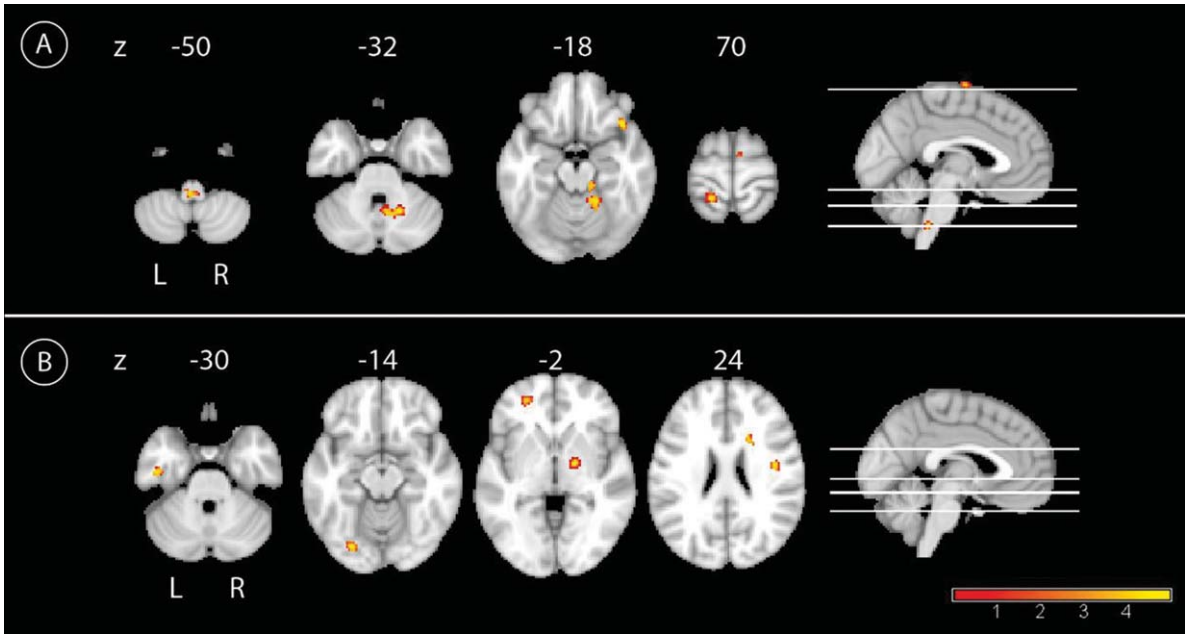

Fig. 4. Longitudinal interaction effect. A) Comparison of the longitudinal effect of the CR between groups with the contrast intervention group > control group over time with the yellow color representing higher connectivity with the PCC in the IG compared to the CG, $p < 0.001$, uncorrected, and a minimal cluster size of 50. B) The results for the interaction effect with the contrast control group > intervention group with the yellow color representing higher connectivity with the PCC in the CG compared to the IG, $p < 0.001$, uncorrected, and a minimal cluster size of 50.

Table 3
Longitudinal results for each group separately

Contrasts		Brain Region, right (R) or left (L)	Cluster size (voxel)	Peak MNI coordinates (mm)			Peak-level T-statistic
				x	y	z	
Longitudinal: IG	FU > BL	Supplementary Motor Cortex, L	285	0	–6	75	16.36
		Postcentral Gyrus, L	114	–18	–37	69	10.42
		Precuneus, L	86	–12	–27	64	9.19
		Insula, R	52	36	4	–14	8.00
		Paracentral Lobule, L	58	–12	–52	64	7.99
	BL > FU	Fusiform Gyrus, L	119	–21	–72	–21	6.16
Longitudinal: CG	FU > BL	Temporal Inferior Lobe, L	193	–45	–25	–20	10.50
		Cerebelum, Crus II, R	122	50	–54	–45	9.30
		Middle Frontal Lobe, R	76	26	18	49	6.72
	BL > FU	Middle Temporal Lobe, L	88	–50	–34	3	11.64
		Fusiform Gyrus, L	97	–27	–76	–5	9.47
		Cerebelum, Lobule VI, R	78	22	–55	–30	8.75

Results from the paired *t*-Test comparing both timepoints for each group separately, thresholded at $p < 0.001$, uncorrected for multiple comparisons and a minimal cluster size of 50 voxel. QoL, Quality of Life; IG, intervention group; CG, control group; MNI, Montreal Neurological Institute.

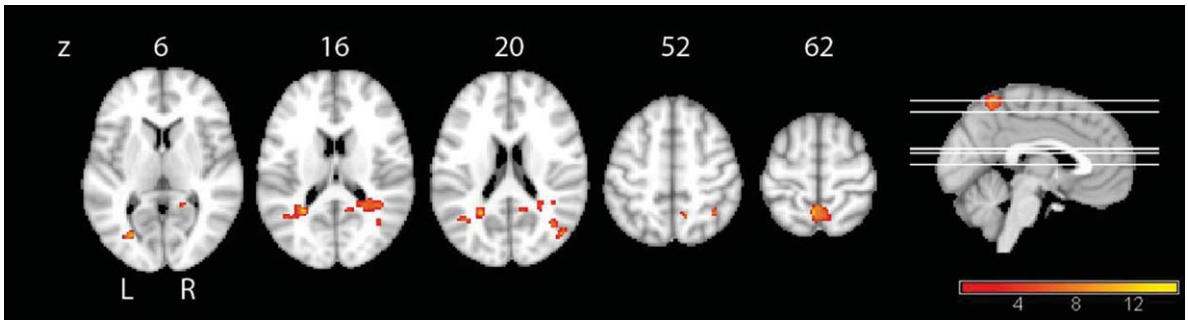

Fig. 5. Linear regression analysis of QoL and connectivity. Positive correlation of the QoL and functional difference images for the IG, with the yellow color representing regions that show increased connectivity with the PCC over time that are correlated with increased values in quality of life over time, $p < 0.001$, uncorrected, and a minimal cluster size of 50.

