Inauguraldissertation
zur Erlangung des akademischen Doktorgrades (Dr. phil.)
im Fach Psychologie
an der Fakultät für Verhaltens- und Empirische Kulturwissenschaften
der Ruprecht-Karls-Universität Heidelberg

Titel der publikationsbasierten Dissertation:

Herausforderungen des ‚Mild Cognitive Impairment'-Konzepts: Die Beeinträchtigung von Aktivitäten des täglichen Lebens und die Klassifikation von Subtypen

vorgelegt von
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Jahr der Einreichung
2016

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Danksagung

An erster Stelle möchte ich mich bei meinem Betreuer Herrn Prof. Dr. Frölich bedanken, der mir die vielen Facetten der MCI- und Demenzforschung aufzeigte und mir kontinuierlich wertvollen Input gab, um das Vorankommen der Doktorarbeit zu fördern. Zudem bahnte er internationale Kontakte zu renommierten Forscherpersönlichkeiten und ermöglichte mir auf diese Weise Zugang zu einem großen wissenschaftlichen Netzwerk.

Des Weiteren gilt mein Dank Herrn Prof. Dr. Wahl für sein konstruktives Feedback sowie die Übernahme des Zweitgutachtens.

Mein Promotionsvorhaben konnte nur durch die finanzielle Unterstützung der Robert Bosch Stiftung umgesetzt werden. Neben dem monatlichen Stipendium konnte ich durch die großzügige Reisekostenpauschale nationale und internationale Kongresse besuchen, dort meine Forschungsergebnisse präsentieren und gewinnbringende Kontakte zu anderen Wissenschaftlern knüpfen.

Dem Netzwerk Alternsforschung (NAR) in Heidelberg gilt mein Dank für das Bereitstellen einer hervorragenden Forschungsinfrastruktur sowie das stets offene Ohr bei Anliegen aller Art.

Durch meine klinische Tätigkeit in der Mannheimer Gedächtnisambulanz konnte ich mein theoretisches Wissen tagtäglich um praktische Erfahrungen mit Patienten und deren Angehörigen erweitern. Mein herzlicher Dank gilt an dieser Stelle allen Patienten und Angehörigen, die sich bereit erklärten, an meinem Forschungsprojekt mitzuwirken.

Außerdem danke ich meinen Kolleginnen in der Gedächtnisambulanz für motivierende Gespräche und viele entspannte Mittagspausen, die mir halfen, den Kopf wieder freizubekommen.

Meinen Freunden danke ich für ihr Verständnis für die eine oder andere „promotionsbedingte“ Absage.

Meinen Eltern und meiner Schwester danke ich für ihre Unterstützung in allen Lebenslagen.

Schlussendlich möchte ich mich noch von ganzem Herzen bei Thomas bedanken, der während jeder Phase der Promotion für mich da war und durch gelegentlichen wohldosierten Druck sehr zur Vollendung des Projekts beigetragen hat – ab jetzt gibt es wieder freie Wochenenden, versprochen!

Vorbemerkung

Die vorliegende publikationsbasierte Dissertation ist an der Schnittstelle zwischen Psychologie und Psychiatrie angesiedelt. Als empirische Wissenschaft beschäftigt sich die Psychologie mit der Beschreibung, Erklärung und Entwicklung menschlichen Verhaltens. Die Psychiatrie als Teilgebiet der Medizin konzentriert sich auf die Diagnostik und Therapie psychischer Erkrankungen.

Der interdisziplinäre Charakter der Arbeit hat seinen Ursprung im Graduiertenkolleg Demenz, dessen Zielsetzung es war, das Thema Demenz aus unterschiedlichen wissenschaftlichen Perspektiven zu beleuchten, um dessen Komplexität gerecht zu werden. Auch in der Zusammensetzung der Autorenteams, welche unter anderem aus Psychologen, Psychiatern, Neurologen (und in einer Arbeit sogar einem Informatiker) bestehen, spiegelt sich der interdisziplinäre Ansatz.

Liste der wissenschaftlichen Veröffentlichungen zur publikationsbasierten Dissertation

I. Schrift

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., Dubois, B., Eriksdotter, M., Ewers, M., Graessel, E., Kramberger, M. G., Law, E., Mecocci, P., Molinuevo, J. L., Nygård, L., Olde-Rikkert, M. G. M., Orgogozo, J. M., Pasquier, F., Peres, K., Salmon, E., Sikkes, S. A. M., Sobow, T., Spiegel, R., Tsolaki, M., Winblad, B., & Frölich, L. (2015). Mild Cognitive Impairment and Deficits in Instrumental Activities of Daily Living - a Systematic Review. *Alzheimer's Research & Therapy, 7*, 17.

II. Schrift

Jekel, K., Damian, M., Storf, H., Hausner, L., & Frölich, L. (in press). Development of a Proxy-Free Objective Assessment Tool of IADL in MCI Using Smart Home Technologies. *Journal of Alzheimer's Disease.*

III. Schrift

Damian, M., Hausner, L., Jekel, K., Richter, M., Frölich, L., Almkvist, O., Boada, M., Bullock, R., De Deyn, P. P., Frisoni, G. B., Hampel, H., Jones, R. W., Kehoe, P., Lenoir, H., Minthon, L., Olde Rikkert, M. G., Rodriguez, G., Scheltens, P., Soininen, H., Spiru, L., Touchon, J., Tsolaki, M., Vellas, B., Verhey, F. R., Winblad, B., Wahlund, L. O., Wilcock, G., & Visser, P.J. (2013). Single-Domain Amnestic Mild Cognitive Impairment Identified by Cluster Analysis Predicts Alzheimer's Disease in the European Prospective DESCRIPA Study. *Dementia & Geriatric Cognitive Disorders, 36,* 1-19.

Abbildungsverzeichnis

Abkürzungsverzeichnis

AD	Alzheimer-Demenz
ADL	Aktivitäten des täglichen Lebens (Activities of Daily Living)
BADL	Basale Aktivitäten des täglichen Lebens
DLB	Lewy-Body-Demenz
DSM-IV	Diagnostisches und statistisches Manual psychischer Störungen
FTD	Fronto-Temporale Demenz
IADL	Instrumentelle Aktivitäten des täglichen Lebens
ICD-10	Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme
MCI	Mild Cognitive Impairment
MMST	Mini Mental Status Test
SD	Standardabweichung
VaD	Vaskuläre Demenz

1. Einleitung

In der Allgemeinbevölkerung herrscht überwiegend die Meinung, dass kognitive Defizite eine normale Begleiterscheinung des Älterwerdens sind. Es ist richtig, dass mit steigendem Alter beispielsweise die Informationsverarbeitungsgeschwindigkeit oder auch die Kapazität des Kurzzeitgedächtnisses abnimmt. Gehen solche Defizite jedoch über einen alterskorrigierten Normbereich hinaus, können sie auf eine beginnende demenzielle Erkrankung hindeuten. Demenzen zählen zu den häufigsten Erkrankungen im Alter. Aufgrund des demografischen Wandels ist mit einer stetigen Zunahme dieser altersassoziierten Erkrankungen zu rechnen. Dies bedeutet – neben der psychischen Belastung von Betroffenen und Angehörigen – einen erheblichen finanziellen Aufwand für die Versorgung von demenziell Erkrankten. In diesem Zusammenhang kommt der Früherkennung von Demenzen eine wesentliche Bedeutung zu. Es ist anzunehmen, dass einer manifesten Demenz ein bereits Jahre zuvor einsetzender pathologischer Abbauprozess vorausgeht. Diesen Prozess rechtzeitig zu erkennen, ist essentiell für den Einsatz geeigneter Präventions- und Interventionsmaßnahmen. Dem Gedanken der Früherkennung folgend, wurden diverse Konzepte geprägt, die das Stadium zwischen normalem Altern und einer demenziellen Erkrankung genauer beschreiben. Dadurch soll eine Gruppe von Personen identifiziert werden, die – im Vergleich zur Allgemeinbevölkerung – ein erhöhtes Risiko haben, eine Demenz zu entwickeln.

Eines der verbreitetsten Konzepte ist das des *Mild Cognitive Impairment* (MCI), welches kognitive Defizite beschreibt, die über die Altersnorm hinausgehen, aber noch keine Demenzdiagnose rechtfertigen. Seit der Einführung des Konzepts wird es kontrovers diskutiert: unter anderem herrscht Uneinigkeit darüber, wie stark eine Person mit MCI in ihren *instrumentellen Aktivitäten des täglichen Lebens* (IADL) eingeschränkt ist. Ein weiterer Kritikpunkt ist das Fehlen von reliablen, speziell für MCI-Populationen entwickelten IADL-Messinstrumenten. Als dritter Kritikpunkt ist die

prognostische Validität des MCI-Konzepts zu nennen, da die Konversionsraten zur Demenz von Studie zu Studie teilweise beträchtlich schwanken.

Die vorliegende Arbeit soll Ansätze zur Schärfung des MCI-Konzepts generieren, um langfristig eine präzisere Früherkennung demenzieller Erkrankungen zu erreichen. In der ersten Studie wird untersucht, welche IADL schon im MCI-Stadium beeinträchtigt sind. Basierend auf Studie 1 erfolgt in der zweiten Studie die Entwicklung eines neuen IADL-Messinstruments sowie dessen praktische Erprobung. Schließlich soll in Studie 3 ein neuer Ansatz zur MCI-Subtypklassifikation vorgestellt werden, welcher die prognostische Validität des MCI-Konzepts möglicherweise optimieren könnte.

Insgesamt möchte die Arbeit einen Grundstein für eine verbesserte Definition des MCI-Konzepts legen sowie Handlungsempfehlungen für die klinische Praxis ableiten.

2. Theoretischer Hintergrund

2.1 Das „normale“ kognitive Altern

In der psychologischen Alternsforschung wird zwischen einem „normalen“, einem krankhaften und einem optimalen Alternsprozess unterschieden (Gerok & Brandstädter, 1992). Normales Altern zeichnet sich definitionsgemäß durch ein Erreichen der durchschnittlichen Lebensspanne bei nur altersbedingt üblichen Funktionseinbußen aus. Im Gegensatz dazu beschreibt der Begriff des krankhaften Alterns das Auftreten von Krankheiten und erheblichen Funktionseinschränkungen, die zu einer Verkürzung der Lebensdauer führen. Das optimale Altern ist gekennzeichnet durch günstige Voraussetzungen, welche zu einer Verlängerung der Lebensspanne und einer besseren Funktionsfähigkeit gegenüber dem Durchschnitt einer vergleichbaren Population führen.

Nun stellt sich die Frage, wo die Grenze zwischen altersüblichen und krankhaften Einbußen zu ziehen ist. Normales Altern wird oftmals durch statistische Normwerte definiert, welche an den für die Alterskohorte typischen Verläufen festgemacht werden. Abweichungen von dieser Norm werden dementsprechend als krankhaft bewertet. Erschwert wird die Festlegung einer Norm dadurch, dass der Alternsprozess als solcher sehr vielfältig ist und interindividuell unterschiedlich verläuft. So beschreibt Paul Baltes Altern als einen Prozess, der nicht sequentiell und unidirektional erfolgt, sondern durch ein Wechselspiel zwischen dem Verlust und Aufbau von Kompetenzen gekennzeichnet ist (Multidirektionalität). Zudem sind nicht alle Funktionen gleichermaßen von einem altersbedingten Abbau betroffen (Multidimensionalität) (Baltes, 1987).

Trotz des interindividuell heterogenen Alternsprozesses gibt es zahlreiche richtungsweisende Befunde zum Verlauf der kognitiven Leistungsfähigkeit über die Lebensspanne. Eine Auswahl an Forschungsergebnissen zu altersnormalen kognitiven Veränderungen wird im Folgenden dargestellt.

Cattell und Horn teilten die kognitive Leistungsfähigkeit in eine fluide und eine kristalline Komponente auf (Horn & Catell, 1967; Cattell, 1971). Die fluide Intelligenz, welche unter anderem die Merkfähigkeit oder Verarbeitungsgeschwindigkeit umfasst, erreicht im dritten Lebensjahrzehnt ihren Höhepunkt und nimmt dann mit steigendem Alter kontinuierlich ab. Demgegenüber steht die kristalline Intelligenz (allgemeines Wissen, Wortschatz, Lernstrategien), welche mit zunehmendem Alter weitgehend stabil bleibt bzw. sogar leicht zunimmt (Gerstorf, Ram, Lindenberger, & Smith, 2013; Salthouse, 2010a).

Genauere Analysen der verschiedenen kognitiven Domänen zeigen, dass das episodische Gedächtnis (Enkodierung, Speicherung und Abruf von Episoden und Ereignissen aus dem eigenen Leben) mit zunehmendem Alter schlechter wird. Das semantische Gedächtnis (Wortschatz, Faktenwissen) hingegen weist erst im sehr hohen Alter Defizite auf (Ronnlund, Nyberg, Bäckman, & Nilsson, 2005). Die Geschwindigkeit, mit der Informationen verarbeitet werden, zeigt ebenfalls von der dritten Lebensdekade an eine kontinuierliche Abnahme (Salthouse, 2010b). Bezüglich der Exekutivfunktionen finden sich Alterseffekte für das simultane Bearbeiten verschiedener Aufgaben (Lezak, 2012), die Unterdrückung von automatischen Handlungstendenzen (Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000) oder das induktive Denken (Singh-Manoux et al., 2012). Wie oben bereits erwähnt, liegt die Schwierigkeit darin, diese normalen Alternsprozesse sicher von krankhaften Verläufen abzugrenzen.

Im Folgenden wird als ausgeprägte Variante eines krankhaften Alternsprozesses zunächst das Erkrankungsbild der Demenz beschrieben.

2.2 Definition und Epidemiologie der Demenz

Demenzen gehören zu den häufigsten altersassoziierten Erkrankungen. Laut ICD-10 treten Demenzen als Folge einer chronischen oder fortschreitenden Krankheit des

Gehirns auf (Weltgesundheitsorganisation, 2006). Sie sind charakterisiert durch Störungen des Gedächtnisses, des Denkvermögens, der Orientierung, der Auffassung, der Lernfähigkeit, der Sprache sowie des Urteilsvermögens. Neben den kognitiven Defiziten treten Veränderungen in der emotionalen Kontrolle, im Sozialverhalten und bezüglich der Motivation auf. Nach ICD-10 müssen die kognitiven Beeinträchtigungen seit mindestens sechs Monaten bestehen und so ausgeprägt sein, dass sie die Alltagsbewältigung massiv behindern. Mit einem Anteil von ungefähr 60% ist die Alzheimer-Krankheit die häufigste Demenzform, gefolgt von vaskulären Demenzen mit 15 bis 20% (Zaudig & Berberich, 2001).

Schätzungen zufolge leiden weltweit 35 Millionen Menschen an einer Demenzerkrankung (Brodaty et al., 2011). Mit zunehmendem Alter steigt die Prävalenz der Demenz exponentiell an: bei den 65- bis 69-Jährigen ist etwa 1% betroffen, bei den über 90-Jährigen sind es schon mehr als 30% (Ziegler & Doblhammer, 2009). Generell lässt sich sagen, dass sich die Prävalenzraten im 5-Jahres-Abstand verdoppeln. Aufgrund der steigenden Lebenserwartung wird geschätzt, dass im Jahr 2030 etwa 66 Millionen Menschen weltweit von einer Demenz betroffen sein könnten, im Jahr 2050 bereits 115 Millionen (Prince et al., 2013). In Deutschland sind ungefähr 1,2 Millionen Menschen an einer Demenz erkrankt, das entspricht etwa 8% aller über 65-Jährigen (Eschweiler, Leyhe, Kloppel, & Hull, 2010). Bleiben Fortschritte in Prävention und Therapie aus, könnte sich die Anzahl Demenzkranker in Deutschland bis zum Jahr 2050 auf etwa drei Millionen erhöhen (Bickel, 2010).

Für das Jahr 2002 bezifferte das statistische Bundesamt die jährlichen Krankheitskosten der Demenz auf 5,6 Milliarden Euro, wobei den Großteil stationäre und teilstationäre Pflegeleistungen ausmachten (Statistisches Bundesamt, 2004). Die durchschnittlichen Kosten hängen vom Schweregrad der Demenzerkrankung und dem damit zusammenhängenden Pflegebedarf ab: bei Personen mit einer leichten Demenz liegen die Kosten im Durchschnitt bei 15000 Euro jährlich, im schweren

Demenzstadium bei 42000 Euro (Leicht et al., 2011). Durch diese Zahlen wird deutlich, dass Demenzen – neben der psychischen Belastung von Betroffenen und deren Angehörigen – erhebliche sozioökonomische Konsequenzen mit sich bringen. Folglich besteht ein großer Bedarf hinsichtlich verbesserter Früherkennung sowie geeigneter Präventions- und Therapiemaßnahmen.

Einer manifesten Demenz geht ein schleichender pathologischer Abbauprozess voraus, der schon Jahre vorher beginnt. In dieser Phase treten Beeinträchtigungen des episodischen Gedächtnisses, der Exekutivfunktionen und der Wahrnehmungsgeschwindigkeit auf (Bäckman, Jones, Berger, Laukka, & Small, 2005). Um Personen zu identifizieren, die von diesem Abbauprozess betroffen sind – ohne dass die kognitiven Defizite bereits so schwer ausgeprägt sind, dass eine massive Störung der Alltagskompetenz evident ist – wurden neuropsychologische Konzepte geschaffen, die ein Stadium zwischen normalem Altern und einer Demenzerkrankung beschreiben. Dies soll eine Früherkennung demenzieller Erkrankungen ermöglichen. Das am weitesten verbreitete Konzept ist aktuell das des Mild Cognitive Impairment.

2.3 Mild Cognitive Impairment (MCI)

2.3.1 Definition und Epidemiologie

Als Mild Cognitive Impairment wird ein Stadium zwischen normalem Altern und einer demenziellen Erkrankung bezeichnet. Es beschreibt kognitive Defizite, die nicht altersgemäß sind, aber auch nicht die Diagnose einer Demenz rechtfertigen. Auf Petersen et al. geht die ursprüngliche Definition des MCI anhand folgender Kriterien zurück: 1) subjektive Gedächtnisbeeinträchtigung, 2) unterdurchschnittliche Gedächtnisleistung, 3) durchschnittliche Leistungen in anderen kognitiven Funktionen, 4) intakte ADL und 5) nicht dement (Petersen et al., 1999). Durch diese Kriterien sollte die klinische Charakterisierung einer Personengruppe mit hohem Demenzrisiko

ermöglicht werden (Artero, Petersen, Touchon, & Ritchie, 2006). In nachfolgenden Studien zeigten sich jedoch eine schlechte prädiktive Validität der Kriterien in Bezug auf die Demenzkonversion, eine schlechte Anwendbarkeit in der klinischen Praxis (Ritchie, Artero, & Touchon, 2001; Ritchie & Touchon, 2000) sowie Zweifel bezüglich der „intakten ADL“ (Nygård, 2003). Infolgedessen erarbeitete eine internationale Expertengruppe um Winblad und Petersen revidierte MCI-Kriterien: 1) nicht normal, nicht dement, 2) Verschlechterung der Kognition (a. Patient und/oder Bezugsperson berichten über Verschlechterung *plus* Beeinträchtigung in objektiven Tests *und/oder* b. Evidenz einer Verschlechterung in objektiven kognitiven Tests), 3) erhaltene basale ADL/minimale Beeinträchtigung instrumenteller ADL (Winblad et al., 2004). Mit dieser Revision fand das MCI-Konzept auch Anwendung auf Personen mit Defiziten in nicht-mnestischen Funktionen und subtilen Beeinträchtigungen der IADL.