Table 4
Longitudinal results of QoL and functional connectivity correlation analysis

Contrasts		Brain Region right (R) or left (L)	Cluster size (voxel)	MNI peak coordinates (mm)			Peak-level T-Statistic
				x	y	z	
QoL – IG	Positive Correlations	Precuneus, L	461	–4	–54	63	4.76
			295	–27	–52	16	4.77
		Precuneus, R	104	22	–48	27	4.00
		Middle Temporal Lobe, R	324	40	–48	13	3.92
			52	46	–72	21	4.52
			50	40	–63	18	3.98
		Gyrus Calcarinus, L	82	–27	–73	6	4.53
		Inferior Parietal Cortex, R	65	38	–54	52	4.30

Linear regression with the functional difference-images as a dependent and the difference-values of the behavioral parameter QoL as an independent variable (assessed with the DEMQOL), thresholded at $p < 0.001$, uncorrected for multiple comparisons and a minimal cluster size of 50 voxel. QoL, Quality of Life; IG, intervention group; CG, control group; MNI, Montreal Neurological Institute.

weeks, eight weeks, six months), and the target groups (AD, mild cognitive impairment, healthy elderly subjects) [25, 26, 28, 45].

At baseline, the full sample of our study showed the typical pattern of the DMN, replicating previous findings in similar cohorts [13, 18]. Additionally,

we compared both groups at baseline and found differences in a few regions, for instance higher connectivity in the right angular cortex in IG. However, this cluster also showed at follow-up, when comparing both groups, thus we do not expect an interference with other results. The interaction effect over time revealed an increase of connectivity with the PCC in regions of the cerebellum in the IG compared with the CG group. Studies have indicated that the cerebellum is relevant to all resting-state networks including the DMN [46, 47] and that the functional connectivity of the cerebellum also shows decline in AD [48, 49]. Furthermore, the cerebellum has been shown to take part in procedural or implicit memory [50, 51], which is known to be relatively preserved throughout the progress of AD compared to declarative memory [52]. Since our CR aimed at the implementation of routines, an effect on the functional connectivity between the PCC and the cerebellum may be plausible. CG showed increases of functional connectivity over time relative to the IG group in several brain regions, although with smaller clusters when compared to the contrast IG > CG. Still, the fMRI data did not provide unambiguous evidence for IG effects compared with CG. Similarly, a previous rs-fMRI study did not find clear effects of a cognitive intervention [25].

Irrespective of the treatment, connectivity with the PCC increased from baseline to follow-up in the bilateral precuneus and paracentral in the whole sample. We might interpret the increase of connectivity as an unspecific effect of intervention. On the one hand, we would expect that the cognitive intervention improved PCC function, as the region of precuneus and PCC represents a central hub within the DMN [53] with important contributions to the control of attention [21]. On the other hand, our results contradict the classical hypothesis of an early deterioration of this region in the disconnection cascade of the DMN from MCI to AD [20, 54], which would have expected a decrease over time. Possibly, due to the region's high connectivity, it is still capable to activate cognitive resources. Such compensating processes have been suggested to be part of the network's deterioration, as several researchers described an increase of connectivity between the PCC/precuneus region and frontal areas [20, 23]. We also noticed a decrease of connectivity over time in the whole sample, especially in temporal regions. Generally, this aligns with the progression of neural degeneration in AD, in which temporal regions are affected already at early stages [16, 55–57]. Analysis within the treatment groups suggest that these effects are mainly driven by the IG sample, but due to the small number of cases in either group, this interpretation requires independent confirmation.

When we assessed the effect of quality of life as the only neuropsychological endpoint that was significantly associated with IG versus CG intervention, we found an increase of quality of life to be associated with an increase of connectivity in the precuneus and the middle temporal lobe, but only in the IG. This was a *post hoc* comparison, where the independent variable was determined from the most significant behavioral effects. Therefore, we can only speculate on the meaning of such effect. There was a decrease of activity in the temporal lobe from BL to FU in the whole group. Thus the increase of quality of life, which only occurred in the IG group, might facilitate the compensating effects of cognitive rehabilitation on the temporal lobe.

In addition, one needs to consider the influence of medication on the outcome of behavioral and functional connectivity values, especially since the two groups differed slightly with regard to antidementive medication. We attempted to limit this effect, ensuring stable doses in each patient three months prior and during the intervention. Furthermore, we cannot rule out an effect of head motion, since the whole sample consisted of patients with AD. Nevertheless, maximum head motion correction revealed that none of the subjects exceeded 1.5 mm. Only two subjects showed minimal head motion at baseline, one subject from the control group showed 1 mm, and another subject from the control group 0.5 mm. Thus, we expect only minimal interference from head motion.

The main limitation of our study constitutes the small sample size and therefore, all our results need replication in larger studies.