Aufgrund mangelnder Vorgaben zur Operationalisierung der Kriterien schwanken die Angaben zur Prävalenz des MCI. Eine populationsbasierte Studie der Mayo-Klinik mit 3000 Probanden, die zwischen 70 und 89 Jahre alt waren, beobachtete eine Prävalenz von 15% (Roberts et al., 2008). Die niedrigste Prävalenzrate fanden Ganguli et al. mit 3 bis 4% bei über 65-Jährigen (Ganguli, Dodge, Shen, & DeKosky, 2004), die höchste Prävalenzrate berichtete eine österreichische Arbeitsgruppe mit 24% (Fischer et al., 2007). Trotz der variierenden Angaben kommt Petersen in einer Übersichtsarbeit zu dem Schluss, dass der Großteil der durchgeführten epidemiologischen Studien im Durchschnitt eine Prävalenzrate zwischen 14 und 18% bei über 70-Jährigen in der Allgemeinbevölkerung findet (Petersen et al., 2009). Die Zahl der jährlichen Neuerkrankungen liegt zwischen 8 und 58 Fällen pro 1000 Personen (Ritchie, 2004).

2.3.2 Abgrenzung zu anderen Konzepten

Das von Petersen 1999 eingeführte und 2004 von einer Arbeitsgruppe um Petersen und Winblad revidierte MCI-Konzept (Winblad et al., 2004) findet in der klinischen Anwendung und Forschung am meisten Beachtung (Dierckx, Engelborghs, De Raedt, De Deyn, & Ponjaert-Kristoffersen, 2007) und bildet daher auch die Grundlage für die vorliegende Arbeit. Für das Stadium zwischen einem normalen Alternsprozess und einer demenziellen Erkrankung existieren in der Literatur neben dem MCI-Konzept noch über 25 weitere Konstrukte und Termini (Zaudig, 2001). Viele davon haben die Entwicklung des MCI-Konzepts nach Petersen/Winblad beeinflusst. Im Folgenden soll daher ein kurzer Überblick über die wichtigsten alternativen Konzepte gegeben werden.

Benign Senescent Forgetfulness (gutartige Altersvergesslichkeit)

Mit dem Begriff *Benign Senescent Forgetfulness* wird der kognitive Abbau im Alter als natürlicher und normaler Prozess beschrieben. Dieses von Kral 1962 eingeführte Konzept bezeichnet einen altersabhängigen Prozess, der allgemeine Vergesslichkeit und Schwierigkeiten mit dem Abruf von Sachinformationen wie Namen und Daten beinhaltet. Das Allgemeinwissen ist jedoch erhalten und Betroffene sind sich ihrer Defizite bewusst. Im Gegensatz dazu steht die *Malignant Senescent Forgetfulness*, welche eine rasch voranschreitende, altersbedingte Gedächtnisbeeinträchtigung sowie ein mangelndes Bewusstsein bezüglich der Defizite umfasst (Kral, 1962).

Age-Associated Memory Impairment (AAMI)

Von einer Arbeitsgruppe des National Institute of Mental Health wurde das Konzept des *Age-Associated Memory Impairment* definiert, welches Personen beschreibt, die mindestens 50 Jahre alt sind und von Gedächtnisproblemen im Alltag berichten (Crook et al., 1986). Diese subjektiv empfundenen Gedächtnisdefizite müssen sich schleichend entwickelt haben und durch mindestens ein neuropsychologisches Testverfahren objektiviert werden (mindestens eine Standardabweichung unter der

Norm). Es darf keine internistische, neurologische oder psychiatrische Erkrankung vorliegen, welche die kognitiven Defizite erklären könnte. Kritisiert wird das Konzept wegen seiner Orientierung an den Normwerten junger Erwachsener, wodurch altersbedingte physiologische Veränderungen pathologisiert werden (O'Brien & Levy, 1992).

Age-Associated Cognitive Decline (AACD)

Das Konzept des *Age-Associated Cognitive Decline* wurde Anfang der 90er Jahre von einer Arbeitsgruppe um Levy entwickelt (Levy, 1994). Die Kriterien umfassen eine schleichende Abnahme kognitiver Fähigkeiten (fremd- oder eigenanamnestisch) sowie eine um mindestens eine Standardabweichung unter der Norm liegende Testleistung in einem der folgenden Bereiche: Aufmerksamkeit, Konzentration, Denken, Sprache, visuell-räumliches Vorstellungsvermögen.

Cognitive Impairment, No Dementia (CIND)

In der groß angelegten *Canadian Study of Health and Aging* wurde das Konzept des *CIND* untersucht. Dieses beschreibt über 65-jährige Personen, die Defizite in der kognitiven Leistungsfähigkeit haben, welche nicht den Schweregrad einer Demenz erfüllen. Ätiologisch werden keinerlei einschränkende Bedingungen definiert und auch keine Grenzwerte vorgegeben (Graham et al., 1997).

Leichte (neuro)kognitive Störung

In den beiden internationalen Klassifikationssystemen *International Statistical Classification of Diseases and Related Health Problems* (ICD-10; Weltgesundheitsorganisation, 2006) und *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Organisation, 2000) finden sich Kategorien, die kognitive Defizite beschreiben, welche aufgrund ihrer leichten Ausprägung keine Demenzdiagnose rechtfertigen. Im ICD-10 findet sich unter der Kodierung F06.7 die *leichte kognitive Störung*, deren Kernsymptome

Gedächtnisprobleme, Lernschwierigkeiten und verminderte Konzentrationsfähigkeit sind. Zudem werden eine organische Ursache sowie eine Reversibilität der kognitiven Defizite gefordert. Analog dazu existiert in den Experimentalkriterien des DSM-IV-TR die *leichte neurokognitive Störung*. Auch hier wird eine organische Ursache gefordert, jedoch keine Reversibilität. Zudem muss die Störung mindestens zwei Wochen bestehen. Lässt sich keine eindeutige organische Ursache der kognitiven Defizite feststellen, kann die Diagnose *altersbedingter kognitiver Abbau* vergeben werden. Im neu entwickelten DSM-V findet man die *mild neurocognitive disorder*, welche aus dem MCI-Konzept nach Petersen/Winblad abgeleitet wurde. Diese fordert einen substanziellen Abbau der kognitiven Funktionsfähigkeit, welcher in eine demenzielle Erkrankung übergehen *kann* (Sachs-Ericsson & Blazer, 2015).

Biologisch validierte Konzepte

Eine europäische Arbeitsgruppe um Dubois verfolgt das Ziel, die Konstrukte, welche den Bereich zwischen normalem Altern und einer Demenzerkrankung beschreiben, aufzugeben und durch die Definition einer *prodromalen Alzheimer-Erkrankung* zu ersetzen (Dubois et al., 2010; Dubois et al., 2007). Die Forschungskriterien für eine *prodromale Alzheimer-Erkrankung* beinhalten als Hauptkriterium eine objektivierbare und spezifische Störung des episodischen Gedächtnisses. Zusätzlich muss mindestens einer der folgenden Biomarker Alzheimer-typische Veränderungen aufzeigen: a) Vorliegen einer mediotemporalen Hirnatrophie (strukturelle Hirnveränderung), b) Hypoperfusion oder Hypometabolismus parietotemporal (funktionelle Hirnveränderung), c) Abnahme von β-Amyloid, Zunahme von phospho-Tau oder Gesamt-Tau im Liquor (Liquorveränderung), d) familiäre Alzheimer-Mutation (genetische Prädisposition). Anhand dieser Kriterien soll schon frühzeitig eine mögliche Alzheimer-Erkrankung diagnostiziert werden können. Zudem soll der kontinuierliche Prozess einer neurodegenerativen Erkrankung stärker hervorgehoben werden.

Ein ähnliches Konzept ist das *MCI due to Alzheimer's Disease* (Albert et al., 2011), welches von einer US-amerikanischen Arbeitsgruppe entwickelt wurde. Das klinische Bild des *MCI due to Alzheimer's Disease* zeichnet sich durch eine Abnahme der kognitiven Leistungsfähigkeit aus. Diese muss vom Betroffenen oder dessen Angehörigen berichtet sowie durch entsprechende kognitive Tests objektiviert werden. Die unabhängige Funktionsfähigkeit im Alltag ist bis auf minimale Defizite erhalten. Zudem müssen vaskuläre, traumatische oder andere medizinische Faktoren als Ursache des kognitiven Abbaus ausgeschlossen werden. Mit Hilfe von Biomarkern erfolgt schließlich eine Einteilung in vier Stadien, welche die Wahrscheinlichkeit angeben, dass die Ursache des MCI eine Alzheimer-Erkrankung ist: liegen Biomarker vor, die sowohl eine β-Amyloid-Pathologie (Abnahme von β-Amyloid im Liquor oder zerebrale Amyloid-Ablagerungen) als auch einen neurodegenerativen Abbau (Hippocampus-Degeneration, erhöhtes Tau-Protein im Liquor) nachweisen, ist die Wahrscheinlichkeit hoch, dass das MCI durch eine zugrundeliegende Alzheimer-Erkrankung bedingt ist. Finden sich keine entsprechenden Biomarker, ist eine zugrundeliegende Alzheimer-Erkrankung als unwahrscheinlich einzustufen.

Die beiden vorgestellten Ansätze sind vielversprechend und verbessern die prädiktive Validität: bei gleichzeitigem Vorliegen von MCI-Symptomen sowie pathologischen Liquorwerten entwickeln 90% der Betroffenen innerhalb von zehn Jahren eine Alzheimer-Demenz (Buchhave et al., 2012).

Subjektive kognitive Beeinträchtigung

Für das Konzept der *subjektiven kognitiven Beeinträchtigung* existiert keine eindeutige Definition. Vielmehr liegt eine *subjektive kognitive Beeinträchtigung* dann vor, wenn der Patient über Gedächtnisprobleme oder andere kognitive Defizite klagt, diese Beschwerden mit geeigneten neuropsychologischen Testverfahren jedoch nicht objektiviert werden können. Das Interesse an diesem Konzept wächst stetig, da einige Längsschnittstudien belegen, dass Personen mit subjektiven Beschwerden ein

höheres Demenzrisiko haben als gleichaltrige Personen ohne solche Beschwerden (Jessen, Wiese, Bachmann, & et al., 2010; Reid & Maclullich, 2006).

2.3.3 MCI-Subtypen

Das ursprüngliche MCI-Konzept nach Petersen (1999) hatte zum Ziel, eine Population von Menschen zu bestimmen, die sich im Frühstadium einer Alzheimer-Erkrankung befinden. Daher wurden bei der Kriterienfestlegung ausschließlich mnestische Defizite berücksichtigt. In der Praxis zeigte sich jedoch, dass auch nicht-mnestische Defizite ein erhöhtes Risiko für die Entwicklung einer Demenz darstellen (Ritchie et al., 2001). Auf einer internationalen Expertenkonferenz im Jahr 2003 wurden daher breitere Einschlusskriterien definiert, welche verschiedene Formen kognitiver Defizite beinhalten (Winblad et al., 2004). Petersen spezifizierte vier verschiedene MCI-Subtypen (Abbildung 1), welche der heterogenen Natur der kognitiven Defizite und der variierenden Ätiologie Rechnung tragen (Petersen, 2004).

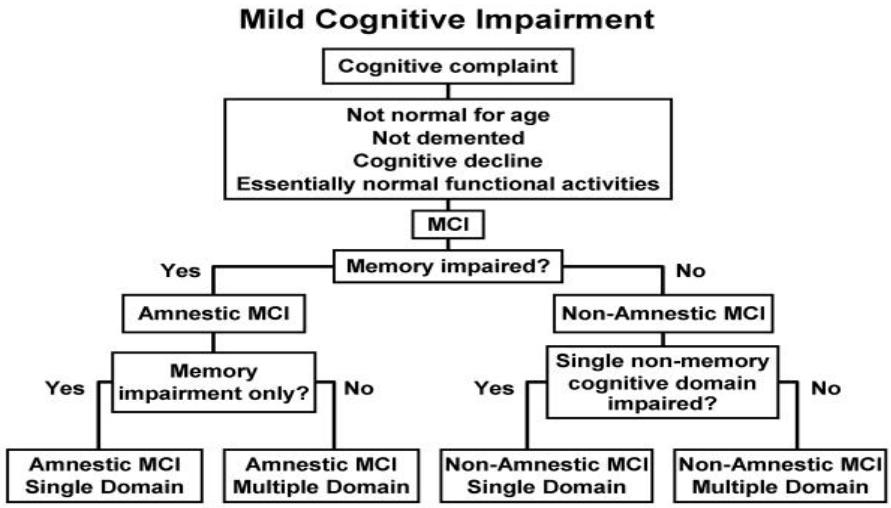

Abbildung 1: Flowchart zur Diagnose der MCI-Subtypen (Petersen, 2004, S. 186)

Der *single-domain* Subtyp des *amnestic MCI* beschreibt Personen, die ausschließlich Defizite im mnestischen Bereich haben und entspricht am ehesten den Originalkriterien von Petersen (1999). Hat eine Person Defizite im mnestischen

Bereich und in mindestens einer nicht-mnestischen Domäne, fällt sie in die Kategorie des *multiple-domain amnestic MCI*. Personen ohne mnestische Defizite, aber mit Defiziten in einem anderen kognitiven Funktionsbereich (beispielsweise Exekutivfunktionen, Sprache), werden als *single-domain non-amnestic MCI* bezeichnet. Treten Defizite in mehreren kognitiven Bereichen auf – bei intakter Gedächtnisleistung – spricht man von einem *multiple-domain non-amnestic MCI*. In einer populationsbasierten Studie der Mayo-Klinik wurde festgestellt, dass die amnestischen Subtypen mit einem Verhältnis von 2:1 häufiger vorkommen als die nicht-amnestischen Subtypen (Roberts et al., 2008).

Nach Petersen (2004) liegen den Subtypen verschiedene Ursachen zugrunde (Abbildung 2). So lassen mnestische Defizite am ehesten an eine neurodegenerative Genese, aber auch – je nach klinischem Bild – an eine depressive Erkrankung denken. Nicht-mnestische Defizite weisen eher auf eine zugrundeliegende fronto-temporale Demenz oder eine Lewy-Body-Demenz hin.

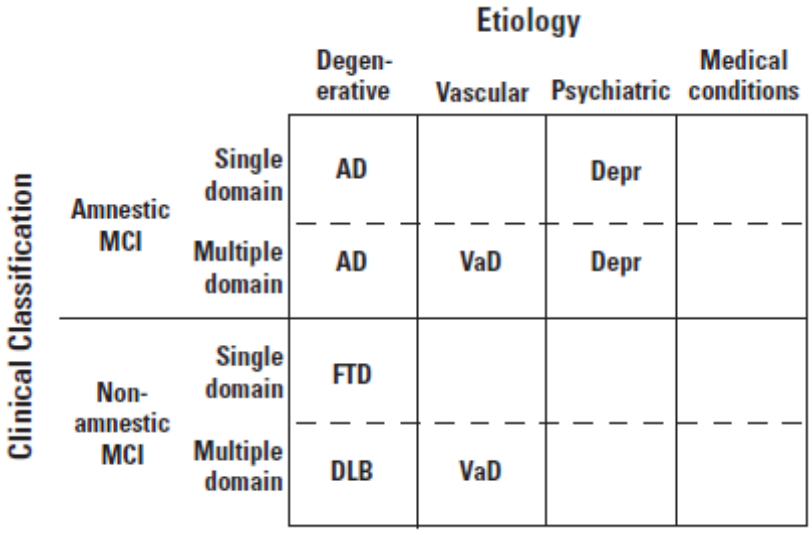

Abbildung 2: Vermutete Ätiologie der MCI-Subtypen (Petersen, 2004, S. 188)
AD = Alzheimer-Demenz, VaD = Vaskuläre Demenz, Depr = Depression, FTD = Fronto-Temporale Demenz, DLB = Lewy-Body-Demenz

Bislang gibt es nur unzureichende Evidenz für den klinischen und prognostischen Nutzen der Subtypen (Ritchie & Ritchie, 2012). Einige Forschergruppen verfolgen

daher den Ansatz, anhand von Cluster-Analysen empirisch abgeleitete MCI-Subgruppen mit gemeinsamer Ätiologie und ähnlichem Verlauf zu bestimmen (Delano-Wood et al., 2009; Libon et al., 2010). Delano-Wood et al. (2009) identifizierten auf diese Weise einen amnestischen, einen dysexekutiven und einen gemischten/multiple-domain Subtyp. Diese waren nicht deckungsgleich mit den konventionellen Subtypen nach Petersen (2004). Die Ergebnisse konnten von Libon et al. (2010) repliziert werden.

2.3.4 Konversion zur Demenz

In der Allgemeinbevölkerung liegen die Inzidenzraten einer Demenzerkrankung bei 1 bis 2% pro Jahr (Petersen et al., 2001). Im Vergleich dazu haben Personen mit MCI ein deutlich erhöhtes Risiko, eine Demenzerkrankung zu entwickeln. In zwei amerikanischen Studien konnten jährliche Konversionsraten von 10 bis 15% festgestellt werden (Farias, Mungas, Reed, Harvey, & DeCarli, 2009; Ritchie, 2004). Eine deutsche Studie fand jährliche Konversionsraten von 7 bis 10% (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). Jedoch variieren die Verlaufsformen des MCI erheblich: so zeigten sich in Langzeitbeobachtungen oftmals auch eine Rückbildung der gefundenen Defizite (Larrieu et al., 2002; Ritchie et al., 2001) oder über Jahre hinweg stabile Verläufe (Gauthier et al., 2006).

Im Bestreben, die prognostische Validität zu verbessern, wurden in einigen Studien die zuvor beschriebenen MCI-Subtypen (vgl. 2.3.3) auf ihr Demenz-Konversionsrisiko hin untersucht. In einer populationsbasierten Längsschnittstudie fanden sich in einem 30-Monats-Zeitraum Konversionsraten zur Alzheimer-Demenz von 49% für Probanden mit amnestic MCI und 27% für Probanden mit non-amnestic MCI. Für Probanden, die zur Baseline-Untersuchung kognitiv unbeeinträchtigt waren, lag die Konversionsrate bei 13% (Fischer et al., 2007). In einer italienischen Studie mit 2866 Patienten einer Gedächtnisambulanz fanden sich jährliche Konversionsraten von 38% für single-domain amnestic MCI, 20% für non-amnestic MCI und 16% für multiple-

domain amnestic MCI. Mit 53% entwickelten die Patienten am häufigsten eine Alzheimer-Demenz (Maioli et al., 2007). Es wird diskutiert, dass sich die verschiedenen MCI-Subtypen zu bestimmten Demenztypen entwickeln: Personen mit einem amnestic MCI entwickeln am ehesten eine Alzheimer-Demenz (Dubois & Albert, 2004; Panza et al., 2006), die non-amnestischen Subtypen am ehesten eine vaskuläre Demenz oder andere Demenzformen. Jedoch gibt es auch Studien, die gegen diese subtypenspezifische Verläufe sprechen (Busse et al., 2006; Fischer et al., 2007).

2.4 Aktivitäten des täglichen Lebens

Mit kognitiven Beeinträchtigungen gehen oftmals auch Schwierigkeiten in der Funktionsfähigkeit im Alltag einher (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000). Diese Funktionsfähigkeit im Alltag wird über das Konzept der Aktivitäten des täglichen Lebens (ADL) erfasst. Defizite in den ADL bilden derzeit die entscheidende diagnostische Schwelle zur Abgrenzung des Mild Cognitive Impairment von einer manifesten Demenz. Die Erfassung dieser Schwelle ist sehr stark methoden- und definitionsabhängig, weswegen im Folgenden der Begriff ADL genauer bestimmt sowie die gängigen Messinstrumente im Detail vorgestellt werden sollen.

2.4.1 Begriffsbestimmung

ADL werden in basale und instrumentelle ADL unterteilt: zu den *basalen ADL* (BADL) zählen grundlegende Selbstversorgungstätigkeiten wie Körperpflege und Nahrungsaufnahme, während die *instrumentellen ADL* (IADL) komplexere Aktivitäten wie beispielsweise den Umgang mit Medikamenten, das Einhalten von Terminen und die Regelung finanzieller Angelegenheiten umfassen (Lawton & Brody, 1969; Nygård, 2003). Von einigen Autoren wird noch eine dritte Gruppe von ADL postuliert, die

sogenannten *advanced ADL* (AADL): dies sind Alltagstätigkeiten, denen eher aufgrund von Interesse nachgegangen wird als aufgrund einer Notwendigkeit. Zudem sind sie stark durch Kultur und Motivation beeinflusst (Bennett et al., 2006; Reuben, Laliberte, Hiris, & Mor, 1990). Auf das Konzept der AADL soll in der vorliegenden Arbeit nicht näher eingegangen werden, da es in der MCI- und Demenzforschung eine geringe Bedeutung hat.

2.4.2 Messverfahren

Zur Erfassung der ADL existieren eine Reihe von Messinstrumenten. Dabei handelt es sich mehrheitlich um Fragebögen. Zudem gibt es leistungsbasierte Verfahren, d.h. der Betroffene selbst muss alltagsnahe Aufgaben lösen und anhand der Leistung erfolgt die Beurteilung der ADL-Funktionsfähigkeit. Im Folgenden werden exemplarisch einige häufig eingesetzte Instrumente vorgestellt.

Fragebögen

Aufgrund der einfachen Handhabbarkeit werden in der klinischen Praxis zur Erfassung von ADL hauptsächlich Fragebögen eingesetzt (Strauss, Sherman, & Spreen, 2006). Zu den wohl bekanntesten Fragebögen zählen der *Barthel-Index* (Mahoney & Barthel, 1965) als Maß für BADL sowie die *Instrumental Activities of Daily Living - Physical Self Maintenance Scale* (Lawton & Brody, 1969). Letztere erfasst BADL und IADL über zwei – bei Bedarf auch getrennt einsetzbare – Fragebögen. Ein weiteres international eingesetztes Messinstrument ist das *Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory* (ADCS-ADL; Galasko et al., 1997), welches mit 23 Items sowohl BADL als auch IADL abfragt. Die ADCS-ADL wurde von einer Forschergruppe um Pedrosa für MCI-Populationen modifiziert, indem Items mit höherem Schwierigkeitsgrad eingefügt wurden (ADCS-MCI-ADL; Pedrosa et al., 2010). Ein im deutschsprachigen Raum häufig eingesetztes Verfahren ist die *Bayer-ADL* (Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998),

welche zwei Items für BADL, achtzehn Items für IADL und fünf Items für kognitive Funktionen enthält. Bei allen genannten Fragebögen handelt es sich um Fremdbeurteilungsskalen, d.h. eine Bezugsperson des Betroffenen gibt Auskunft über die relevanten Bereiche. Verschiedene Studien liefern Belege dafür, dass schon im MCI-Stadium die Selbstbeurteilungsfähigkeit der Betroffenen eingeschränkt ist (Vogel et al., 2004). Patienten mit MCI nehmen ihre ADL-Defizite nicht adäquat wahr und überschätzen ihre Fähigkeit bezüglich verschiedener Aktivitäten des täglichen Lebens (Albert et al., 1999; Okonkwo et al., 2009; Tabert et al., 2002). Lediglich Farias et al. fanden Belege für eine erhaltene Selbstbeurteilungsfähigkeit bei MCI-Patienten (Farias, Mungas, & Jagust, 2005). Vorteile der Fragebögen sind deren Zeit- und Kosteneffizienz sowie die Möglichkeit der Erfassung von alltagsnahem Verhalten über einen längeren Zeitraum. Ein Nachteil der ADL-Erfassung über die Befragung von Bezugspersonen ist, dass deren Urteil je nach psychischer Belastung und/oder Nähe zum Betroffenen Verzerrungen unterliegen kann (DeBettignies, Mahurin, & Pirozzolo, 1990; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). Auch ist nicht immer eine Bezugsperson verfügbar, die Auskunft geben kann. Ein weiterer genereller Nachteil ist in der Vielfalt der verfügbaren Messverfahren zu sehen, ohne dass ein „Goldstandard“ für die ADL-Erfassung existiert. Zudem gibt es bis auf wenige Ausnahmen (ADCS-MCI-ADL) keine speziell für MCI-Populationen entwickelte Messinstrumente, weswegen oft Fragebögen eingesetzt werden, welche ursprünglich für Personen mit Demenz vorgesehen waren.

Leistungsbasierte Verfahren

Leistungsbasierte Verfahren (engl. *performance-based measures*) zeichnen sich dadurch aus, dass die zu beurteilende Person während der Ausführung spezifischer ADL beobachtet und bewertet wird. Für die leistungsbasierte Erfassung finanzieller Fähigkeiten ist beispielhaft das *Financial Capacity Instrument* (FCI; Marson et al., 2000) zu nennen. Das FCI erfasst sieben finanzielle Domänen, darunter unter

anderem basale finanzielle Fähigkeiten (Geld zählen) oder finanzielles Konzeptwissen (Verständnisfragen, z.B. was sind Schulden?). Für eine Erfassung mehrerer ADL-Funktionsbereiche ist exemplarisch das *Direct Assessment of Functional Status* (Loewenstein et al., 1989) zu nennen. Hier werden Aufgaben zu sechs verschiedenen BADL- und IADL-Bereichen gestellt: zeitliche Orientierung (Fragen zu Uhrzeit, Datum), Kommunikation (Telefonbenutzung, Brief für Versand vorbereiten), finanzielle Fähigkeiten (Münzen benennen, Überweisung ausstellen), Einkaufen (Lebensmittel wiedererkennen), Körperpflege (Zähneputzen, Anziehen) und Nahrungsaufnahme. Auch die virtuelle Realität findet Anwendung: im *Virtual Action Planning Supermarket* (Werner, Rabinowitz, Klinger, Korczyn, & Josman, 2009) muss der Proband in einem virtuellen Supermarkt vorgegebene Produkte kaufen; dabei werden unter anderem die Gesamtzeit für den Einkauf, die zurückgelegte Wegstrecke und falsch ausgewählte Produkte aufgezeichnet. Neuere Ansätze nutzen *Smart Homes* zur Untersuchung der ADL-Funktionsfähigkeit. Mit Hilfe von Sensoren und Videokameras werden objektive Daten erhoben, die dann zur automatisierten Bewertung der ADL herangezogen werden können (Dawadi, Cook, Schmitter-Edgecombe, & Parsey, 2013; König et al., 2015; Sacco et al., 2012). Vorteile der leistungsbasierten Verfahren sind in der besseren ökologischen Validität sowie in der Unabhängigkeit von auskunftsfähigen Bezugspersonen zu sehen. Der Vorteil der ökologischen Validität wird jedoch nicht von allen Forschern geteilt – so wird kritisiert, dass man den Probanden seiner natürlichen Routine und Wohnumgebung beraubt, welche Hinweisreize für die erfolgreiche Bewältigung von ADL geben können (Gold, 2012). Ein weiterer Nachteil der leistungsbasierten Verfahren ist darin zu sehen, dass sie nur einen kleinen Aspekt der Realität abbilden, nämlich die Leistung des Probanden am Tag der Beurteilung. Zudem braucht es mindestens eine Person, welche die Untersuchung durchführt, was personelle und somit auch finanzielle Ressourcen bindet.

2.4.3 Einflussfaktoren auf die ADL-Funktionsfähigkeit

Es gibt zahlreiche Faktoren, welche die Funktionsfähigkeit im Alltag beeinflussen. Ganz allgemein gehen ein höheres Lebensalter (Cahn et al., 1996) sowie ein niedriger Bildungsgrad mit einem schlechteren Funktionsniveau im Alltag einher (Artero, Touchon, & Ritchie, 2001). Auch depressive Symptome (Cahn et al., 1996) und eingeschränkte motorische Funktionen (Bennett et al., 2006) wirken sich negativ auf die Bewältigung von BADL und IADL aus. Will man den Einfluss von kognitiven Defiziten auf die ADL-Funktionsfähigkeit untersuchen, ist es demzufolge wichtig, die zuvor genannten demographischen und klinischen Variablen zu kontrollieren.

Insgesamt belegen Studien, dass ein schlechterer kognitiver Status mit einer höheren Einschränkung der ADL-Funktionsfähigkeit einhergeht (Foldi et al., 2011; Jefferson, Paul, Ozonoff, & Cohen, 2006). Royall und Kollegen untersuchten in einer Meta-Analyse 68 Studien, welche die kognitiven Korrelate der ADL-Funktionsfähigkeit genauer beleuchteten. Sie kamen zu dem Schluss, dass neben dem allgemeinen kognitiven Status vor allem exekutiven Prozessen eine bedeutsame Rolle zukommt (Royall et al., 2007).

2.4.4 ADL bei Personen mit MCI

Mit einer Abnahme kognitiver – vor allem exekutiver – Fähigkeiten geht häufig eine verminderte Funktionsfähigkeit im Alltag einher. Je anspruchsvoller die durchzuführende ADL ist, desto komplexer sind auch die zu deren Durchführung benötigten kognitiven Ressourcen (De Vriendt et al., 2012). Daher sind bei neurodegenerativen Erkrankungen im frühen Krankheitsverlauf zunächst Defizite der instrumentellen ADL zu beobachten, erst später kommen Defizite der basalen ADL hinzu (Tuokko, Morris, & Ebert, 2005; Yeh et al., 2011). Für die Diagnose einer Demenz ist es zwingend notwendig, dass neben kognitiven Defiziten auch die Funktionsfähigkeit im Alltag deutlich eingeschränkt sein muss. Die Rolle der instrumentellen ADL bei Personen mit MCI ist bislang nicht abschließend geklärt. In

den von Petersen im Jahr 1999 veröffentlichten Kriterien wurde postuliert, dass bei Personen mit MCI Gedächtnisprobleme auftreten, die Personen aber im Alltag ohne Probleme zurechtkommen, d.h. keinerlei Beeinträchtigung der ADL, weder der basalen noch instrumentellen, aufweisen. Studien, die in der Folgezeit durchgeführt wurden, stellten das Kriterium der „intakten ADL“ von Petersen et al. (1999) jedoch in Frage. Da instrumentelle ADL hochorganisierte kognitive Netzwerke benötigen, sind sie anfällig für kognitive Abbauprozesse, die im MCI-Stadium auftreten (Agüero-Torres, Thomas, Winblad, & Fratiglioni, 2002; Njegovan, Man-Son-Hing, Mitchell, & Molnar, 2001). In einer Literaturübersicht zu basalen und instrumentellen Alltagsaktivitäten bei Personen mit MCI und leichter Demenz kam Nygård (2003) zu dem Schluss, dass die instrumentellen ADL schon vor dem Beginn einer Demenzerkrankung beeinträchtigt sind. Die Konsensus-Kriterien zur Diagnose von MCI nach Winblad et al. (2004) berücksichtigen diese Befunde, indem sie „minimale Beeinträchtigungen“ der instrumentellen ADL zulassen. Mittlerweile weisen zahlreiche Studien in die Richtung, dass Menschen mit MCI im Vergleich zu Gesunden Defizite in einer Vielzahl von instrumentellen ADL haben (Ahn et al., 2009; Aretouli & Brandt, 2010; Kim et al., 2009; Perneczky et al., 2006). Die Anzahl und Art der defizitären IADL variiert zwischen den Studien, jedoch sind Domänen wie das Benutzen des Telefons, das Einhalten von Terminen oder die Einnahme von Medikamenten oft betroffen. Weitere Bereiche, in denen Menschen mit MCI im Vergleich zu Gesunden größere Probleme haben, sind die Regelung finanzieller Angelegenheiten (Marson et al., 2009; Triebel et al., 2009) oder das Bedienen eines Kraftfahrzeugs (Wadley et al., 2009). Auch konnten eine generelle Verlangsamung bei der Ausführung von IADL beobachtet werden (Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008) sowie Defizite bei der Handhabung technischer Geräte (Malinowsky, Almkvist, Kottorp, & Nygård, 2010; Munoz-Neira et al., 2012; Rosenberg, Kottorp, Winblad, & Nygård, 2009). Im Vergleich zu Menschen mit einer leichten Demenz sind die IADL bei Menschen mit MCI jedoch weniger stark beeinträchtigt (Boeve et al., 2003;

Giovannetti et al., 2008; Peres et al., 2006). Das Erkennen von IADL-Defiziten im MCI-Stadium erscheint essentiell für die Prognose des Krankheitsverlaufs, wie mehrere Längsschnittstudien zeigen: in MCI-Populationen haben Probanden, welche Einschränkungen der IADL aufweisen, ein erhöhtes Konversionsrisiko zur Demenz (Artero et al., 2008; Peres et al., 2006; Triebel et al., 2009).

2.5 Herausforderungen des MCI-Konzepts

Das MCI-Konzept wurde seit seiner Einführung intensiv beforscht und weiterentwickelt, wodurch es zu großen Fortschritten in der Früherkennung demenzieller Erkrankungen kam. Neben all seinen Vorzügen hat das Konzept aber auch mit vielen Kritikpunkten zu kämpfen.

So ist das MCI-Konzept aus neuropsychologischer Sicht nicht ausreichend definiert. In den Kriterien (Petersen et al., 1999; Winblad et al., 2004) wird zwar eine Objektivierung der kognitiven Beeinträchtigung gefordert, jedoch werden weder Cut-Off-Werte genannt noch Empfehlungen zu geeigneten Messinstrumenten gegeben. Aufgrund dieser mangelnden Operationalisierung variieren die Cut-Off-Werte in der Literatur zwischen ein bis zwei Standardabweichungen unter der Altersnorm (Stephan et al., 2013). Dies führt verständlicherweise zu inkonsistenten Resultaten und macht eine Vergleichbarkeit schwierig. Erhebliche Unterschiede in den MCI-Prävalenzraten sind durch den jeweils angewendeten Cut-Off-Wert (Mansbach, Mace, & Clark, 2015) sowie durch die Anzahl und Art der eingesetzten neuropsychologischen Messinstrumente erklärbar (Bondi et al., 2008; Jak et al., 2009). Auch die inkonsistenten Befunde bezüglich der prädiktiven Validität des MCI-Konzepts lassen sich auf mangelnde Empfehlungen zur Operationalisierung zurückführen. Einige Studien versuchen unter Hinzunahme von Biomarkern die prädiktive Validität der MCI-Diagnose zu verbessern (Haldenwanger, Eling, Kastrup, & Hildebrandt, 2010; van Rossum, Vos, Handels, & Visser, 2010). Die Klassifikation von MCI-Subtypen

gestaltet sich ebenfalls schwierig, da auch hier genaue Angaben zur Operationalisierung fehlen. Einen Lösungsansatz sehen diverse Autoren im Einsatz von Cluster-Analysen, welche zur Spezifikation empirisch abgeleiteter MCI-Subtypen genutzt werden können (Clark et al., 2013; Delano-Wood et al., 2009).

Eine weitere Kontroverse existiert bezüglich der ADL-Funktionsfähigkeit. In den revidierten MCI-Kriterien von Winblad (2004) werden erhaltene BADL gefordert sowie minimale IADL-Defizite erlaubt. Auch hier gibt es keine Empfehlungen zu Messinstrumenten oder zu Cut-Off-Werten. Je nach eingesetztem Messinstrument variiert das Ausmaß der gefundenen IADL-Beeinträchtigungen (Gold, 2012). Eine genauere Eingrenzung zu erhebender IADL-Bereiche sowie Angaben zum Ausmaß der „erlaubten" Beeinträchtigung wären hilfreich.

2.6 Ziele der vorliegenden Arbeit

Wie in den vorangegangenen Abschnitten erläutert, hat das MCI-Konzept die Forschung zur Früherkennung demenzieller Erkrankungen enorm stimuliert. Das Hauptproblem des Konzepts ist darin zu sehen, dass keine Vorgaben zur Operationalisierung der Kriterien gemacht werden. Dadurch kommt es zum Einsatz verschiedenster Messinstrumente und variierender Grenzwerte. Dies führt wiederum zu inkonsistenten Ergebnissen und macht die Bestimmung einer Hochrisikogruppe (bezüglich einer Konversion zur Demenz) schwierig. Übersichtsarbeiten fordern eine präzisere und vor allem operationale Definition der MCI-Kriterien (Ritchie & Ritchie, 2012; Stephan et al., 2013).

Die erste Studie dieser Arbeit hat daher zum Ziel, die Kontroverse um Beeinträchtigungen der IADL-Funktionen im MCI-Stadium näher zu beleuchten. Anhand einer systematischen Literaturanalyse wird untersucht, welche IADL-Funktionen schon im MCI-Stadium defizitär sind und welche Erhebungsmethoden sich zu deren Erfassung am besten eignen. Neben der qualitativen Beschreibung der

IADL-Defizite soll auch deren quantitatives Ausmaß bestimmt werden. Zudem wird die Beeinträchtigung der IADL bei verschiedenen MCI-Subtypen untersucht und es erfolgt eine kritische Betrachtung der Kriterien-Operationalisierung.