Conclusions

In conclusion, our results suggest that the analysis of functional connectivity provides valuable insights into the effects of CR on the brain that are worth to be further investigated, i.e., the role of the precuneus in compensatory processes and the function of the cerebellum within the DMN. It is important to further investigate why different concepts of treatment may have different effects on resting-state networks in order to better target vulnerable and compensatory cortical networks, to slow down progression of the disease and to enhance cognitive resources.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Early Changes in Alpha Band Power and DMN BOLD Activity in Alzheimer's Disease: A Simultaneous Resting State EEG-fMRI Study

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Simultaneous resting state functional magnetic resonance imaging (rsfMRI)–resting state electroencephalography (rsEEG) studies in healthy adults showed robust positive associations of signal power in the alpha band with BOLD signal in the thalamus, and more heterogeneous associations in cortical default mode network (DMN) regions. Negative associations were found in occipital regions. In Alzheimer's disease (AD), rsfMRI studies revealed a disruption of the DMN, while rsEEG studies consistently reported a reduced power within the alpha band. The present study is the first to employ simultaneous rsfMRI-rsEEG in an AD sample, investigating the association of alpha band power and BOLD signal, compared to healthy controls (HC). We hypothesized to find reduced positive associations in DMN regions and reduced negative associations in occipital regions in the AD group. Simultaneous resting state fMRI–EEG was recorded in 14 patients with mild AD and 14 HC, matched for age and gender. Power within the EEG alpha band (8–12 Hz, 8–10 Hz, and 10–12 Hz) was computed from occipital electrodes and served as regressor in voxel-wise linear regression analyses, to assess the association with the BOLD signal. Compared to HC, the AD group showed significantly decreased positive associations between BOLD signal and occipital alpha band power in clusters in the superior, middle and inferior frontal cortex, inferior temporal lobe and thalamus ($p < 0.01$, uncorr., cluster size ≥ 50 voxels). This group effect was more pronounced in the upper alpha sub-band, compared to the lower alpha sub-band. Notably, we observed a high inter-individual heterogeneity. Negative associations were only reduced in the lower alpha range in the hippocampus, putamen and cerebellum. The present study gives first insights into the relationship of resting-state EEG and fMRI characteristics in an AD sample. The results suggest that positive associations between alpha band power and BOLD signal in numerous regions, including DMN regions, are diminished in AD.

Keywords: Alzheimer's disease, alpha rhythm, electroencephalography, functional magnetic resonance imaging, default mode network

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INTRODUCTION

In Alzheimer's disease (AD), resting state functional magnetic resonance imaging (rsfMRI), and resting state electroencephalography (rsEEG) have only been used separately to measure pathological changes. RsfMRI studies showed decreased activity (Greicius et al., 2004; Zhu et al., 2013; Li et al., 2015) and disrupted functional connectivity (Greicius et al., 2004; Zhang et al., 2009, 2010; Agosta et al., 2012; Koch et al., 2012; Weiler et al., 2014; Xia et al., 2014) in the default mode network (DMN) in AD. The DMN includes the anterior and posterior cingulate cortex, precuneus, medial prefrontal cortex, inferior parietal cortex, and hippocampal formation (Shulman et al., 1997; Raichle et al., 2001; Greicius et al., 2003; Buckner et al., 2008). Functionally, it has been associated with episodic memory (Mazoyer et al., 2001; Buckner et al., 2008; Weiler et al., 2014) and self-referential thinking (Raichle et al., 2001; Greicius et al., 2004; Buckner et al., 2008; Knyazev, 2013). Furthermore, rsEEG analyses showed reduced power within the alpha band (8–12 Hz) at early AD stages, as well as a slowing of the alpha rhythm and increased presence of lower frequency bands (Brenner et al., 1986; Dierks et al., 1993; Huang et al., 2000; Jeong, 2004). The alpha band is the dominant rhythm in healthy adults during a state of relaxed wakefulness, keeping the eyes closed (Berger, 1929; Zschocke and Hansen, 2012; Hinrichs, 2015). It originates from thalamo-cortical neurons projecting to the occipital cortex (Lorincz et al., 2009; Hughes et al., 2011; Zschocke and Hansen, 2012; Babiloni et al., 2015) – a projection pathway that may be disrupted in AD, as shown previously in studies using a computational model (Bhattacharya et al., 2011) and fMRI functional connectivity (Zhou et al., 2013). Functionally, alpha band power was shown to correlate positively with internal mental processes (Knyazev et al., 2011). Moreover, subdivisions of the alpha band may be related to different cognitive functions: the lower alpha band (8–10 Hz) may be associated with attention, while the upper alpha band (10–12 Hz) may be associated with memory processes (Klimesch, 1999). In addition, alpha band power has been suggested to play a role in an inhibitory gating mechanism of the visual system, suppressing unattended visual information (Berger, 1929; Palva and Palva, 2007; Tuladhar et al., 2007; Zumer et al., 2014). Power within the alpha band has been shown to correlate negatively with hemodynamic activity in the occipital cortex (Goldman et al., 2002; Moosmann et al., 2003; Gonçalves et al., 2006; Mantini et al., 2007; Scheeringa et al., 2012).

In order to assess the temporal association within subjects, the two modalities need to be measured simultaneously. The simultaneous rsfMRI-rsEEG measurement allows investigating the correlation of the BOLD signal fluctuation (as measured with rsfMRI) with the power fluctuation in specific frequency bands (as measured with rsEEG) over time. This method has previously been applied in young healthy subjects, correlating power fluctuations within the alpha band with BOLD signal fluctuations within each voxel. Most of these studies found that alpha band power fluctuation correlated positively with BOLD signal fluctuations in the thalamus (Goldman et al., 2002; Moosmann et al., 2003; Gonçalves et al., 2006) and in cortical DMN regions (Mantini et al., 2007; Jann et al., 2009, 2010; Scheeringa et al., 2012). On the other hand, some studies reported only weak or no positive associations (Laufs et al., 2003a; Gonçalves et al., 2006; Mo et al., 2013). Negative associations were found between alpha band power fluctuation and BOLD signal fluctuation in occipital, parietal, and frontal cortical regions in young HC subjects (Goldman et al., 2002; Laufs et al., 2003a, 2006; Moosmann et al., 2003; Gonçalves et al., 2006; Mantini et al., 2007; Scheeringa et al., 2012).