In Studie 2 wird ein neues leistungsbasiertes Verfahren zur Erfassung von IADL untersucht, welches speziell für MCI-Populationen entwickelt wurde. Damit soll der Frage nachgegangen werden, ob leistungsbasierte Verfahren für die IADL-Erfassung möglicherweise besser geeignet sind als Fremdbeurteilungsverfahren.

Neben den IADL-Defiziten wird auch das Ausmaß der kognitiven Beeinträchtigung, welches eine MCI-Diagnose rechtfertigt, stark diskutiert. In der dritten Studie erfolgen daher eine empirische Ableitung von MCI-Subtypen und eine Bestimmung des Konversionsrisikos zur Demenz. Damit soll untersucht werden, ob die von Petersen postulierten Subtypen in der Realität wirklich anzutreffen sind, oder ob es andere Risikoprofile gibt, welche bislang wenig Beachtung fanden. Zudem wird geprüft, ob sich die Cluster bezüglich Alzheimer-spezifischer Biomarker unterscheiden.

Insgesamt soll die Arbeit die Herausforderungen des MCI-Konzepts genauer analysieren und Möglichkeiten zur Schärfung der Kriterien aufzeigen. Handlungsempfehlungen für die klinische Praxis sollen abgeleitet und damit ein Beitrag zur Verbesserung der Früherkennung demenzieller Erkrankungen geleistet werden.

3. Zusammenfassung der Studien

Im Folgenden wird ein kurzer Überblick über Zielsetzung, methodisches Vorgehen und relevante Ergebnisse der in die Dissertationsschrift eingehenden Studien gegeben. Unter Punkt 8.3 finden sich die Originalartikel in voller Länge.

3.1 Studie 1

“Mild Cognitive Impairment and Deficits in Instrumental Activities of Daily Living - a Systematic Review”

Hintergrund und Zielsetzung

In den ursprünglichen MCI-Kriterien wurde davon ausgegangen, dass sich Patienten mit MCI nur durch Gedächtnisbeeinträchtigungen auszeichnen, die BADL und IADL aber vollständig erhalten sind. In den revidierten Kriterien (Winblad et al., 2004) wurden minimale Beeinträchtigungen der IADL erlaubt. Es wird weiterhin kontrovers diskutiert, welche IADL genau und in welchem Ausmaß betroffen sind. Bislang existiert keine Übersichtsarbeit, die systematisch IADL-Beeinträchtigungen bei MCI-Patienten analysiert. Daher fasst die vorliegende Arbeit den aktuellen Forschungsstand zu IADL-Defiziten bei MCI-Patienten zusammen. Zudem sollen die eingesetzten Messverfahren zur IADL-Erfassung untersucht sowie IADL-Defizite der MCI-Subtypen analysiert werden.

Methodik

Die Datenbanken PsycINFO, PubMed und Web of Science wurden im Dezember 2013 nach relevanter Literatur durchsucht. Insgesamt wurden 497 Artikel identifiziert und von zwei unabhängigen Ratern hinsichtlich ihrer Eignung für die Studie beurteilt. Eingeschlossen wurden alle Artikel, die seit 1999 publiziert wurden und sich schwerpunktmäßig mit der Untersuchung von IADL-Defiziten bei Patienten mit MCI im

Vergleich zu Gesunden und/oder Dementen befassten. Insgesamt wurden 37 Artikel in die vorliegende Arbeit aufgenommen.

Wesentliche Ergebnisse

Für die Erfassung der IADL wurden in den 37 eingeschlossenen Studien insgesamt 31 verschiedene Messinstrumente eingesetzt, welche zum größten Teil zur IADL-Erfassung bei Patienten mit Demenz entwickelt wurden. In 35 Studien wurden überwiegend ausgeprägte IADL-Defizite bei Patienten mit MCI gefunden. Das Ausmaß der Defizite war bei MCI-Patienten größer als bei kognitiv unbeeinträchtigten Personen und kleiner als bei Personen mit einer demenziellen Erkrankung. Eingeschränkte finanzielle Kompetenzen wurden in der Mehrzahl der Studien beobachtet, gefolgt von Umgang mit Medikamenten, Telefonbenutzung, Einhalten von Terminen, Umgang mit Alltagstechnologie und Wiederfinden von Gegenständen. Die Effektstärken waren sowohl für die Gruppenvergleiche zwischen kognitiv unbeeinträchtigten Personen und Patienten mit MCI als auch für Gruppenvergleiche zwischen Patienten mit MCI und Patienten mit einer Demenz durchweg moderat bis groß. Im Vergleich zu Fragebogendaten zeigten leistungsbasierte Verfahren leichte Vorteile (d.h. größere Effektstärken) in der Aufdeckung von IADL-Defiziten. Bezüglich der MCI-Subtypen wurde beobachtet, dass bei den amnestischen Subtypen größere IADL-Defizite auftraten als bei den nicht-amnestischen.

Diskussion

In der systematischen Literaturanalyse zeigte sich, dass MCI-Patienten zum Teil deutliche IADL-Defizite aufweisen und vor allem diejenigen IADL beeinträchtigt sind, welche komplexe kognitive Leistungen beanspruchen. Die Vergleichbarkeit der Ergebnisse über die Studien hinweg gestaltete sich aufgrund der Vielzahl der eingesetzten Messinstrumente sowie variierender neuropsychologischer Grenzwerte als schwierig. Eine zuverlässige Erfassung der IADL-Defizite in MCI-Populationen ist jedoch wichtig, um Patienten zu identifizieren, die ein erhöhtes Risiko aufweisen, zur

Demenz zu konvertieren. Zukünftige Forschung sollte auf die Etablierung einheitlicher – und auf die Entwicklung von speziell auf MCI-Patienten zugeschnittenen – Messverfahren abzielen. Ein Schwerpunkt sollte dabei auf leistungsbasierte Verfahren gelegt werden.

3.2 Studie 2

“Development of a Proxy-Free Objective Assessment Tool of IADL in MCI Using Smart Home Technologies”

Hintergrund und Zielsetzung

Smart Home-Technologien werden normalerweise zur Unterstützung der Alltagsbewältigung sowie zur Detektion von Notfallsituationen eingesetzt. Dabei finden Bewegungs- und Drucksensoren oder Videosysteme Anwendung. Ein weiteres Einsatzgebiet der Smart Home-Technologien könnte – aufgrund der großen generierten Datenmengen – die Erfassung von Aktivitäten des täglichen Lebens (ADL) sein. Beeinträchtigungen der ADL sind – neben ausgeprägten kognitiven Defiziten – ein zentrales Kriterium der Demenzdiagnose. Aktuelle Studien zeigen, dass schon Patienten mit Mild Cognitive Impairment Beeinträchtigungen der instrumentellen ADL zeigen. Üblicherweise geschieht die Erfassung der ADL über Fremdbeurteilungsverfahren. Dies kann durch Urteilsverzerrungen oder bei alleinstehenden Patienten ohne auskunftsfähige Bezugsperson zu Problemen führen. Leistungsbasierte Verfahren sind eine mögliche Alternative. In der vorliegenden Studie wurde ein leistungsbasiertes Verfahren zur IADL-Erfassung unter Einsatz von Smart Home-Technologien erprobt.

Methodik

Die Smart Home-Umgebung bestand aus einer möblierten Zweiraumwohnung. Diese war mit Bewegungssensoren und Video-Kameras ausgestattet, welche eine Verhaltensbeobachtung und das Aufzeichnen von Daten ermöglichten. 11 Probanden

mit MCI und 10 Probanden ohne kognitive Beeinträchtigung sollten in der Smart Home-Umgebung nach einer Explorationsphase von fünf Minuten sechs standardisierte Aufgaben lösen; dazu gehörten unter anderem das Zubereiten einer Mahlzeit, das Bedienen elektrischer Geräte sowie das Wiederfinden von Gegenständen. Zur Berechnung von Gruppenunterschieden wurden Kolmogorov-Smirnov-Z Tests angewendet sowie zur Bestimmung von Korrelationen der Spearman'sche Rangkorrelationskoeffizient. Die Diagnosegruppen waren nach Alter und Geschlecht gematched.

Wesentliche Ergebnisse

Es zeigte sich, dass die MCI-Gruppe bei der Aufgabenbearbeitung insgesamt mehr Zeit brauchte als die kognitiv unbeeinträchtigte Gruppe (1384 vs. 938 Sekunden, $p < .001$). Zudem erzielte die MCI-Gruppe weniger Punkte (48 vs. 57 Punkte, $p < .001$), d.h. sie beging mehr Fehler. Eine Analyse der einzelnen Aufgaben erbrachte signifikante Gruppenunterschiede für die Telefonbenutzung, das Bedienen des Fernsehers sowie das Wiederfinden der Gegenstände. Sowohl Bearbeitungsdauer als auch Fehler bei der Aufgabenbearbeitung korrelierten moderat mit dem kognitiven Status der Probanden sowie mit traditionellen ADL-Maßen (Bayer-ADL, ADCS-MCI-ADL). Die Probanden bewerteten das Smart Home-IADL-Szenario als realistisch und fühlten sich während der Aufgabenbearbeitung nicht unwohl.

Diskussion

Die durchgeführte Pilotstudie zeigte, dass die Smart Home-Umgebung von den Probanden sehr gut angenommen wurde und die Durchführbarkeit ausgezeichnet war. Die ersten Ergebnisse sind – trotz der relativ kleinen Stichprobe – vielversprechend. Insgesamt bieten Smart Home-Umgebungen die Möglichkeit einer objektiven, teilweise automatisierten und ökologisch validen IADL-Erfassung, die nicht zwingend das Vorhandensein einer auskunftsfähigen Bezugsperson voraussetzt. Zukünftige Studien sollten mit einer größeren Probandenanzahl die Leistung innerhalb

verschiedener MCI-Subtypen untersuchen. Zudem wären prospektive Studien gewinnbringend, anhand derer sich gewisse „Smart Home-Prädiktoren“ für eine Demenzentwicklung ableiten ließen.

3.3 Studie 3

“Single-Domain Amnestic Mild Cognitive Impairment Identified by Cluster Analysis Predicts Alzheimer’s Disease in the European Prospective DESCRIPA Study”

Hintergrund und Zielsetzung

Personen mit MCI haben ein erhöhtes Risiko, eine Alzheimer-Demenz zu entwickeln. Bestimmte MCI-Subtypen haben dabei ein höheres Konversionsrisiko als andere, jedoch herrscht in der Literatur Uneinigkeit darüber, welcher Subtyp am ehesten als Prodromalstadium der Alzheimer-Demenz gewertet werden kann. Dies liegt vor allem auch an der unzureichenden neuropsychologischen Operationalisierung der Subtypen hinsichtlich des Ausmaßes der kognitiven Defizite. Die vorliegende Studie soll einen Beitrag zur besseren Charakterisierung der Subtypen leisten, indem sie in einem ersten Schritt einen datenbasierten Ansatz zur Bestimmung kognitiver Leistungsprofile von Probanden mit MCI anwendet. In einem zweiten Schritt werden für die empirisch gefundenen Subtypen Konversionsraten zur Alzheimer-Demenz berechnet.

Methodik

Insgesamt wurden 881 Probanden mit MCI von 20 europäischen Gedächtnisambulanzen eingeschlossen und über 5 Jahre nachverfolgt. Es wurden verschiedene kognitive Variablen, Zeitpunkt der Konversion zur Alzheimer-Demenz sowie Biomarker (Liquor, MRT) analysiert. Zur Identifikation von Probandenclustern mit unterschiedlichen kognitiven Profilen wurden hierarchische Clusteranalysen (HCA) durchgeführt. Die erste HCA schloss alle Probanden mit vollständigem kognitiven

Datensatz ein, die zweite HCA schloss nur Probanden mit sehr leichtem MCI (MMST ≥ 28) ein. ANOVAs und ANCOVAs wurden berechnet, um zu untersuchen, ob die Cluster sich hinsichtlich der Konversion zur Alzheimer-Demenz und spezifischer Biomarker unterscheiden.

Ergebnisse

Die erste Clusteranalyse (n = 485) ergab vier verschiedene Cluster. Die höchsten Konversionsraten zur Alzheimer-Demenz fanden sich für das Cluster mit Gedächtnisproblemen und ausgeprägten Defiziten der Exekutivfunktionen (47%), gefolgt von einem Cluster mit ausschließlich mnestischen Defiziten (32%). Die zweite HCA, welche nur Probanden mit einem MMST-Wert ≥ 28 einschloss, erbrachte ebenfalls eine 4-Cluster-Lösung, wobei diesmal das Cluster mit den rein mnestischen Defiziten die höchste Konversionsrate zur Alzheimer-Demenz aufwies (19%). Dieses hatte im Vergleich zu den anderen Clustern ein signifikant unterschiedliches Biomarker-Profil.

Diskussion

Die vorliegende Studie zeigt, dass Personen mit mnestischen Defiziten das größte Risiko hatten, innerhalb eines 5-Jahres-Zeitraums zur Alzheimer-Demenz zu konvertieren, interessanterweise sogar dann, wenn die mnestischen Defizite nur sehr leicht ausgeprägt waren. Dies wurde durch die Biomarkeranalysen bestätigt. Aus diesem Grund sollten schon leichte Gedächtnisdefizite ernstgenommen und davon ausgehend Präventionsmaßnahmen eingeleitet werden. Die gefundenen Clusterlösungen sollten in weiteren MCI-Stichproben überprüft werden. Interessant wäre in diesem Zusammenhang auch der Einfluss von IADL-Maßen auf die Clusterbildung.

4. Diskussion

Die vorliegende Arbeit hatte zum Ziel, die Herausforderungen des MCI-Konzepts – im Speziellen die Beeinträchtigung der IADL und die Klassifikation von Subtypen – näher zu untersuchen und dadurch mögliche Ansätze zur besseren Operationalisierung der MCI-Kriterien zu generieren. Das MCI-Konzept hat die Forschung zur Früherkennung von demenziellen Erkrankungen enorm stimuliert. Jedoch weist das Konzept wie unter 2.5 beschrieben einige Schwächen auf. Dies ist laut Petersen am ehesten auf die sehr schnelle Übernahme der 1999 veröffentlichten Forschungskriterien in die klinische Praxis zurückzuführen (Petersen et al., 2014). Der größte Schwachpunkt ist darin zu sehen, dass keine Vorgaben zur Operationalisierung der Kriterien gemacht werden (Stephan et al., 2013). Dies führt zu inkonsistenten Ergebnissen, unter anderem bezüglich epidemiologischer Daten sowie im Hinblick auf das Konversionsrisiko zur Demenz (Forlenza, Diniz, & Gattaz, 2010).

In der ersten Studie wurde der Forschungsstand bezüglich IADL-Defiziten bei Personen mit MCI anhand einer umfassenden Literaturanalyse dargestellt. Zudem erfolgte eine kritische Betrachtung der zur MCI-Definition verwendeten Kriterien. Hauptbefundlich zeigte sich, dass deutliche IADL-Defizite schon im MCI-Stadium vorliegen. Diese sind stärker ausgeprägt als bei kognitiv unbeeinträchtigten Personen und schwächer als bei Personen mit einer Demenzerkrankung. Die Defizite wurden über eine Vielzahl von internationalen Studien hinweg und relativ unabhängig vom eingesetzten Messinstrument gefunden. Dadurch wurde die Sinnhaftigkeit der revidierten Kriterien nach Winblad, welche IADL-Defizite bei Personen mit MCI erlauben (Winblad et al., 2004), bestätigt. Es gibt Belege dafür, dass kognitive Leistungen ein Prädiktor für die ADL- und IADL-Funktionsfähigkeit sind (Burdick et al., 2005; Tekin, Fairbanks, O'Connor, Rosenberg, & Cummings, 2001). Von daher erscheint es logisch, dass bei Personen mit MCI nicht nur das kognitive

Funktionsniveau im Bereich zwischen altersnormalen Leistungen und einer Demenz liegt, sondern eben auch das IADL-Funktionsniveau.

Im Vergleich zu einem narrativen Review (Gold, 2012) wurden in Studie 1 nicht nur Fragebogenverfahren untersucht, sondern auch Interviews und leistungsbasierte Verfahren. Für letztere zeigten sich im Hinblick auf die gefundenen Effektstärken leichte Vorteile bezüglich der Detektion von IADL-Defiziten. Generell konnte in den letzten Jahren ein steigendes Forschungsinteresse an leistungsbasierten Verfahren zur Erfassung von IADL bei MCI verzeichnet werden (Binegar, Hynan, Lacritz, Weiner, & Cullum, 2009; Lawrence, Giovannetti, Seligman, Libon, & Sestito, 2013; Schmitter-Edgecombe, McAlister, & Weakley, 2012; Wadley et al., 2008). Eine aktuelle Studie, die aufgrund ihres Erscheinungsdatums in unserer Übersichtsarbeit keine Berücksichtigung fand, zeigt ebenfalls die Überlegenheit von leistungsbasierten Verfahren im Vergleich zur Selbst- und Fremdeinschätzung (Puente, Terry, Faraco, Brown, & Miller, 2014). Unabhängig von der Art des eingesetzten Messinstruments ist eine sorgfältige und eigenständige Erfassung der IADL von zentraler Bedeutung. Beeinträchtigungen der IADL lediglich als Resultat der kognitiven Defizite zu betrachten und im klinischen Alltag als zweitrangig zu behandeln, würde zu kurz greifen. Zwar gibt es Belege für einen engen Zusammenhang zwischen kognitiver Leistung und IADL-Funktionsniveau (Braungart Fauth, Zarit, Malmberg, & Johansson, 2007; Dodge et al., 2005; Farias, Harrell, Neumann, & Houtz, 2003), jedoch erlaubt eine neuropsychologische Testung verschiedener kognitiver Parameter keine exakte Vorhersage des individuellen IADL-Funktionsniveaus. Nur durch die differenzierte Erfassung der IADL durch geeignete Messverfahren wird eine angemessene Beratung der Betroffenen und Angehörigen zu Unterstützungsangeboten im Alltag möglich. Auch können durch eine sorgfältige IADL-Einschätzung Ressourcen des Betroffenen identifiziert und gegebenenfalls gestärkt werden. Die routinemäßige Erfassung von IADL in der klinischen Praxis ist noch unter einem weiteren Gesichtspunkt bedeutsam: Personen mit MCI und IADL-Defiziten haben ein deutlich erhöhtes

Konversionsrisiko zur Demenz als solche ohne IADL-Defizite (Luck et al., 2011; Triebel et al., 2009).

Schwerpunktmäßig erscheint bei Personen mit MCI die Fokussierung auf kognitiv anspruchsvolle IADL sinnvoll. Dies macht auch eine Studie von Reppermund et al. deutlich: zur Untersuchung von ADL-Defiziten bei Personen mit MCI und kognitiv Unbeeinträchtigten setzten sie die Bayer-ADL ein. Anhand einer Faktorenanalyse konnten die einzelnen Items der Bayer-ADL in solche mit *high* (beispielsweise an fremden Orten zurechtkommen, zwei Dinge auf einmal erledigen) bzw. *low* (beispielsweise Essen zubereiten, Benutzen von Haushaltsgeräten) *cognitive demand* eingeteilt werden. Zur Baseline-Erhebung zeigten sich sowohl bezüglich des *high* als auch des *low cognitive demand* Faktors signifikante Gruppenunterschiede. Interessanterweise waren aber nur Defizite bezüglich des *high cognitive demand* Faktors prädiktiv für eine demenzielle Entwicklung bei der Follow Up-Untersuchung zwei Jahre später (Reppermund et al., 2013). Auch die Geschwindigkeit, mit der diese Aktivitäten im Vergleich zu früher durchgeführt werden, sollte erfragt und bei leistungsbasierten Verfahren miterfasst werden. Wadley et al. (2008) berichten von einer qualitativ korrekten Aufgabenbearbeitung bei Personen mit MCI, jedoch brauchten diese signifikant mehr Zeit als kognitiv unbeeinträchtigte Personen. Zur Optimierung der MCI-Kriterien könnten eben solche speziellen Bereiche angeführt werden, um eine Fokussierung auf IADL zu erreichen, die schon früh im Erkrankungsverlauf beeinträchtigt sind. Eine französische Studie beschränkte sich beispielsweise auf die Erfassung von vier IADL-Funktionen (Telefonbenutzung, Umgang mit Medikation, Regelung finanzieller Aktivitäten, Nutzung öffentlicher Verkehrsmittel) und fand signifikante Gruppenunterschiede zwischen Personen mit MCI und kognitiv unbeeinträchtigten Probanden (Peres et al., 2006).

Durch die systematische Literaturrecherche zu Studie 1 traten die zuvor erwähnten Schwachpunkte des MCI-Konzepts deutlich zutage: es existiert kein „Goldstandard“, der spezielle Testverfahren empfiehlt und Grenzwerte vorgibt. In Studie 1 wurden

über die 37 eingeschlossenen Arbeiten hinweg 31 verschiedene IADL-Messinstrumente identifiziert. Die neuropsychologischen Grenzwerte zur Bestimmung der kognitiven Defizite schwankten zwischen einer und eineinhalb Standardabweichungen unterhalb der Altersnorm. Einige der eingeschlossenen Studien nannten keine expliziten Grenzwerte bzw. orientierten sich nur am MMST-Wert. Hier ist der Einschluss von Probanden mit deutlich erniedrigtem MMST-Wert zu diskutieren: eine koreanische Studie berichtete für ihre MCI-Gruppe einen mittleren MMST-Wert von 23 Punkten (Kim et al., 2009). Dies wirft die Frage auf, ob hier Probanden eingeschlossen wurden, bei denen möglicherweise bereits eine manifeste Demenz vorlag, welche die gefundenen IADL-Defizite erklärt. Um solchen Problemen vorzubeugen, erscheint es sinnvoll, Untersuchungen mit MCI-Populationen durchzuführen, welche nur leicht ausgeprägte kognitive Defizite aufweisen und deren MMST deutlich höher liegt. Dieses Postulat wurde in Studie 2 und 3 befolgt. Zudem wurde in Studie 1 deutlich, dass die zur IADL-Erfassung eingesetzten Messinstrumente fast ausschließlich für den Einsatz bei Demenzkranken entwickelt wurden. Von daher erscheint es möglich, dass durch den Einsatz sensitiverer – d.h. speziell für MCI-Populationen entwickelte – Messverfahren noch weitaus deutlichere Beeinträchtigungen der IADL hätten gefunden werden können (Gold, 2012).

In der zweiten Studie wurde diesem Kritikpunkt nachgegangen und ein neues leistungsbasiertes Verfahren zur Erfassung von IADL bei Menschen mit MCI in einer Smart Home-Umgebung erprobt. Die leistungsbasierte Erfassung sollte eine Einschätzung der IADL ohne die Befragung eines Angehörigen ermöglichen. Dabei zeigten sich signifikante Gruppenunterschiede zwischen den MCI-Probanden und den kognitiv unbeeinträchtigten Probanden. Zum einen benötigte die MCI-Gruppe mehr Zeit, um die Aufgaben zu bearbeiten. Zum anderen erzielte die MCI-Gruppe eine geringere Punktzahl, d.h. sie machte mehr Fehler bei der Aufgabenbearbeitung als die Kontrollgruppe. Die in Studie 2 festgestellte längere Bearbeitungsdauer ist konform mit den Ergebnissen von Wadley et al. (2008), die anhand eines

leistungsbasierten IADL-Messverfahrens fünf IADL-Domänen erfassten (u.a. Finanzen, Medikation, Telefonbenutzung) und eine reduzierte Bearbeitungsgeschwindigkeit für MCI-Probanden dokumentierten. Im Gegensatz zu unseren Ergebnissen berichten die Autoren eine qualitativ gleichwertige Aufgabenbearbeitung zwischen MCI-Probanden und kognitiv Unbeeinträchtigten, d.h. die MCI-Gruppe konnte die Aufgaben nur langsam, aber mit Erfolg zu Ende führen. In unserer Studie zeigten sich jedoch Gruppenunterschiede hinsichtlich der Telefonbenutzung, des Bedienens des Fernsehapparats und des Wiederfindens zuvor verstauter Gegenstände. Bezüglich der Kaffee- und Sandwichzubereitung sowie des Verstauens der Gegenstände zeigten sich keine qualitativen Unterschiede. Dies könnte durch die vermutete Aufgabenschwierigkeit zu erklären sein. Folgt man dem Ansatz von Reppermund et al. (2013) würde man das Zubereiten von Getränken und Speisen sowie das Verräumen von Objekten eher einem *low cognitive demand* Faktor zuordnen, welcher auch bei Personen mit MCI kaum Beeinträchtigungen aufweist und nicht prädiktiv für die Entwicklung demenzieller Erkrankungen ist. Die Bedienung elektronischer Geräte sowie das Wiederfinden von Objekten wären dementsprechend eher als Aufgaben mit *high cognitive demand* einzustufen.

Studie 2 macht deutlich, dass Smart Homes nicht nur als Assistenzsysteme für die Unterstützung im Alltag angewendet werden können, sondern auch für die Detektion von IADL-Defiziten. Durch den Einsatz von Sensor- und Videotechnologie haben Smart Homes das Potential für eine vollautomatisierte und objektive IADL-Erfassung. Erste Erfolge in der Videoerkennung von ADL-Defiziten wurden von einigen Forschergruppen erzielt (Dawadi et al., 2013; König et al., 2015; Romdhane et al., 2012; Sacco et al., 2012). Auch die Entwicklung von Softwarealgorithmen zur Analyse von Verhaltensmustern rückt mehr und mehr in den Fokus (Liming, Nugent, & Hui, 2012). Durch den weiter voranschreitenden technologischen Fortschritt erscheint es denkbar, solche Systeme zukünftig in Privatwohnungen oder Pflegeeinrichtungen zu implementieren, um leicht erhebbare und reliable Daten zu Problemen in der

Alltagsbewältigung gewinnen zu können (Kaye et al., 2011). Auch ist es möglich, intraindividuelle Unterschiede in der Alltagsbewältigung über einen längeren Zeitraum zu erfassen (Dodge et al., 2015). Abweichungen von Verhaltensroutinen, Einbußen in der Bearbeitungsgeschwindigkeit oder zunehmendes Suchverhalten könnten als erste Warnhinweise einer demenziellen Entwicklung gelten. Auch in unserer Studie fanden sich signifikante Gruppenunterschiede zuungunsten der MCI-Gruppe bezüglich des Suchverhaltens. Solche Defizite können durch Fragebogenverfahren teilweise gar nicht abgebildet werden, vor allem wenn die befragten Angehörigen nicht mit dem Betreffenden zusammenwohnen und/oder ihn nur selten sehen. Im Vergleich zu Fragebogenverfahren erlaubt die leistungsbasierte Erhebung mit Smart Home-Technologien Rückschlüsse darauf, *wie* eine Aufgabe bearbeitet wird und nicht nur, *ob* diese noch ausgeführt werden kann. Zudem bietet ein Smart Home im Vergleich zu einem Laborsetting eine ökologisch validere Umgebung. In dieser können die Probanden von sogenannten *contextual cues* profitieren, welche die Aufgabenausführung erleichtern (Loewenstein & Mogosky, 1999). Trotz dieser Vorteile bleibt anzumerken, dass Smart Home-Umgebungen aufwendig zu realisieren und kostenintensiv sind. Zukünftige Studien sollten prüfen, ob Smart Home-Umgebungen anderen leistungsbezogenen Verfahren, die in einem Laborsetting durchgeführt werden können, überlegen sind. Insgesamt unterstreicht Studie 2 die Nützlichkeit von leistungsbasierten Verfahren, wobei – im Gegensatz zu anderen Arbeiten (siehe auch Studie 1) – auch die Fremdbeurteilungsverfahren signifikante Gruppenunterschiede aufzeigten. Bei der Auswahl der Probanden wurde, wie auch schon in Studie 1 postuliert, darauf geachtet, nur Personen mit leichtem MCI einzuschließen (MMST-Werte > 25). Eine Schwäche von Studie 2 ist – neben der relativ kleinen Stichprobe – das Querschnittdesign, welches keine Aufschlüsse erlaubt, ob und wann die untersuchten MCI-Patienten eine Demenz entwickeln.

Studie 3 hatte zum Ziel, unter Anwendung eines datenbasierten Verfahrens neuropsychologische Risikoprofile einer Demenzentwicklung in einer MCI-Stichprobe

zu identifizieren. Die erste Clusteranalyse (n = 485) ergab vier verschiedene Cluster. Die höchsten Konversionsraten zur Alzheimer-Demenz fanden sich für das Cluster mit Gedächtnisproblemen und ausgeprägten Defiziten der Exekutivfunktionen (47%), gefolgt von einem Cluster mit ausschließlich mnestischen Defiziten (32%). Das erstgenannte Cluster entspricht am ehesten dem multiple-domain amnestic MCI nach Petersen (2004). Da jedoch dieses Cluster mit der höchsten Konversionsrate gleichzeitig auch das mit dem niedrigsten MMST-Durchschnittswert war, wurde eine zweite Clusteranalyse mit einem Subsample gerechnet, dessen MMST-Werte ≥ 28 waren. Damit sollte dem Gedanken der Früherkennung in den Anfangsstadien einer kognitiven Beeinträchtigung Rechnung getragen werden. Diese erbrachte ebenfalls eine 4-Cluster-Lösung, wobei diesmal das Cluster mit ausschließlich mnestischen Defiziten die höchste Konversionsrate zur Alzheimer-Demenz aufwies (19%). Zudem zeigte sich für dieses Cluster ein Alzheimer-spezifisches Risikoprofil bezüglich der Biomarker und neuropsychologischer Testwerte. Insgesamt brachte die Studie Subtypen hervor, die nicht ganz deckungsgleich mit den von Petersen (2004) postulierten sind. Die Clusterlösung ohne MMST-Beschränkung zeigte dagegen deutliche Übereinstimmungen mit den von Delano-Wood et al. (2009) sowie Libon et al. (2010) empirisch abgeleiteten Subtypen. Datenbasierte Ansätze haben somit das Potential, bislang unentdeckte Risikomuster zu identifizieren. Auch zeigte sich durch Studie 3, dass die Subgruppen stark von der Operationalisierung der Kriterien abhängen (kein festgelegter MMST-Wert vs. MMST ≥ 28). Insgesamt bietet die empirische Ableitung von Subtypen die Chance, klinisch relevante Risikoprofile zu erstellen. Es wäre von großem Interesse, populationsbasierte Studien, welche die Konversion zur Demenz untersuchen, um datenbasierte Subtypenanalysen zu ergänzen. In Kombination mit Biomarkern könnte dies einen wertvollen Beitrag zur Schärfung von Hochrisikoprofilen leisten. Auch der Einbezug von IADL-Maßen wäre gewinnbringend: welchen Einfluss haben sie auf die Clusterbildung? Leisten diese

Cluster einen besseren Beitrag, was die Einschätzung des Konversionsrisikos zur Demenz betrifft?

Bezüglich der Biomarker zeigte sich in Studie 3, dass diese nützlich sein können für eine präzisere Bestimmung des Konversionsrisikos zur Demenz. Im klinischen Alltag sind Biomarker jedoch nicht zu 100% zuverlässig für die Vorhersage einer demenziellen Entwicklung, sondern dienen mehr einer Optimierung des diagnostischen Urteils sowie der ätiologischen Einordnung. Gomar et al. zeigten in einer longitudinalen Studie mit MCI-Probanden, dass kognitive Variablen und IADL-Beeinträchtigungen robustere Prädiktoren einer demenziellen Entwicklung sind als die meisten Biomarker (Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011). Anhand einer Metaanalyse kamen Schmand und Kollegen zu dem Ergebnis, dass Gedächtnisdefizite ein besserer Prädiktor für eine demenzielle Entwicklung sind als das Ausmaß der mediotemporalen Hirnatrophie. Liquorveränderungen hingegen sind bezüglich der prädiktiven Validität mit Gedächtnisdefiziten gleichzusetzen (Schmand, Huizenga, & van Gool, 2010). Diese Ergebnisse belegen, dass zum aktuellen Zeitpunkt keineswegs auf eine kognitive Testung, welche zudem kosten- und zeiteffizient ist, verzichtet werden kann. Eine umfangreiche Abklärung der kognitiven Defizite ermöglicht eine auf den Betroffenen und seine Angehörigen zugeschnittene Beratung. Mit den vorangegangenen Aussagen soll keineswegs die Nützlichkeit der Biomarker geschmälert, sondern die Wichtigkeit einer differenzierten Untersuchung betont werden. Eine alleinige Konzentration aller Forschungsressourcen auf Biomarker wäre nicht zielführend. Vielmehr sollte genau analysiert werden, welche Biomarker in Kombination mit kognitiven Variablen und IADL-Maßen die beste Vorhersage einer demenziellen Entwicklung liefern.

Insgesamt zeigt sich durch die drei vorliegenden Arbeiten, dass das MCI-Konzept ein heterogenes und komplexes klinisches Konstrukt ist. Dies erschwert eine gute Operationalisierung der Kriterien und damit auch eine Optimierung der prädiktiven

Validität. Zielsetzung dieser Dissertation war es, Ansätze zur Verbesserung der MCI-Kriterien zu generieren. Es lässt sich schlussfolgern, dass das Kriterium der „minimal beeinträchtigten IADL“ einer grundlegenden Überarbeitung bedarf, da sich sowohl in Studie 1 als auch in Studie 2 große Unterschiede zwischen Probanden mit MCI und kognitiv unbeeinträchtigten Personen zeigten. Die Formulierung „minimal beeinträchtigt“ ist in dem Sinne zu revidieren, dass schon im MCI-Stadium deutlich ausgeprägtere IADL-Defizite vorliegen können, vor allem in Bereichen, die kognitiv anspruchsvoll sind (Finanzen, Benutzung elektronischer Geräte). Wenn möglich, sollte der Einsatz leistungsbasierter Verfahren erfolgen. Dabei sollte darauf geachtet werden, speziell für MCI-Populationen entwickelte bzw. in MCI-Populationen validierte Instrumente einzusetzen. Die Frage nach exakten neuropsychologischen Grenzwerten kann nicht abschließend geklärt werden, jedoch sehen wir in diesem Bereich eine große Chance in empirisch abgeleiteten Subtypen. Diese bringen datenbasierte Risikoprofile hervor, die näher an der klinischen Realität sind als die konventionellen Subtypen nach Petersen (2004). In den MCI-Kriterien sollten daher Vorgaben zu kognitiven Domänen gemacht werden, welche unabdingbar zur Diagnosestellung überprüft werden müssen (z.B. unmittelbarer und verzögerter Abruf verbalen Materials). Die Ergänzung der MCI-Kriterien um exakte neuropsychologische Grenzwerte erscheint aufgrund der vorliegenden eigenen Befunde kontraindiziert. Viel eher sollten Risikokonstellationen genannt werden (beispielsweise verzögerter Abruf der Wortliste deutlich schlechter als unmittelbarer Abruf) und die Wichtigkeit einer ausführlichen neuropsychologischen Testung betont werden. Durch die empirische Ableitung von Subtypen könnte eine bessere neuropsychologische Definition des MCI-Konzepts allgemein und der Subtypen im Besonderen gelingen. Der Vergleich verschiedener Kriterien und deren prädiktiver Validität ist zwingend notwendig zur Schärfung des Konzepts (Bondi et al., 2014; Clark et al., 2013). Bondi et al. (2014) konnten zudem zeigen, dass neben objektivierbaren kognitiven Defiziten die Inklusion von ADL-Werten stabilere MCI-Diagnosen erbrachte.

Zukünftige Studien sollten das Ziel der Ableitung empirischer Subtypen unter Einbezug von IADL-Maßen verfolgen. Eine Validierung der so gefundenen Subtypen durch Biomarker wäre sinnvoll. Insgesamt sehen wir in der Fokussierung auf IADL-Defizite und der datenbasierten Ableitung von Risikoprofilen eine große Chance, die Früherkennung demenzieller Erkrankungen zu verbessern. Je frühzeitiger kognitive Defizite im Sinne eines MCI erkannt werden, desto eher kann man den Betroffenen sekundäre Präventionsmaßnahmen anbieten. Dadurch eröffnet sich ein potentiell größeres Zeitfenster für die Diagnose und Therapie modifizierbarer Risikofaktoren.

5. Praktischer Nutzen und Handlungsempfehlungen

Durch die vorliegende Arbeit lassen sich einige Handlungsempfehlungen für die klinische Praxis ableiten. So sollte verstärkt auf die Erfassung von IADL-Defiziten bei älteren Personen geachtet werden. Defizite in der Alltagsbewältigung in Kombination mit leichten kognitiven Defiziten können schon ein Warnsignal für ein erhöhtes Demenzrisiko darstellen und müssen daher ernstgenommen werden. Es erscheint auch sinnvoll, Personen, die häufig Kontakt zu älterem Klientel haben (Hausärzte, Pflegekräfte, Angehörige), diesbezüglich zu schulen. Zudem sollten leistungsbasierte Verfahren nach Möglichkeit verstärkt eingesetzt werden. Vor allem die Nutzung ökologisch valider Messinstrumente sowie der Einsatz von Smart Home-Technologien, welche zukünftig eine vollautomatisierte und objektive IADL-Einschätzung leisten könnten, sollten bedacht werden. Personen mit (leichten) kognitiven Problemen und IADL-Defiziten sollten als Hochrisikogruppe für demenzielle Erkrankungen betrachtet und regelmäßigen Verlaufsuntersuchungen unterzogen werden, vorzugsweise in spezialisierten Gedächtnisambulanzen. Auch sollte das Augenmerk auf Patienten mit kognitiven Defiziten, die noch knapp innerhalb vorgegebener Normen liegen, gerichtet werden. Die Bestimmung von Biomarkern kann helfen, das Risiko einer demenziellen Entwicklung und deren Ätiologie genauer einzuschätzen. Jedoch muss man beachten, dass dies aufgrund von Kosten und Verfügbarkeit meist nur in spezialisierten Einrichtungen möglich ist. Es erscheint daher sinnvoll, im Forschungskontext MCI-Subtypen mit besonders hohem Demenzrisiko durch Biomarker zu validieren. In der Praxis sollten dann aber Kriterien angewendet werden, die auch ohne die Bestimmung von Biomarkern zu einer zuverlässigen Diagnose führen. Für zukünftige Forschungsprojekte sollte der Fokus auf Probanden gelegt werden, die sehr leichte kognitive Beeinträchtigungen aufweisen, um dem Gedanken der Früherkennung Rechnung zu tragen.