The present study is the first to employ simultaneous fMRI-EEG measurement in AD patients. Its aim was to explore its feasibility and to investigate the relationship of alpha band power fluctuation and BOLD signal fluctuation in AD patients compared to HC subjects. As previous research showed alpha band power to correlate significantly with gray matter volume in AD (Babiloni et al., 2009, 2013, 2015), we additionally controlled for volume of the hippocampus, which is affected early in the disease (Devanand et al., 2007; den Heijer et al., 2010; Frisoni et al., 2010; Jack et al., 2011). We hypothesized to find positive associations between occipital alpha band power fluctuation and BOLD signal fluctuation in regions of the DMN in both groups (AD and HC), with a reduced association in the AD group. Secondly, we hypothesized to find positive associations of alpha band power fluctuation and BOLD signal fluctuation in the thalamus in both groups, but a weaker association in AD. Finally, we expected to find negative associations with BOLD signal fluctuation in the occipital cortex, with reduced associations in the AD group (Moretti, 2004).

MATERIALS AND METHODS

Participants

The groups consisted of $n = 14$ individuals each, matched for age and gender (see **Table 1** for demographic and clinical characteristics). Initially, $n = 18$ patients with mild AD and $n = 17$ elderly healthy control (HC) subjects participated in the study, of which one patient aborted the scan session, and three patients were excluded due to radiological abnormalities. Three female participants in the HC group were randomized out, in order to match the groups for gender. Patients were recruited via the memory clinic at the University Medicine Rostock (UMR); HC subjects were recruited via the database of the UMR, containing healthy subjects who were originally recruited via advertisement. HC were required to score within one standard deviation on all subscales of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (Morris et al., 1989). Patients were clinically diagnosed with probable AD dementia according to the NINCDS-ADRDA and NIA-AA criteria (McKhann, 1984; McKhann et al., 2011). All subjects underwent general medical, neurological and psychiatric assessment. Neuropsychological assessment was conducted using the CERAD battery. Laboratory analyses and APOE genotype sequencing were carried out. Subjects exhibited no neurological or radiological abnormalities (e.g., normal pressure hydrocephalus or extensive microinfarcts), and no

psychiatric diseases. AD patients showed no signs of dementia not due to AD (e.g., vascular dementia). The study was approved by the local ethics committee of the University Rostock. All participants gave written informed consent, and all procedures were carried out in accordance with the Helsinki declaration.

Data Acquisition

Electroencephalography and fMRI data were recorded simultaneously during 7.5 min of resting state (eyes-closed). For the EEG recording, MRI-compatible measurement devices (Brain Products, Gilching, Germany) and the software Brain Vision Recorder[1] were used. EEG was recorded at 32 electrodes that were positioned according to the international 10-20-system (Jasper, 1958). The reference electrode was located between Fz and Cz, the ground electrode at AFz. Impedances of the electrodes of interest (O1, O2, and Oz) were kept below 8 kΩ, except for one AD patient (18 kΩ). An additional ECG channel was attached to detect cardio-ballistic artifacts. EEG data were sampled at 5 kHz. The EEG amplifier sampling interval was phase-synchronized to the fMRI main frequency via the Syncbox (Brain Products, Gilching, Germany) in order to preclude EEG-fMRI-sampling-jitter artifacts. The EEG hardware (i.e., amplifier and powerpack) was placed at the head end of the scanner tube and weighted with sand bags to prevent hardware motion.

Functional magnetic resonance imaging images were acquired using a 3-Tesla Siemens Magnetom scanner with a T2-weighted echo-planar imaging sequence (TR: 2.6 s, TE: 30 ms, FOV: 224 mm, thickness: 3.5 mm, number of slices: 180). The anatomical images were recorded using a T1-weighted MPRAGE sequence (TR: 2.5 s, TE: 4.37 ms, FOV 256 mm, thickness: 1 mm, number of slices: 192). Foam wedges were used to stabilize the head. Subjects were instructed to stay awake, keeping their eyes closed. The EEG signal was visually controlled for signs of sleep (offline).

Data Preprocessing

EEG Data

Data were preprocessed using Brain Vision Analyzer software (Version 2.0, Brain Products, Gilching, Germany). First, data were downsampled to 250 Hz. Imaging and ECG pulse artifacts were eliminated using the average artifact subtraction method described by Allen et al. (1998, 2000), which is included in the Brain Vision Analyzer software. Briefly, the imaging artifacts were automatically marked based on recurring patterns, the thus-defined intervals were averaged and their means subtracted from each interval. ECG pulse artifacts were removed by constructing an average ECG artifact template and subtracting it from the EEG data. Data were high-pass (0.5 Hz) and low-pass (70 Hz) filtered. Additionally, a notch filter was applied at 50 Hz. Using Independence Component Analysis (ICA), artifacts caused by eye movement, temporal electrode noise and residual pulse artifacts were removed. In case the electrode noise could not be eliminated by removing two independent components, the disturbed channel was removed and interpolated by topographical triangulation (occipital channels were not affected by this). After ICA, the data were again visually inspected for residual artifacts. No sleep patterns (i.e., K-complexes or sleep spindles) were present. EEG data from the AD group showed more artifacts such as eye movement and muscle activation, especially during the second half of the scan time, possibly constituting a sign of growing unrest. Two AD subjects showed a shift in frequency from alpha to theta over time. These artifacts were removed. The EEG signal was re-referenced to a common reference, obtained by averaging across all channels.

The electrodes O1, O2, and Oz were chosen as electrodes of interest, since alpha activity is best expressed at occipital electrodes (Moosmann et al., 2003; Laufs et al., 2003a; Mo et al., 2013). The arithmetic mean of electrophysiological activity from O1, O2, and Oz was calculated. Using complex demodulation, the EEG time courses of power within the total (8–12 Hz), lower (8–10 Hz), and upper (10–12 Hz) alpha band were extracted for each individual and exported to MATLAB (Mathworks, Inc., Sherborn, MA, United States) for the creation of statistical model regressors.

MRI Data

Functional magnetic resonance imaging data preprocessing was performed using SPM8[2] implemented in Matlab 7 (Mathworks, Natick) and the VBM8 toolbox (Version 414[3]). The first six volumes were removed to eliminate saturation effects. Slices were referenced to the temporally middle slice. After realignment of the functional images, the anatomical images were coregistered to the realigned mean functional image. The structural T1-weighted MPRAGE images were segmented into gray matter, white matter and cerebrospinal fluid compartments and warped to standard MNI space, using the default MNI standard template and the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) method (Ashburner, 2007) implemented in VBM8. The resulting deformation fields were used to warp the functional images to standard space. Spatial smoothing of the normalized functional images was performed with a Gaussian Kernel of 8 mm full-width half-maximum (FWHM). In order to reduce slow drift artifacts, a high-pass filter with a cut-off period of 128 s was applied to the voxel time

[1] www.brainproducts.com

TABLE 1 | Demographic and clinical characteristics of the study subjects; mean ± SD (range).

	AD ($n = 14$)	HC ($n = 14$)	p^*
Age	75.3 ± 5.7 (64–82)	73.4 ± 3.1 (68–79)	0.276
Gender (male/female)	10/4	10/4	n. a.
Education (years)	14.4 ± 2.7 (8–17)	13.6 ± 2.8 (11–20)	0.417
MMSE score	24.6 ± 3.1 (17–28)	28.7 ± 0.8 (27–30)	<0.001
APOE status (E2/E3; E2/E4; E3/E3; E3/E4; E4/E4)	0; 2; 4; 6; 1	2; 1; 7; 2; 1	n. a.

*Independent samples t-test, 2-sided.

[2] http://www.fil.ion.ucl.ac.uk/spm/

[3] http://dbm.neuro.uni-jena.de/vbm8/

courses. From the segmented gray matter images, gray matter volume of the left and right hippocampus was calculated for each subject, using binarized inclusive masks that had been created for the IXI template in MNI space according to the international harmonization protocol for hippocampus segmentation (Grothe et al., 2012; Boccardi et al., 2015). The volume of the left and right hippocampus was pooled and normalized by dividing it by the total intracranial volume.

A regressor containing one-second intervals of artifact-free, averaged spectral power of the pooled occipital electrodes and an additional on/off regressor of no interest (containing timing information of artifacts longer than 1 s) were created. Separate regressors were built for power within the total alpha (8–12 Hz), lower alpha (8–10 Hz) and upper alpha band (10–12 Hz). The regressors of interest were convolved with an *a priori* defined hemodynamic response function (HRF) (Cohen, 1997) within the SPM first-level (single subject) processing pipeline (for a diagram see Supplementary Figure 1).

Statistical Analysis

For comparing relative alpha band power at the pooled occipital channels (O1, O2, and Oz) between groups, Fast Fourier transformation (FFT) across 1-s-segments was used. Two-sided independent samples *t*-tests were used to compare relative alpha power and normalized hippocampal gray matter volume between groups. Separate general linear models were specified for total alpha, lower alpha and upper alpha, respectively, using SPM8 (Friston et al., 2007). The models included a regressor variable containing the power information for the respective HRF-convolved alpha band, a mean term regressor, a covariate regressor containing the artifact information, and the covariates age, gender, and years of education. For the first-level analysis, positive and negative t-contrasts were specified for each subject, testing for the effects of the alpha band power regressor, controlled for the artifact regressor. This resulted in individual statistical parametric maps of positive and of negative associations of the total, lower or upper alpha power fluctuation over time, respectively, with the BOLD fluctuation in each voxel of the brain. The resulting maps of EEG regressor weights were used for group comparisons in one- and two-sample *t*-tests. The one-sample *t*-tests were performed for the AD and HC group separately, testing for positive and negative associations of each alpha regressor weight across all subjects in the respective group. For the two-sample *t*-test, a contrast of HC > AD was defined for positive and negative associations, respectively. The second-level analyses were additionally controlled for the covariate regressor normalized hippocampal gray matter volume.

All statistical results were restricted to voxels within gray matter, by thresholding the default IXI template in VBM8 at $p < 0.3$ and using it as inclusive mask. Statistical significance levels were set at $p < 0.01$ (uncorrected for multiple comparisons). Only clusters with a voxel count ≥ 50 were considered. Resulting clusters were visually compared to a functional connectivity based DMN atlas (Shirer et al., 2012).