6. Zusammenfassung

Die vorliegende Arbeit untersuchte die Schwierigkeiten und Herausforderungen des Mild Cognitive Impairment-Konzepts. Hierbei wurde ein Schwerpunkt auf die Aktivitäten des täglichen Lebens (ADL) sowie auf die Klassifikation von MCI-Subtypen gelegt. Dadurch sollten Möglichkeiten zur Schärfung des MCI-Konzepts aufgezeigt und somit ein Beitrag zur Verbesserung der Früherkennung demenzieller Erkrankungen geleistet werden.

In Studie 1 wurde der Forschungsstand zu Beeinträchtigungen der instrumentellen ADL (IADL) bei Personen mit MCI analysiert. Es zeigte sich, dass zum Teil ausgeprägte IADL-Defizite im MCI-Stadium existieren, vor allem in den Bereichen Finanzen, Telefonbenutzung, Umgang mit Medikamenten sowie Handhabung technischer Geräte. Amnestische MCI-Subtypen hatten größere IADL-Defizite als nicht-amnestische. Zudem waren leistungsbasierte Instrumente den Fragebogenverfahren leicht überlegen. Davon ausgehend wurde in Studie 2 ein neues leistungsbasiertes Verfahren zur Messung von IADL in einer Smart Home-Umgebung entwickelt und überprüft. Die MCI-Gruppe benötigte bei der Aufgabenbearbeitung insgesamt mehr Zeit und machte mehr Fehler als die kognitiv unbeeinträchtigte Gruppe. Sowohl Bearbeitungsdauer als auch Fehler bei der Aufgabenbearbeitung korrelierten moderat mit dem kognitiven Status der Probanden und auch mit traditionellen ADL-Maßen (Bayer-ADL, ADCS-MCI-ADL). Da sich in Studie 1 zeigte, dass ein großer Problempunkt des MCI-Konzepts in der fehlenden Operationalisierung der Kriterien liegt – sowohl hinsichtlich der IADL-Beeinträchtigungen als auch der kognitiven Defizite – wurde in Studie 3 eine datenbasierte Methode zur MCI-Subtypklassifikation erprobt. Dabei wurde eine 4-Cluster-Lösung ermittelt, die nicht ganz deckungsgleich mit den konventionellen Subtypen nach Petersen war. Der amnestische MCI-Subtyp zeigte das höchste Konversionsrisiko zur Alzheimer-Demenz, auch dann, wenn die kognitiven Defizite

nur sehr leicht ausgeprägt waren. Die Befunde wurden durch Biomarker-Analysen unterstützt.

Insgesamt konnten durch die vorliegende Arbeit Ansätze zur Verbesserung der MCI-Kriterien aufgezeigt werden. Zum einen sollten IADL, die besonders sensitiv bezüglich kognitiver Defizite sind, in den MCI-Kriterien genauer spezifiziert werden. Zudem sollten zur IADL-Erfassung eher leistungsbasierte Messverfahren eingesetzt werden. Zur präziseren Operationalisierung der Kriterien können datenbasierte Ansätze einen wertvollen Beitrag leisten.

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8. Anhang

8.1 Erklärung gemäß § 8 Abs. (1) c) und d) der Promotionsordnung der Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Erklärung gemäß § 8 (1) c) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation selbstständig angefertigt, nur die angegebenen Hilfsmittel benutzt und die Zitate gekennzeichnet habe.

Erklärung gemäß § 8 (1) d) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation in dieser oder einer anderen Form nicht anderweitig als Prüfungsarbeit verwendet oder einer anderen Fakultät als Dissertation vorgelegt habe.

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Peer-Review-Tätigkeiten

Alzheimer Disease & Associated Disorders
Alzheimer's & Dementia
BMC Geriatrics
Journal of Alzheimer's Disease
PLOS One

8.3 Originalartikel

Manuskript 1

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., Dubois, B., Eriksdotter, M., Ewers, M., Graessel, E., Kramberger, M. G., Law, E., Mecocci, P., Molinuevo, J. L., Nygård, L., Olde-Rikkert, M. G. M., Orgogozo, J. M., Pasquier, F., Peres, K., Salmon, E., Sikkes, S. A. M., Sobow, T., Spiegel, R., Tsolaki, M., Winblad, B., & Frölich, L. (2015). Mild Cognitive Impairment and Deficits in Instrumental Activities of Daily Living - a Systematic Review. *Alzheimer's Research & Therapy, 7*, 17.

Spezifikation des eigenen Beitrags

Die Erstautorin konzeptionierte die vorliegende Studie, führte die Literatursuche und Bewertung der gefundenen Artikel durch (unterstützt von MD, LH und LF), wertete die eingeschlossenen Arbeiten detailliert aus und erstellte das Manuskript. Zudem koordinierte die Erstautorin den Schriftverkehr mit den Ko-Autoren.

Jekel et al. Alzheimer's Research & Therapy (2015) 7:17
DOI 10.1186/s13195-015-0099-0

alzheimer's research&therapy

RESEARCH Open Access

Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review

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Abstract

Introduction: There is a growing body of evidence that subtle deficits in instrumental activities of daily living (IADL) may be present in mild cognitive impairment (MCI). However, it is not clear if there are IADL domains that are consistently affected across patients with MCI. In this systematic review, therefore, we aimed to summarize research results regarding the performance of MCI patients in specific IADL (sub)domains compared with persons who are cognitively normal and/or patients with dementia.

Methods: The databases PsycINFO, PubMed and Web of Science were searched for relevant literature in December 2013. Publications from 1999 onward were considered for inclusion. Altogether, 497 articles were retrieved. Reference lists of selected articles were searched for potentially relevant articles. After screening the abstracts of these 497 articles, 37 articles were included in this review.

Results: In 35 studies, IADL deficits (such as problems with medication intake, telephone use, keeping appointments, finding things at home and using everyday technology) were documented in patients with MCI. Financial capacity in patients with MCI was affected in the majority of studies. Effect sizes for group differences between patients with MCI and healthy controls were predominantly moderate to large. Performance-based instruments showed slight advantages (in terms of effect sizes) in detecting group differences in IADL functioning between patients with MCI, patients with Alzheimer's disease and healthy controls.

Conclusion: IADL requiring higher neuropsychological functioning seem to be most severely affected in patients with MCI. A reliable identification of such deficits is necessary, as patients with MCI with IADL deficits seem to have a higher risk of converting to dementia than patients with MCI without IADL deficits. The use of assessment tools specifically designed and validated for patients with MCI is therefore strongly recommended. Furthermore, the development of performance-based assessment instruments should be intensified, as they allow a valid and reliable assessment of subtle IADL deficits in MCI, even if a proxy is not available. Another important point to consider when designing new scales is the inclusion of technology-associated IADL. Novel instruments for clinical practice should be time-efficient and easy to administer.

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Introduction

Mild cognitive impairment (MCI) is a controversial clinical entity, initially conceptualized as a transitional zone between normal aging and dementia. The most commonly used criteria for MCI—also known as Mayo criteria—were proposed by Petersen *et al*. [1,2]. These criteria require (1) a memory complaint, (2) normal activities of daily living, (3) normal general cognitive function, (4) abnormal memory for age and (5) absence of dementia. These criteria have been modified to expand the original MCI concept, including impairments in cognitive domains other than memory. Thus, the clinical phenotypes of amnestic MCI and nonamnestic MCI have been developed, which can both be further classified as single-domain or multiple-domain [3]. Discussion about the MCI criteria and their operationalization is ongoing [4], as the criteria neither specify methods to assess cognitive or functional capacity nor provide cut-off points for cognitive or functional scales to differentiate MCI from mild dementia.

Another important point of discussion is the existence of deficits in activities of daily living (ADL). ADL are divided into basic activities of daily living (BADL) and instrumental activities of daily living (IADL). BADL include self-maintenance skills such as bathing, getting dressed or eating, and IADL consist of more complex activities such as using public transportation, managing finances, or shopping [5]. The assessment of ADL is usually done by using rating scales, which are administered either to the patient or a proxy. Controversy exists about the ability of patients with MCI to adequately rate themselves, as they lack awareness of IADL deficits and overestimate their functional capacity [6-8]. Farias *et al*., however, reported no lack of awareness in patients with MCI compared with healthy controls [9]. There is evidence that proxies are not always a reliable source of information, as they have a tendency to over- or underestimate IADL deficits [8,10,11]. In some cases, a proxy is not available or has massive knowledge gaps. Direct measures requiring the patient to solve specific IADL-related tasks have better validity and do not have reporter bias. However, they allow observation of only a small excerpt of real-world performance and are quite time-consuming.

It is assumed that IADL require more complex neuropsychological processing capacity than BADL and therefore are more prone to deterioration triggered by cognitive decline [12,13]. Functional deficits have been observed early in the course of decline [14-16]. In an analysis of studies with a focus on BADL and IADL in subjects with MCI, dementia or no cognitive deficits, Nygård [17] suggested that IADL can be impaired before the onset of dementia and should therefore be included in the diagnosis of MCI.

These findings were taken into account by Winblad *et al*. [18], who proposed the following criteria for MCI: (1) not normal, not demented; (2) cognitive decline; and (3) preserved BADL and/or minimal impairment in complex instrumental functions. Thus, the criterion of "normal activities of daily living" has been revised to a less stringent one allowing for discrete IADL deficits in patients with MCI.

Over the last 15 years, a large amount of research has been conducted on IADL deficits in MCI. The aim of the present review is to summarize research results regarding the performance of patients with MCI in specific IADL (sub)domains compared with persons who are cognitively normal and/or patients with dementia. In addition, sample characteristics and applied IADL assessment methods—performance-based instruments versus self- and/or informant-reported questionnaires or interviews—are investigated.

Methods

Data sources

To identify relevant published papers, the electronic databases PubMed, Web of Science and PsycINFO were searched in December 2013. Publication dates were set from January 1999 to December 2013. This restriction was chosen to identify only papers that were published after the introduction of Petersen's MCI definition [2]. The search terms "mild cognitive impairment" (MeSH term) or "MCI" were used in combination with the terms "activities of daily living" (MeSH term) or "ADL" or "instrumental activities of daily living" or "IADL" or "everyday functioning" or "functional ability" or "functional capability" or "functional deficits" or "functional impairment." After removal of duplicates, 497 articles were retrieved from the 3 searched databases.

Selection criteria

Titles and abstracts of the retrieved articles were screened by two authors (KJ and MD) independently and were rated to assess their relevance to the research question. If inconsistencies occurred, a third author (LH) was consulted. The following selection criteria were applied. (1) The abstract indicated that the focus of the study was the investigation of IADL in MCI versus healthy controls and/or dementia patients. (2) General IADL and/or specific subdomains were investigated. (3) The method of IADL assessment was standardized. (4) MCI was defined according to Petersen and/or Winblad criteria [2,3,18]. (5) No other concepts, such as cognitive impairment, no dementia [19,20], aging-associated cognitive decline [21] or age-associated memory impairment [22], were used. (6) The original article was written in English.

Articles that met the outlined criteria were included in the present review. Reference lists of the selected articles were searched to retrieve further relevant articles. Effect sizes (Cohen's *d*) were calculated to allow a better evaluation of clinical relevance.

Results

In total, 34 of the 497 papers were selected for review. Owing to the broad focus of the search terms to ensure retrieval of all relevant articles, the majority of articles did not meet the inclusion criteria (that is, no definition of MCI criteria, use of concepts other than Petersen and/or Winblad criteria). A further three articles were selected from among the reference lists of the selected papers. Thus, the content of the present review is formed from a total of 37 articles.

Mild cognitive impairment sample characteristics

For the diagnosis of MCI, the criteria of Petersen or Winblad were applied across studies; their operationalization, however, varied. One-third of the studies used the original Petersen criteria supplemented by cutoffs on specific neuropsychological tests [15,23-34]. In the remaining studies, the use of the original clinical criteria published by Petersen *et al.* [2] was reported without specific cutoff values or with a combination of Petersen and Winblad criteria. Mean Mini Mental State Examination (MMSE) [35] scores ranged from 23.1 [36] to 28.7 points [37] for MCI samples, from 26.5 [36] to 29.4 points [30,38] for normal control samples and from 16.4 [39] to 25.5 points [40] for Alzheimer's disease (AD) samples. In each examined study, however, the MMSE score for the MCI group was lower than that for the comparative control group and higher than that for the dementia sample.

Study types and/or designs

The majority of the reported studies followed a cross-sectional design (29 studies [15,23-26,29,30,33,34,36-38,40-56]), and eight studies applied a longitudinal design [27,28,32,57-61]. In five of the longitudinal studies, risk of conversion to AD depending on IADL impairment was also assessed [27,28,32,58,60].

Assessment instruments used

Altogether, 31 different instruments were used to assess IADL in patients with MCI (see Table 1 for details), including performance-based instruments, self- and informant-report rating questionnaires, and structured interviews. Of the 37 studies, 15 relied solely on informant-report rating questionnaires [23,28,29,31,33,40-43,45-48,54,58], 10 relied solely on performance-based assessments [24,26,30,32,38,50-53,57] and 6 relied solely on self-report rating instruments [27,36,55,56,59,61]. Three studies used both informant-report questionnaires and performance-based assessments [25,34,60]. Interestingly (and inconsistently), in three studies [15,25,44], the IADL of patients with MCI were rated by informants, whereas normal control subjects rated their IADL functioning themselves.

Mild cognitive impairment subtypes

According to Petersen *et al.* [1], MCI has two major subtypes: amnestic and nonamnestic. Both can be further divided into single-domain and multidomain types. Among the 37 studies included in this review, IADL performance was analyzed between MCI subtypes in 8 studies [23,31,33,37,40,48,58,61].

Instrumental activities of living in patients with mild cognitive impairment

Among the 37 studies included in this review, all but 2 studies [38,42] found IADL deficits in patients with MCI compared with control subjects without cognitive impairment on at least one applied instrument. In the following sections, we first report results of studies investigating global IADL (see Table 2), then results of studies in which informant-report measures were used and studies using self-report measures (see Table 3).

Global instrumental activities of daily living rating instruments

Performance-based instruments

Schmitter-Edgecombe *et al.* [34] designed the Day-Out Task (DOT), which requires multitasking in a real-world setting. Participants have to prepare for a day out and complete related tasks such as planning a bus route or packing specific items in a picnic basket. Patients with MCI required more time to complete the DOT than healthy controls and made more errors while solving the subtasks. By means of the Timed IADL, Wadley *et al.* [50] investigated both the speed and accuracy of patients with MCI in solving tasks related to shopping, finances, medication, telephone use and locating information on food labels. Patients with MCI took significantly longer than normal controls to solve the tasks and were less accurate. Using the Direct Assessment of Functional Status (DAFS), Pereira *et al.* [60] found that patients with MCI performed significantly worse than healthy controls and better than AD patients. Financial and shopping skills were the items that differentiated patients with MCI from healthy controls. Binegar *et al.* [57] applied the Texas Functional Living Scale and detected a significant but small difference between patients with MCI and controls. Interestingly, they mentioned that the performance of patients with MCI on this direct measure was much better (47 points) than that of patients with mild AD (31 points) in a previously conducted study [65].

Table 1 Instruments used for instrumental activities of daily living assessment[a]

Abbreviation	Full instrument name	Type	IADL domains	Psychometric properties
Performance-based assessment instruments				
DAFS [62]	Direct Assessment of Functional Status	P	6 domains: time orientation, communication, financial skills, shopping, grooming, eating	Good interrater and test–retest reliability, good evidence of discriminant and convergent validity, ceiling effects for time orientation, identify change and shopping
DOT [34]	Day-Out Task	P	8 tasks to prepare a day out (including packing a picnic basket, planning a bus route, gathering correct change for bus ride)	Interrater reliability: 96.92% agreement
EPT [63]	Everyday Problems Test	P	Problem solving related to medication use, meal preparation, telephone use, shopping, financial management, household management, transportation	Test–retest reliability: $r = 0.93$, internal consistency (Cronbach's α) = 0.88. Validity: significant correlations with direct observation of older adults' performance of everyday tasks ($r = 0.67$), older adults' self-reports ($r = 0.23$) and dementia patients' self-reports ($r = 0.36$)
FCI [64]	Financial Capacity Instrument	P	7 domains: basic monetary skills, financial conceptual knowledge, cash transactions, checkbook management, bank statement management, financial judgment, bill payment	For all subdomains: test–retest reliability $r > 0.8$, internal consistency (Cronbach's α) > 0.8
META [53]	Management of Everyday Technology Assessment	P	10 technology-related items (including performing actions in a logical sequence, turning a button)	Acceptable person response validity
TFLS [65]	Texas Functional Living Scale	P	5 domains: time/orientation, money, communication, dressing, memory	Test–retest reliability: $r = 0.93$ in AD sample, test–retest reliability in control group: $r = 0.52$, strong correlation with MMSE scores ($r = 0.92$)
TIADL [66]	Timed Instrumental Activities of Daily Living	P	5 domains: shopping, finances, medication, telephone use, locating information on food labels (speed and accuracy)	Test–retest reliability: $r = 0.85$
UAB-DA [67]	University of Alabama at Birmingham Driving Assessment	P	Real-world, standardized route: lane control, gap judgment, turning, maintaining proper speed, stopping distance, signaling, obeying traffic signs, preturn and postturn position, spacing, steer steadiness, precrossing and postcrossing position, and proper scanning of driving space	Not reported
UCSD-UPSA [68]	University of California San Diego Performance-Based Skills Assessment	P	5 domains: household chores, communication, finances, transportation, planning recreational activities	Test–retest reliability: $r = 0.92$
VAPS [52]	Virtual Action Planning Supermarket	P	Virtual reality supermarket, 8 parameters: total distance, total time in seconds, number of items purchased, number of correct actions, number of incorrect actions, number of pauses, combined duration of pauses, time to pay	Validity (correlations between VAPS performance and executive functions): $r = -0.40$ to $r = -0.63$
Self-report and informant-report rating instruments				
ADCS-ADL [69]	Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory	I	23 items (including shopping, hobbies, personal appliances; both IADL and BADL)	Moderate to good retest reliability, floor effects for financial abilities in individuals with dementia
ADCS-MCI-ADL-18 [69]	18-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory adapted for patients with mild cognitive impairment	I	18 items (including shopping, hobbies, personal appliances; both IADL and BADL)	Not reported