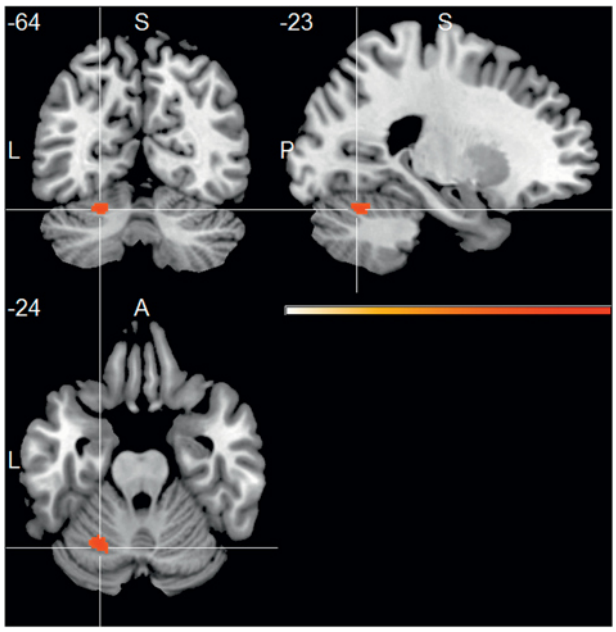

FIGURE 1 | Alzheimer's disease (AD) group effect, showing positive associations of total alpha band power fluctuation and BOLD signal ($p < 0.01$, uncorr., cluster threshold ≥ 50).

RESULTS

Alpha Power Fluctuations

The mean relative alpha band power was not significantly different between the groups (AD: 35.0 ± 17.7%; HC: 32.0 ± 21.6%, Supplementary Table 1). However, at visual inspection, a morphological difference in the form of dysmorphic alpha waves was observed in the AD group.

Association of Alpha Band Power and fMRI BOLD Dynamics

Positive Associations

At group level, the AD group showed positive associations of total alpha band power with BOLD fluctuation in the cerebellum (one sample *t*-test, $p < 0.01$, uncorr., **Figure 1** and Supplementary Table 2). Lower alpha band power correlated positively with clusters in the right inferior temporal lobe, right hippocampus, left putamen and cerebellum ($p < 0.01$, uncorr.) (Supplementary Table 2). In contrast, power within the upper alpha frequency showed no significant positive associations in any regions.

The HC group showed positive associations of total alpha band power with mainly frontal and temporal cortical regions, including superior, middle and inferior frontal cortex, temporal pole, parietal cortex, thalamus, putamen and cerebellum (one sample *t*-test, $p < 0.01$, uncorr., **Figure 2** and Supplementary Table 3). Within the lower alpha frequency, fewer associations were present, which were located mainly in frontal regions, left inferior temporal lobe, thalamus and cerebellum. Most associations were found within the upper frequency, located

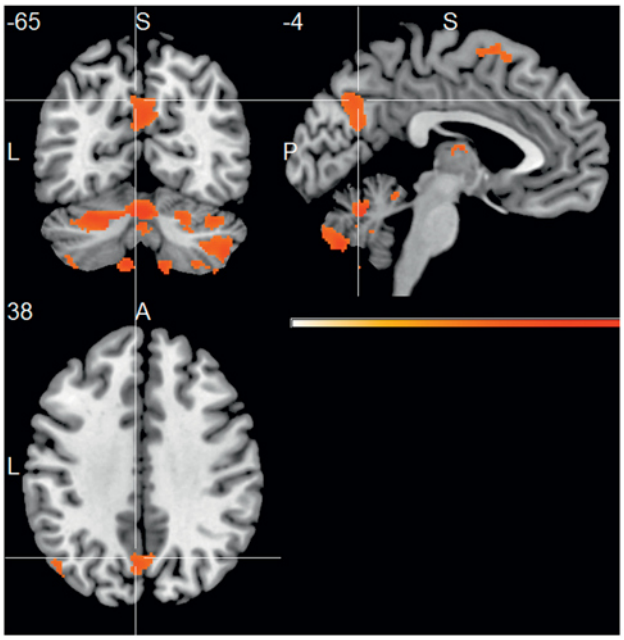

FIGURE 2 | Healthy controls (HC) group effect, showing positive associations of total alpha band power fluctuation and BOLD signal ($p < 0.01$, uncorr., cluster threshold ≥ 50).

mainly in the hippocampus, thalamus, occipital, temporal and frontal cortex, including anterior cingulate cortex and middle cingulate, putamen and caudate nucleus, as well as cerebellum (Supplementary Table 3).

Compared to the HC group, the AD group showed significantly decreased positive associations of total alpha band power with BOLD fluctuation in clusters in the frontal cortex (superior, middle, inferior, precentral gyrus, and anterior cingulate cortex), inferior temporal lobe and thalamus (two-samples t-test, $p < 0.01$, uncorr., **Figure 3** and Supplementary Table 4). Similar decreased associations were found for the upper alpha band power (superior frontal lobe, insula and parietal lobe) (**Figure 4** and Supplementary Table 4). Regarding the lower alpha band power, the AD group showed decreased positive associations with scattered clusters in the superior frontal lobe, compared to the HC group (Supplementary Table 4).

At the individual level, first-level analyses revealed positive associations of power within the total alpha band range with regions that belong to the DMN (Shirer et al., 2012) in $n = 6$ HC subjects and in $n = 3$ AD patients (**Table 2**). For an example, see Supplementary Figures 2, 3.

Normalized hippocampal gray matter volume was lower in the AD group, although not significantly (independent samples t-test; $T(26) = 1.735$, $p = 0.095$). Entering it as covariate regressor in the general linear models did not essentially change the results of the one- and two-sample t-tests (Supplementary Figures 4–6).

Negative Associations

At group level, the AD group showed negative associations of total band alpha power with clusters in the occipital, frontal and temporal cortex (one-sample t-test, $p < 0.01$, uncorr., Supplementary Table 5). In the upper alpha band, associations were only significant in the occipital cortex. Lower alpha band power showed no significant associations (Supplementary Table 5).

The HC group showed significant negative associations of total alpha band power with clusters in the precentral gyrus and superior temporal cortex (one-sample t-test, $p < 0.01$, uncorr., Supplementary Table 6). No suprathreshold clusters were found in the upper alpha band. Lower alpha band power showed pronounced negative associations with the frontal cortex, mainly in the precentral and paracentral gyrus, and with the parietal cortex, temporal and middle cingulate cortex (Supplementary Table 6).

Compared to the HC group, the AD group did not exhibit significantly reduced negative associations of total or upper alpha band power with BOLD signal fluctuation in any voxel clusters. Regarding the lower alpha band, significantly decreased negative associations were found in the hippocampus, putamen and cerebellum (two-sample t-test, $p < 0.01$, uncorr., Supplementary Table 7).

At the individual level, first-level analyses revealed negative associations of alpha band power with BOLD fluctuations in both anterior and posterior regions in $n = 5$ AD patients and $n = 7$ HC subjects, associations in mainly frontal regions in $n = 3$ AD patients and $n = 2$ HC subjects, and associations in mainly posterior regions in $n = 1$ HC subject.

DISCUSSION

The study successfully applied simultaneous fMRI-EEG to an AD sample for the first time and showed a reduced positive association between alpha band power and BOLD fluctuations in the AD patients, compared to the HC subjects. In the HC group, positive associations between alpha band power and BOLD fluctuations were observed in numerous regions, including DMN regions. Although present in all alpha sub-bands, they were especially evident in the upper alpha frequency band. The reduction of these positive associations in the AD patients might be due to altered functional interaction between the brain regions (Greicius et al., 2004; Zhang et al., 2009, 2010; Agosta et al., 2012; Weiler et al., 2014; Xia et al., 2014). The functional associations were not altered by the correction for hippocampal volume, indicating that they were not driven by atrophy.

Based on previous simultaneous fMRI-EEG studies with healthy participants, we hypothesized to find a positive association of alpha band power and BOLD signal fluctuation in the thalamus in HC subjects (Goldman et al., 2002; Moosmann et al., 2003; Gonçalves et al., 2006). In the light of the disrupted integrity of the thalamo-cortical system, we expected this association to be reduced in the AD patients (Bhattacharya et al., 2011; Zhou et al., 2013). In line with the hypothesis, these associations were present in the HC group and were decreased in the AD group. Additionally, in both groups, we found more positive associations of the upper alpha band

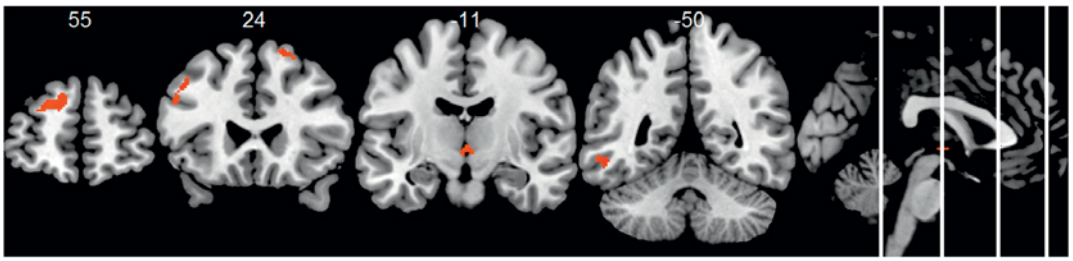

FIGURE 3 | Group comparison HC > AD of positive associations of total alpha band power fluctuation and BOLD signal ($p < 0.01$, uncorr., cluster threshold ≥ 50).

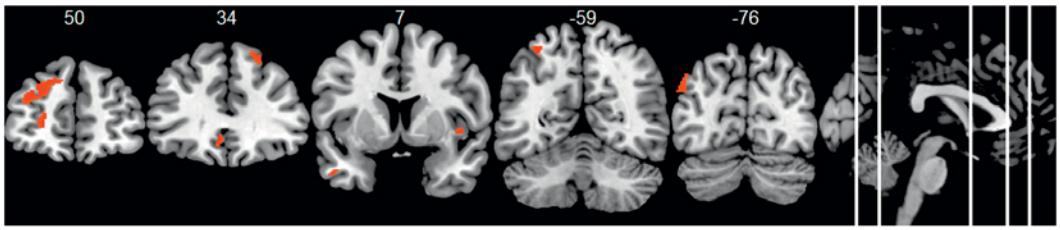

FIGURE 4 | Group comparison HC > AD of positive associations of upper alpha band power fluctuation and BOLD signal ($p < 0.01$, uncorr., cluster threshold ≥ 50).

power with the thalamus compared to the lower alpha band. This might indicate a frequency-specificity. Also, as thalamo-cortical activity underlies alpha generation and modulation (Bhattacharya et al., 2013), future functional connectivity studies might investigate whether decreased associations of alpha band power and thalamic BOLD fluctuations are related to the thalamo-cortical connectivity in AD (Zhou et al., 2013).