Table 1 Instruments used for instrumental activities of daily living assessment[a] *(Continued)*

ADCS-MCI-ADL-24 [45]	24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment	I	24 items (original ADCS-MCI-ADL scale plus 6 MCI-specific items, including driving a car, organizing medication)	Not reported
ADL-PI [70]	Activities of Daily Living-Prevention Instrument	I	15 items (including completing and/or organizing activities, taking medication, using telephone, finding belongings, managing finances)	Retest reliability: from $r = 0.69$ to $r = 0.74$
Bayer-ADL [71]	Bayer Activities of Daily Living Scale	I	25 items (2 BADL items, 18 specific IADL items, 5 items for cognitive functions)	Internal consistency (Cronbach's $\alpha > 0.98$)
DAD [72]	Disability Assessment for Dementia	I	IADL part with 23 items (meal preparation, telephoning, going on an outing, finances, medication, housework, leisure) and BADL part with 17 items	Internal consistency (Cronbach's $\alpha = 0.96$), interrater reliability (ICC = 0.95), test–retest reliability (ICC = 0.96)
DAD-6 [40]	6-item Disability Assessment for Dementia	I	6 items: meal preparation, telephoning, going on an outing, handling finances and correspondence, medication, leisure, housework	Not reported
DHQ [59]	Driving Habits Questionnaire	S	Driving difficulty in 8 different situations and driving frequency	Retest reliability: from $r = 0.65$ to $r = 0.86$ for the 8 situations
ETUQ [56]	Everyday Technology Use Questionnaire	S	86 items (including questions about technology at home and outside, communication)	Acceptable levels of internal scale validity, unidimensionality, and person response validity
FAQ [73]	Functional Activities Questionnaire	S/I	10 items (including finances, shopping, remembering appointments, playing games, preparing a meal, traveling, remembering appointments)	Not reported
FC-ADL [74]	Functional Capacities for Activities of Daily Living	I	50 statements reflecting possible IADL difficulties	Not reported
4-IADL [27]	4 IADL scale items chosen from Lawton and Brody's Instrumental Activities of Daily Living [5]	S	4 items: telephone use, finances, medication, transportation	Not reported
9-IADL [58]	9-item IADL scale	I	9 items: medication responsibility, ability to buy food, to prepare meals, to keep the home clean, to use the telephone, to handle finances, to use public transportation, to orientate oneself outside, to visit people	Not reported
IQCODE [75]	Informant Questionnaire on Cognitive Decline in the Elderly	I	26 items (including finances, communication, memory, household appliances)	Cronbach's $\alpha = 0.96$, correlation with MMSE ($r = 0.74$)
KI-IADL [34]	Knowledgeable Informant report about Instrumental Activities of Daily Living	I	50 questions assessing 10 IADL domains: using the phone, traveling, shopping, preparing meals, household activities, conversation, organization, social functioning, medication management, financial management	Not reported
L&B IADL [5]	Lawton and Brody's Instrumental Activities of Daily Living	S/I	8 items: shopping, grooming, medication responsibility, handling finances, mode of transportation, telephone use, food preparation, telephone use	Interrater correlation: $r = 0.85$
ROIL [76]	Record of Independent Living	I	37 items assessing 3 domains: activities, communication, behavior	Not reported
SR-IADL [77]	Self-report Instrumental Activities of Daily Living	S	Items include handling money, keeping appointments, planning meals (IADL performance and difficulty)	Reliability: $r = 0.74$
S-IADL [78]	Seoul-Instrumental Activities of Daily Living	S/I	15 items (including ability to prepare a balanced meal, remember appointments, ability to keep financial records, remember to take medication)	Good reliability and validity

Table 1 Instruments used for instrumental activities of daily living assessment[a] *(Continued)*

SIB-R [79]	Scales of Independent Behavior–Revised	S/I	13 subscales organized into 4 adaptive behavior clusters: (1) social interaction and communication, (2) personal living, (3) community living, (4) motor skills	Self-report: internal consistency (Cronbach's α) = 0.92, test–retest reliability: $r = 0.80$ Informant-report: internal consistency (Cronbach's α) = 0.95, test–retest reliability: $r = 0.84$
T-ADLQ [54]	Technology–Activities of Daily Living Questionnaire	I	7 subscales (self-care, household care, employment and recreation, shopping and money, travel, communication, technology)	Cronbach's α = 0.86; validity: significant correlations with the MMSE ($r = –0.70$)

[a]AD, Alzheimer's disease; ADL, Activities of daily living; BADL, Basic activities of daily living; I, Informant-report; IADL, Instrumental activities of daily living; ICC, Intraclass correlation coefficient; MMSE, Mini Mental State Examination; P, Performance-based; S, Self-report.

Using the Naturalistic Action Task, Giovanetti *et al*. [24] found that patients with MCI performed significantly worse than healthy controls, but better than persons with mild AD, on all three assessed tasks: preparing toast and coffee, wrapping a gift and preparing a lunch box. When cutoff scores were applied, no controls, but 24% of the patients with MCI and 76% of the AD group, fell within the impaired range. Goldberg *et al*. found a similar pattern of results when they applied a novel performance-based assessment (the University of California San Diego Performance-Based Skills Assessment): The cognitively normal control group outperformed the MCI group, which in turn performed better than the mild to moderate AD group [25]. Interestingly, using the informant-report Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory (ADCS-ADL), they detected no significant differences between patients with MCI and persons who were cognitively normal.

All of the performance-based instruments detected significant differences in IADL functioning between patients with MCI and healthy controls, as well as between patients with MCI and patients with dementia, respectively. Furthermore, patients with MCI needed more time to complete tasks than healthy controls and less time than patients with dementia. Calculated effect sizes were medium to large. In terms of effect sizes, the DAFS was the best measure for detecting differences in global IADL functioning between MCI and healthy controls (Cohen's $d = 1.58$) and between MCI and AD (Cohen's $d = 2.18$).

Informant-report rating instruments

Using the Seoul-IADL, Ahn *et al*. [41] found deficits in patients with MCI compared with healthy controls in the domains of telephone use, meal preparation, medication intake, management of belongings, keeping appointments, talking about recent events and performing leisure activities and/or hobbies. They concluded that IADL requiring memory or frontal cortex executive functioning are at particular risk of decline in MCI. Jefferson *et al*. [43] applied an error-based questionnaire of functional capacity (FC-IADL). The FC-IADL measures specific behaviors such as "getting lost in familiar places" and "does not use tools for the proposed use." On this questionnaire, patients with MCI scored more than 1.5 standard deviations (SD) worse than normal controls. In contrast, no statistically or clinically significant differences were found for the informant-report Lawton and Brody IADL scale.

In contrast, two other studies applying Lawton and Brody's IADL scale [44,45] showed that patients with MCI had deficits compared with controls regarding shopping, taking medications and handling finances.

Using the Record of Independent Living, Boeve *et al*. [42] found no significant differences between patients with MCI and healthy controls, but they did observe differences between patients with MCI and controls compared with dementia patients. This study is exceptional within this review because the participants were 90 to 100 years of age. Furthermore, the MCI group was very small (n = 13, compared with 56 healthy controls and 42 patients with dementia). Perneczky *et al*. [47] applied a questionnaire specifically designed for measuring IADL in MCI—the ADCS-MCI-ADL [69]—and found greater informant-reported impairments for the MCI group than among the age- and sex-matched cognitively normal controls. Pedrosa *et al*. [45] also reported better ADCS-MCI-ADL scores for healthy controls than for patients with MCI. Consistent observations—that is, differences between patients with MCI and healthy controls—in both studies were observed for finding personal belongings, balancing a checkbook, keeping appointments, using a telephone and talking about recent events. Furthermore, Pedrosa et al. compared the original ADCS-MCI-ADL scale with an extended version. (The authors added six items that they considered useful for MCI populations.) The 24-item version distinguished patients with MCI and healthy controls more reliably than the 18-item version [45]. Reppermund *et al*. [29], using the Bayer-ADL scale, found significant differences between patients with MCI and healthy controls. This effect was due to deficits of patients with MCI in the domains of observing important dates or events, reading, describing recent

Table 2 Studies investigating global instrumental activities of daily living functioning[a]

Author	Year	MCI criteria	Number of subjects	Mean age, yr (SD)	Mean MMSE score (SD)	IADL measures used	Results and effect sizes (Cohen's *d*)
Performance-based instruments							
Binegar *et al.* [57]	2009	Petersen	30 MCI	MCI 72.8 (7.9)	MCI 27.3 (2.2)	TFLS	Total score: MCI < NC ($d = 0.61$); subscales: significant for memory subscale ($d = 0.85$), but not for time/orientation, money, communication, dressing
		Clinical	30 NC	NC 73.7 (6.9)	NC 29.2 (1.0)		
				ns	significant		
Giovannetti *et al.* [24]	2008	Petersen	25 MCI	MCI 72.2 (6.7)	MCI 27.6 (1.4)	NAT	Total score: NC > MCI > AD; MCI versus NC: $d = 1.05$, MCI versus AD: $d = 1.46$ Error score: NC < MCI < AD; MCI versus NC: $d = 0.74$, MCI versus AD: $d = 1.78$
		1.5 SD below	18 NC	NC 73.1 (3.2)	NC 28.5 (1.0)		
		MMSE ≥25	25 mild AD	AD 73.6 (3.8)	AD 22.4 (2.8)		
				ns	(NC = MCI) > AD, $P < 0.05$		
Goldberg *et al.* [25]	2010	Petersen	26 MCI	MCI 77.5 (7.1)	MCI 26.1 (2.3)	UCSD-UPSA	UCSD-UPSA: NC > MCI > AD; MCI versus NC: $d = 0.86$, MCI versus AD: $d = 1.81$ ADCS-ADL: (NC = MCI) > AD; MCI versus AD: $d = 1.81$
		1.5 SD below	50 NC	NC 68.8 (9.9)	NC 28.5 (1.5)	Additional informant-report: ADCS-ADL (NC: self-report)	
		CDR 0.5	22 AD	AD 78.4 (5.4)	AD 20.3 (3.4)		
		MMSE ≥24					
Pereira [60]	2010	Petersen	31 MCI	MCI 72.6 (7.0)	MCI 27.3 (2.3)	DAFS	DAFS total score NC > MCI > AD; MCI versus NC: $d = 1.58$, MCI versus AD: $d = 2.18$ DAFS subdomains: NC > MCI for finances and shopping, but not time orientation, communication, grooming, eating, which were worse only in AD; IQCODE total score: NC > MCI > AD; MCI versus NC: $d = 1.00$, MCI versus AD: $d = 0.77$
		Clinical	32 NC	NC 71.6 (5.6)	NC 28.8 (1.5)		
			26 AD	AD 77.9 (6.0)	AD 19.5 (5.5)	Additional informant-report: IQCODE	
				AD > (MCI/NC)	AD < (MCI = NC)		
Schmitter-Edgecombe *et al.* [34]	2012	Petersen	38 MCI	MCI 70.5 (8.6)	Not reported	DOT	DOT: MCI < NC for completion time ($d = 0.60$) and accuracy ($d = 0.61$) KI-ADL: MCI < NC ($d = 0.50$)
		1.5 SD below	38 NC	NC 69.3 (7.9)		Additional informant-report: KI-ADL	
				ns			
Wadley *et al.* [50]	2008	Petersen	50 MCI	MCI 70.0 (7.9)	Not reported	Timed IADL	MCI = NC for accuracy MCI < NC for speed ($d = 0.75$), significant subdomains telephone ($d = 0.56$), grocery ($d = 0.75$), medication ($d = 0.51$), nutrition information ($d = 0.52$)
		Clinical	59 NC	NC 67.8 (7.1)			
				ns			

Table 2 Studies investigating global instrumental activities of daily living functioning[a] *(Continued)*

Informant-report rating instruments							
Ahn *et al.* [41].	2009	Petersen/Winblad	66 MCI	MCI 70.8 (7.3)	MCI 24.8 (3.1)	Seoul-IADL	MCI < NC ($d = 1.62$)
		1.5 SD below	61 NC	NC 64.4 (5.6)	NC 27.6 (1.4)		
		CDR 0.5		significant			
Boeve *et al.* [42]	2003	Petersen	13 MCI	MCI 94.3 (2.6)	MCI 26.8 (1.6)	ROIL	MCI = NC, MCI > dementia ($d = 2.93$)
		Clinical	56 NC	NC 93.8 (2.5)	NC 27.9 (2.3)		
			42 Dementia	Dementia 94.8 (2.6)	Dementia 18.6 (5.0)		
				ns	AD < (MCI = NC)		
Brown *et al.* [15]	2011	Petersen	394 MCI	MCI 74.9 (7.4)	MCI 27.0 (1.8)	FAQ (NC: self-report)	Severity of deficits: NC > MCI > AD; MCI versus NC: $d = 1.04$, MCI versus AD: $d = 1.71$ Number of deficits: NC < MCI < AD; MCI versus NC: $d = 1.28$, MCI versus AD: $d = 1.62$
		1.5 SD below	229 NC	NC 75.9 (5.0)	NC 29.1 (1.0)		
		CDR 0.5	193 AD	AD 75.3 (7.5)	AD 23.3 (2.1)		
		MMSE ≥24		ns	significant		
Jefferson *et al.* [43]	2008	Petersen/Winblad	38 MCI	MCI 74.6 (7.5)	MCI 28.0 (1.7)	L&B IADL	L&B IADL: MCI = NC, FC-ADL: MCI < NC ($d = 0.84$)
		Clinical	39 NC	NCI 72.4 (5.5)	NC 29.3 (0.9)	FC-ADL	
				ns	significant		
Mariani *et al.* [44]	2008	Petersen/Winblad	132 MCI	MCI 76.1 (5.8)	MCI 25.7 (1.6)	L&B IADL(MCI: informant-report, NC: self-report)	MCI < NC ($d = 0.29$)
		below normality cutoff	249 NC	NC 72.2 (7.5)	NC 28.1 (1.2)		
				significant	significant		
Pedrosa *et al.* [45]	2010	Petersen/Winblad	30 MCI	MCI 75.7 (6.4)	MCI 24.4 (3.3)	ADCS-MCI-ADL-18 ADCS-MCI-ADL-24 L&B-IADL	ADCS-MCI-ADL-18: NC > MCI > AD; MCI versus NC: $d = 1.39$, MCI versus AD: $d = 2.27$ ADCS-MCI-ADL-24: NC > MCI > AD; MCI versus NC: $d = 1.67$, MCI versus AD: $d = 2.33$ L&B IADL: NC > MCI > AD; MCI versus NC: $d = 2.0$, MCI versus AD: $d = 2.89$
		1 SD below	31 NC	NC 72.2 (8.0)	NC 27.7 (3.0)		
			33 AD	AD 76.1 (7.5)	AD 16.5 (5.2)		
Perneczky *et al.* [47]	2006	Petersen/Winblad	48 MCI	MCI 69.2 (8.3)	MCI 26.5 (2.3)	ADCS-MCI-ADL-18 Bayer-ADL IQCODE	ADCS-MCI-ADL-18: MCI < NC ($d = 1.98$) Bayer-ADL: MCI < NC ($d = 1.95$) IQCODE: MCI < NC ($d = 1.09$)
		1 SD below	42 NC	NC 66.7 (9.3)	NC 29.3 (0.7)		
		CDR 0.5		ns	significant		
Perneczky *et al.* [46]	2006	Petersen/Winblad	45 MCI	MCI 69.2 (8.3)	MCI 26.9 (1.4)	ADCS-MCI-ADL-18 Bayer-ADL	ADCS-MCI-ADL-18: MCI < NC ($d = 1.89$) Bayer-ADL: MCI < NC ($d = 2.44$)
		1 SD below	30 NC	NC 66.7 (9.3)	NC 29.3 (0.7)		
		CDR 0.5		ns			

Table 2 Studies investigating global instrumental activities of daily living functioning[a] *(Continued)*

Reppermund *et al*. [29]	2011	Petersen 1.5 SD below	293 MCI 469 NC	MCI 78.8 (4.7) NC 78.3 (4.7) ns	MCI 28.0 (1.5) NC 28.8 (1.2)	Bayer-ADL	Bayer-ADL total: MCI < NC ($d = 0.32$) Bayer-ADL high cognitive demand: MCI < NC ($d = 0.40$) Bayer-ADL low cognitive demand: MCI = NC
Reppermund *et al*. [28]	2013	Petersen 1.5 SD below	227 MCI 375 NC	MCI 78.6 (4.4) NC 77.9 (4.6) ns	MCI 28.3 (1.4) NC 28.9 (1.2) significant	Bayer-ADL	Bayer-ADL total: MCI < NC ($d = 0.39$) Bayer-ADL high cognitive demand: MCI < NC ($d = 0.40$) Bayer-ADL low cognitive demand: MCI < NC ($d = 0.27$), IADL performance at baseline predicted conversion to dementia at 2-year follow-up
Self-report rating instruments							
Kim *et al*. [36]	2009	Winblad 1 SD below	255 MCI 311 NC	MCI 72.0 (6.0) NC 70.7 (6.0) significant	MCI 23.1 (4.5) NC 26.5 (3.3) significant	Seoul-IADL	MCI < NC ($d = 0.27$)
Peres *et al*. [27]	2006	Petersen 1.5 SD below	285 MCI 828 NC 149 dementia	Total sample: 80.8 (5.6)	Not reported	4-IADL	NC > MCI > dementia
Comparison of MCI subtypes: informant-report rating instruments							
Aretouli *et al*. [23]	2010	Petersen 1.5 SD below CDR 0.5	124 MCI (36 asMCI 45 amMCI 26 nasMCI 17 namMCI) 68 NC	MCI 76.3 (7.5) NC 72.4 (7.3) significant	MCI 28.2 (1.3) NC 29.3 (0.9) significant	ADL-PI IQCODE	ADL-PI: MCI < NC, $P < 0.001$; all MCI subgroups < NC, $P < 0.001$, md = sd; am = nonam IQCODE: MCI < NC, $P < 0.001$; true for all subgroups; multiple > single, am = nonam
Luck *et al*. [58]	2011	Winblad 1 SD below	161 MCI (36 asMCI 42 amMCI 60 nasMCI 23 namMCI) 723 NC	MCI 81.9 (5.0) (aMCI 81.6 (4.8), naMCI 82.2 (5.2)) NC 81.2 (4.7) ns	Not reported	9 IADL items (Schneekloth and Potthoff [80])	MCI < NC (aMCI = naMCI; aMCI < NC ($d = 0.17$), naMCI = NC) MCI + IADL deficits: higher risk of conversion to dementia MCI + IADL: 47.4% versus MCI-IADL: 31.4%; NC + IADL: 26.7% versus NC-IADL: 8.0%