The third hypothesis included finding negative associations with BOLD signal fluctuation in the occipital cortex. Negative associations were found at group level in AD patients in the occipital cortex, as well as superior medial frontal cortex and temporal cortex. However, we did not find negative associations with the occipital cortex in HC subjects at group level. This is in contrast to a number of fMRI-EEG studies in young healthy subjects, showing negative associations of alpha band power with BOLD signal in the occipital cortex (Goldman et al., 2002; Moosmann et al., 2003; Gonçalves et al., 2006; Mantini et al., 2007; Scheeringa et al., 2012). In the light of the overall accepted theory that alpha band represents a hallmark of the resting state of the brain (e.g., Gonçalves et al., 2006), we would have expected it to correlate negatively with BOLD signaling in the respective region. Instead, we found negative associations at HC group level in frontal, temporal and parietal regions. Although unexpected, this result is in line with a few other studies that reported an absence of negative associations with BOLD signal in the occipital cortex (Laufs et al., 2003a,b; Jann et al., 2009).

Interestingly, positive as well as negative associations with the cerebellum were present in almost all subjects. The cerebellum has received little attention in previous fMRI-EEG research (Scheeringa et al., 2012). FMRI studies showed impaired functional connectivity of the cerebellum in AD (Zheng et al., 2017), and a sensitivity of the cortico-cerebellar coupling to amyloid-β load in HC (Steininger et al., 2014). It would be interesting for future research to investigate the association of alpha band power and the integrity of cortical-cerebellar functional processes during rest.

A general limitation of fMRI resting state measurement is its high variability over time (Cole et al., 2010; Chen et al., 2015). The instruction to keep the eyes closed and to stay awake leaves room for spontaneous cognitive processes with varying attentional states. Possibly, the activation of the DMN might have been more robust if a task-based study design had been used, for example involving tasks of self-referential thinking or autobiographical memory (Andreasen et al., 1995; Mitchell, 2006; Gobbini et al., 2007; Spreng and Grady, 2010; Knyazev et al., 2011; Fomina et al., 2015). However, to be able to draw inferences on a potential clinical use, a resting state paradigm was needed. Another limitation is the relatively liberal statistical threshold. As this was the first study to employ simultaneous rsfMRI-rsEEG in

TABLE 2 | First-level analyses: number of subjects (*n*) showing positive associations of alpha band power and BOLD signal fluctuations, significant at $p < 0.01$ (uncorr.).

	Default mode network*	Thalamus
AD		
Total alpha (8–12 Hz)	3	3
Lower alpha (8–10 Hz)	3	2
Upper alpha (10–12 Hz)	4	3
HC		
Total alpha (8–12 Hz)	6	5
Lower alpha (8–10 Hz)	4	3
Upper alpha (10–12 Hz)	7	5

**Encompassing three or more of the following regions: precuneus, PCC, ACC, medial prefrontal cortex, and inferior parietal lobe.*

AD patients, we aimed to assess the feasibility and to explore the associations in the whole brain.

We noted a high regional variability of both positive and negative associations between alpha band power fluctuation and BOLD signal between individual subjects, which has also been reported in previous studies (Goldman et al., 2002; Gonçalves et al., 2006; Laufs et al., 2006). Variability has been suggested to be partly caused by fluctuations in vigilance (Goldman et al., 2002; Laufs et al., 2006). Although our data were visually controlled for sleep, fluctuations in vigilance may have been present, particularly as an increase in artifacts in AD patients toward the end of the scan time was noted. The effect of vigilance on the association patterns of rsEEG and rsfMRI should be addressed in future research. Our results of high inter-individual heterogeneity, taken together with findings of high inter- and intra-individual variability observed in other resting state fMRI-EEG studies (Goldman et al., 2002; Laufs et al., 2003a, 2006; Moosmann et al., 2003; Gonçalves et al., 2006; Jann et al., 2009; Olbrich et al., 2009), also highlight the importance of future research with larger samples to be able to identify subgroups. Furthermore, our results support the necessity to differentiate the alpha band into sub-bands, as more HC subjects showed positive association patterns within the upper sub-band. This agrees with some other studies that investigated separate sub-bands (Laufs et al., 2006; Jann et al., 2009, 2010), linking sub-bands to different cognitive functions (e.g., Klimesch, 1999) and even indicating the possibility of predicting conversion from MCI to AD by calculating the ratio of power in alpha sub-bands (Moretti, 2015).

CONCLUSION

The present study showed diminished positive associations between alpha band power fluctuation and BOLD signal fluctuations in several brain regions in AD patients, compared to HC subjects. These regions included (but were not limited to) DMN and thalamic regions. This study demonstrates the feasibility of measuring simultaneous rsEEG and rsfMRI signal fluctuations in a clinical AD population. Further research is needed to corroborate and expand its results.

AUTHOR CONTRIBUTIONS

KB recruited participants, performed neuropsychological testing, acquired EEG and MRI data, performed preprocessing and analyses, interpreted the data, drafted and revised the manuscript. CF recruited participants, conducted physical examinations, acquired EEG and MRI data, performed preprocessing and analyses, interpreted the data, and drafted the manuscript. CBe performed preprocessing and statistical analyses, interpreted the data, and revised the manuscript. SO contributed to the data interpretation and was involved in drafting the manuscript. CBa contributed to the study design, provided intellectual content for data interpretation, and revised the manuscript. ST was involved in all stages of the study, establishing the study design, recruiting participants, performing physical examinations, and revising the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2017.00319/full#supplementary-material

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