Table 2 Studies investigating global instrumental activities of daily living functioning[a] *(Continued)*

de Rotrou [40]	2012	Petersen Clinical	53 MCI (29 sdMCI 24mdMCI) 55 NC 31 Dementia	MCI 78.6 (7.3) NC 80.9 (4.2) Dementia 80.6 (6.2) ns	MCI 26.2 (2.2) NC 29.1 (1.0) Dementia 25.5 (1.8) All significant	DAD-6	NC > MCI > AD; MCI versus NC: $d = 1.29$, MCI versus AD: $d = 1.66$ NC > sdMCI ($d = 1.59$), sdMCI > mdMCI ($d = 1.37$)
Tam *et al.* [48]	2007	Petersen/Winblad CDR 0.5 1 SD below	54 asMCI 93 amMCI 78 NC 85 AD	asMCI 79.3 (6.1) amMCI 80.1 (6.5) NC 77.1 (5.1) AD 84.5 (5.9)	asMCI 25.4 (3.0) amMCI 22.3 (3.1) NC 27.2 (2.1) AD 17.9 (3.2)	DAD	IADL subscale: (NC = asMCI) > amMCI > AD; amMCI versus NC: $d = 0.98$, asMCI versus amMCI: $d = 0.80$, asMCI versus AD: $d = 2.93$, amMCI versus AD: $d = 1.71$
Teng *et al.* [31]	2010	Petersen MMSE ≥24	1108 MCI (532 asMCI 340 amMCI 162 nasMCI 74 namMCI) 3,036 NC	as 77.0 (9.2) am 75.3 (8.5) nas 74.1 (8.6) nam 73.0 (6.8) NC 74.8 (9.1) significant	as 27.8 (1.8) am 27.4 (1.8) nas 28.2 (1.7) nam 27.8 (1.5) NC 29.0 (1.2)	FAQ	NC > asMCI/amMCI/nasMCI; asMCI = amMCI, nasMCI = namMCI
Yeh *et al.* [33]	2011	Petersen 1 SD below MMSE ≥24	56 asMCI 94 amMCI 64 NC 102 AD	asMCI 77.5 (6.7) amMCI 78.9 (5.8) NC 76.5 (6.6) AD 79.6 (6.1)	asMCI 26.6 (1.6) amMCI 25.8 (1.6) NC 28.5 (1.3) AD 20.9 (3.1)	DAD	NC > MCI (as = am) > AD; asMCI versus NC: $d = 0.9$, amMCI versus NC: $d = 1.06$, asMCI versus AD: $d = 2.23$, amMCI versus AD: $d = 1.9$
Comparison of MCI subtypes: self-report rating instruments							
Wadley *et al.* [61]	2007	Petersen/Winblad 1.5 SD below	84 aMCI 171 naMCI 89 mdMCI 2,110 NC	aMCI 77.0 (7.0) naMCI 76.5 (6.2) mdMCI 78.8 (6.6) NC 72.9 (5.4) significant	aMCI 26.0 (1.9) naMCI 26.2 (2.1) mdMCI 25.1 (1.8) NC 27.6 (1.8)	IADL (Home Care questionnaire)	IADL performance: aMCI/mdMCI < NC, naMCI = NC; aMCI versus NC: $d = 0.23$, mdMCI versus NC: $d = 0.31$; aMCI < naMCI: $d = 0.23$ IADL difficulty: all MCI subgroups < NC; aMCI versus NC: $d = 0.57$, naMCI versus NC: $d = 0.27$, mdMCI versus NC: $d = 0.57$; aMCI < naMCI: $d = 0.23$

Table 2 Studies investigating global instrumental activities of daily living functioning[a] *(Continued)*

Comparison of MCI subtypes and all three types of instruments							
Burton *et al.* [37]	2009	Petersen/Winblad 1 SD below	6 asMCI 39 nasMCI 19 amMCI 28 namMCI 158 NC	asMCI 79.5 (5.7) nasMCI 77.5 (5.6) amMCI 82.0 (5.0) namMCI 79.6 (4.9) NC 73.6 (4.7)	asMCI 26.8 (2.5) nasMCI 28.7 (1.3) amMCI 28.2 (1.3) namMCI 28.7 (1.1) NC 28.9 (1.2)	Performance-based: EPT Self-report: L&B IADL, SIB-R; Informant-report: L&B IADL, SIB-R	Self-report: SIB-R: NC > mdMCI ($d = 0.71$), sdMCI > mdMCI ($d = 0.45$), L&B: MCI = NC; L&B IADL: MCI = NC Informant-report SIB-R: NC > sdMCI ($d = 0.46$), NC > mdMCI ($d = 0.51$); L&B IADL: MCI = NC EPT: NC > sdMCI > mdMCI; sdMCI versus NC: $d = 0.50$, sdMCI versus mdMCI: $d = 1.54$

[a]AD, Alzheimer's disease; ADCS-ADL, Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory; ADCS-MCI-ADL-18, 18-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory adapted for patients with mild cognitive impairment; ADCS-MCI-ADL-24, 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory adapted for patients with mild cognitive impairment; ADL, Activities of daily living; ADL-PI, Activities of Daily Living-Prevention Instrument; am, Amnestic multiple domain; aMCI, Amnestic mild cognitive impairment; as, Amnestic single domain; BADL, Basic activities of daily living; Bayer-ADL, Bayer Activities of Daily Living Scale; CDR, Clinical dementia rating; DAD, Disability Assessment for Dementia; DAD-6, 6-item Disability Assessment for Dementia; DAFS, Direct Assessment of Functional Status; DHQ, Driving Habits Questionnaire; DOT, Day-Out Task; EPT, Everyday Problems Test; ETUQ, Everyday Technology Use Questionnaire; FAQ, Functional Activities Questionnaire; FC-ADL, Functional Capacities for Activities of Daily Living; FCI, Financial Capacity Instrument; FC-IADL, Functional Capacities for Instrumental Activities of Daily Living; IADL, Instrumental activities of daily living; 4-IADL, 4-item Instrumental Activities of Daily Living scale items chosen from Lawton and Brody; 9-IADL, 9-item Instrumental Activities of Daily Living scale; ICC, Intraclass correlation coefficient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; KI-IADL, Knowledgeable Informant report about Instrumental Activities of Daily Living; L&B IADL, Lawton and Brody's Instrumental Activities of Daily Living; MCI, Mild cognitive impairment; md, Multiple domain; META, Management of Everyday Technology Assessment; MMSE, Mini Mental State Examination; nam, Nonamnestic multiple domain; naMCI, Nonamnestic mild cognitive impairment; nas, Nonamnestic single domain; NAT, Naturalistic action task; NC, Normal control; NIA-AA, National Institute on Aging and Alzheimer's Association; ns, nonsignificant; ROIL, Record of Independent Living; sd, Single domain; SD, Standard deviation; S-IADL, Seoul-Instrumental Activities of Daily Living; SIB-R, Scales of Independent Behavior–Revised; SR-IADL, Self-report Instrumental Activities of Daily Living; TADL-Q, Technology–Activities of Daily Living Questionnaire; TFLS, Texas Functional Living Scale; TIADL, Timed Instrumental Activities of Daily Living; UAB-DA, University of Alabama at Birmingham Driving Assessment; UCSD-UPSA, University of California, San Diego Performance-Based Skills Assessment; VAPS, Virtual Action Planning Supermarket.

Table 3 Studies investigating specific instrumental activities of daily living domains[a]

Author	Year	MCI criteria	Number of subjects	Mean age, yr (SD)	Mean MMSE score (SD)	IADL measures	Results and effect sizes (Cohen's *d*)
Financial capacity: performance-based instruments							
Griffith *et al.* [26]	2003	Petersen	21 MCI	MCI 68.1 (8.8)	MCI 28.4 (1.2)	FCI	NC > MCI > AD; MCI versus NC: $d = 1.14$, MCI versus AD $d = 1.21$
		CDR 0.5	21 NC	NC 66.7 (7.2)	NC 29.3 (1.0)		
			22 AD	AD 71.5 (9.2), ns	AD 24.1 (2.6)		
Sherod *et al.* [30]	2009	Petersen	113 MCI	MCI 70.3 (7.4)	MCI 28.1 (1.9)	FCI	NC > MCI > AD; MCI versus NC: $d = 1.03$, MCI versus AD: $d = 0.87$
		1.5 SD below	85 NC	NC 67.2 (8.2)	NC 29.4 (0.9)		
			43 AD	AD 73.8 (8.5)	AD 24.6 (2.9)		
				all significant			
Triebel *et al.* [32]	2009	Petersen	87 MCI	ADcon 74.4 (6.0)	ADcon 27.0 (1.9)	FCI	NC > MCI; ADnon versus NC: $d = 0.83$, ADcon versus NC: $d = 1.83$
		1.5 SD below	(25 ADcon, 62 ADnon)	ADnon 68.5 (7.5)	ADnon 28.6 (1.4)		
			76 NC	NC 66.7 (8.5)	NC 29.4 (1.0)		
Management of everyday technology: performance-based instruments							
Malinowsky *et al.* [53]	2010	Petersen	33 MCI	MCI 70.5 (8.4)	MCI 27.5 (1.9)	META	NC > MCI > AD, MCI versus NC: $d = 0.66$, MCI versus AD: $d = 1.23$
			45 NC	NC 73.2 (9.7)	NC 29.3 (1.1)		
			38 AD	AD 75.3 (9.1)	AD 23.5 (3.3)		
Malinowsky *et al.* [38]	2012	Petersen/ Winblad	33 MCI	MCI 70.8 (8.6)	MCI 27.5 (1.9)	META	NC > AD, MCI = NC
			42 NC	NC 72.6 (9.7)	NC 29.4 (1.0)		
			35 AD	AD 75.5 (9.2)	AD 23.5 (3.4)		
				ns			
Management of everyday technology: informant-report rating instruments							
Munoz-Neira *et al.* [54]	2012	Winblad	21 MCI	MCI 71.3 (9.1)	MCI 26.1 (2.5)	T-ADLQ	Total score: NC > MCI > AD, MCI versus NC: $d = 0.62$, MCI versus AD: $d = 1.47$ Subscales: NC > MCI on 2 subscales: employment and recreation: $d = 0.54$, travel: $d = 0.55$
			44 NC	NC 74.1 (7.3)	NC 27.8 (2.3)		
			63 AD	AD 73.9 (8.7)	AD 17.9 (5.8)		
Management of everyday technology: self-report rating instruments							
Nygård *et al.* [55]	2011	Petersen/ Winblad	37 MCI	MCI 67.0 (7.47)	MCI 27.5 (2.1)	ETUQ (support of proxy possible for patients with AD and MCI)	Perceived relevance of ET: NC > MCI > AD; MCI versus NC: $d = 0.51$, MCI versus AD: $d = 1.26$
			44 NC	NC 69.0 (9.58)	NC 29.1 (1.1)		
			37 AD	AD 72.0 (8.92)	AD 25.4 (2.8)		
				ns	ns		Perceived difficulty of ET: NC < MCI < AD; MCI versus NC: $d = 0.82$, MCI versus AD: $d = 1.26$
Rosenberg *et al.* [56]	2009	Petersen	30 MCI	MCI 74.0 (6.9)	MCI 27.0 (2.4)	ETUQ (support of proxy possible for patients with AD and MCI)	Perceived relevance of ET: NC > MCI = AD; MCI versus NC: $d = 1.66$
			93 NC	NC 74.0 (7.6)	NC 28.0 (1.7)		
			34 AD	AD 73.0 (8.4)	AD 24.0 (3.3)		Perceived difficulty of ET: NC < MCI < AD; MCI versus NC: $d = 0.59$, MCI versus AD: $d = 1.00$
				ns			
Driving capacity: performance-based instruments							
Wadley *et al.* [51]	2009	Petersen	46 MCI	MCI 71.3 (7.8)	Not reported	UAB-DA	MCI < NC, $d = 0.46$
			59 NC	NC 67.1 (6.7)			
				significant			

Table 3 Studies investigating specific instrumental activities of daily living domains[a] *(Continued)*

Driving capacity: self-report rating instruments							
O'Connor *et al.* [59]	2010	Petersen/ Winblad 1.5 SD below	304 MCI (82 aMCI 140 naMCI 82 mdMCI) 2,051 NC	MCI 76.8 (6.5) NC 72.6 (5.3) significant	Not reported	DHQ	(aMCI = naMCI = mdMCI) < NC (driving frequency, driving difficulty, driving space) differed at baseline and faster rates of decline Driving frequency: aMCI versus NC: $d = 0.31$, naMCI versus NC: $d = 0.24$, mdMCI versus NC: $d = 0.14$ Driving difficulty: aMCI versus NC: $d = 0.35$, naMCI versus NC: $d = 0.36$, mdMCI versus NC: $d = 0.45$ Driving space: aMCI versus NC: $d = 0.42$, naMCI versus NC: $d = 0.51$, mdMCI versus NC: $d = 0.43$
Shopping capacity: performance-based instruments							
Werner *et al.* [52]	2009	Petersen	30 MCI 30 NC	MCI 69.3 (7.4) NC 69.6 (7.3) ns	MCI 27.5 (1.3) NC 29.4 (0.7) significant	VAPS	MCI < NC; significant subscales: distance $d = 0.29$, trajectory duration: $d = 1.16$, duration of pauses: $d = 0.89$

[a]AD, Alzheimer's disease; ADcon, Converters to Alzheimer's disease; ADnon, Nonconverters to Alzheimer's disease; aMCI, Amnestic mild cognitive impairment, both single and multiple domains; CDR, Clinical dementia rating; DHQ, Driving Habits Questionnaire; ETUQ, Everyday Technology Use Questionnaire; FCI, Financial Capacity Instrument; MCI, Mild cognitive impairment; mdMCI, Multiple-domain mild cognitive impairment; NC, Normal control; ns, Nonsignificant; UAB-DA, University of Alabama at Birmingham Driving Assessment; VAPS, Virtual Action Planning Supermarket.

events, taking part in a conversation, taking a message, doing two tasks at a time, coping with unfamiliar situations and performing a task while under pressure. Conducting a factor analysis, the authors further subdivided the items into IADL with high or low cognitive demands. Group differences emerged only for the high cognitive demand factor, which consisted mainly of the items mentioned above, which in turn were responsible for the group differences between healthy controls and MCI subjects. The low cognitive demand factor consisted of items such as shopping, using transportation and preparing food. The same work group [28] gathered longitudinal data and again found differences in the Bayer-ADL scale between patients with MCI and healthy controls at baseline and at 2-year follow-up. For healthy controls, Bayer-ADL items with high cognitive demand predicted conversion to MCI and dementia at follow-up. Using the Functional Activities Questionnaire (FAQ), Brown *et al.* [15] detected significant differences between patients with MCI and healthy controls, and patients with MCI showed more deficits than healthy controls regarding financial skills and remembering events.

With the exception of one study [42], differences between patients with MCI and healthy controls were consistently detected. Deficits regarding financial abilities and memory-related IADL such as keeping appointments or remembering events were common themes across studies. With large effect sizes and consistent results across studies, the informant-reported ADCS-MCI-ADL seems to be a useful tool for global IADL assessment. The Lawton and Brody IADL scale delivered mixed results. Jefferson *et al.* detected no significant differences between MCI and healthy controls [43], whereas Pedrosa *et al.* found large effects [45] and Mariani *et al.* discovered small effects [44]. The same holds true for the Bayer-ADL. Large effects were seen in the two studies by Perneczky *et al.* [46,47], but only small effects were reported in the studies by Reppermund *et al.* [28,29].

Self-report rating instruments

Using the Seoul-IADL in a self-rating version, Kim *et al.* [36] found patients with MCI to be significantly impaired in using a telephone, keeping appointments, talking about recent events and using household appliances, thus replicating the findings of Ahn *et al.* with the Seoul-IADL in an informant-rating version [41]. In addition, Kim *et al.* also reported worse performance of the MCI group for transportation and finances. Peres *et al.* [27] investigated restriction to four IADL items from the Lawton and Brody IADL scale in a self-rating version: telephone use, mode of transport, medication responsibility and handling finances. Patients with MCI were more often restricted in IADL (34.3%) than controls (5.4%) and were less restricted than patients with dementia (91.1%). Interestingly, within a 2-year period, IADL-restricted patients with MCI converted to dementia more frequently than IADL-nonrestricted patients with MCI (30.7% versus 7.8%).

Global instrumental activities of daily living and mild cognitive impairment subtypes

When we analyzed MCI subtypes, differences between MCI subtypes and normal controls were reported for all applied measures except of the Lawton and Brody IADL scale. Looking at effect sizes, the IADL deficits tended to be more pronounced in multiple-domains MCI than in single-domain MCI and also in amnestic MCI than in nonamnestic MCI.

Informant-report rating instruments

Focusing on MCI subtypes, Tam *et al.* [48] found that the multiple-domains MCI subgroup had an intermediate IADL performance level between those of normal controls and patients with mild dementia on the Disability Assessment for Dementia (DAD) scale. Using the DAD, IADL performance, as well as subjects' performance regarding initiation or planning and organizing of the IADL subtasks, can be evaluated. The amnestic MCI group had significantly better IADL scores than the multiple-domains MCI group, and their scores were similar to those of the cognitively normal controls. The IADL subscales most frequently impaired in the multiple-domains MCI group were those connected to planning and organizing IADL tasks; initiation of tasks was unaffected.

Aretouli *et al.* [23] found significant differences between healthy controls and patients with MCI for 12 of 15 items on the Activities of Daily Living-Prevention Instrument. Major difficulties were reported for keeping appointments, using the telephone, remembering current events and finding things at home, and minor difficulties were reported for driving and using transportation, managing finances, organizing and completing activities, and taking medication. An analysis of the MCI subtypes revealed that all four subgroups showed deficits compared with normal controls. However, patients with multiple-domains MCI were not significantly different from those with single-domain MCI, and the amnestic groups did not differ significantly from the nonamnestic groups.

Using the DAD, Yeh *et al.* [33] reported more IADL deficits for both single-domain amnestic MCI und multiple-domains amnestic MCI than for healthy controls. Both MCI groups had better DAD scores than the mild AD group. When they looked at the DAD scores in detail, though, multiple-domains amnestic patients with MCI had deficits on a larger number of items than single-domain amnestic patients with MCI. Applying the DAD-6 (a shortened version of the DAD), de Rotrou *et al.* [40] reported similar findings. Using the FAQ, Teng *et al.* [31] reported better results for normal controls than for patients with MCI. In analyzing the subgroups, they found better results for normal controls than for the amnestic MCI group on all investigated IADL items and better scores than the nonamnestic group on managing bills, preparing taxes, keeping up with current events, attending to media, remembering dates and traveling outside the neighborhood. Luck *et al.* [58] investigated performance on nine IADL items and detected worse performance of patients with MCI compared with healthy controls. Analyses of MCI subtypes revealed that this effect was stronger for amnestic MCI subtypes.

Self-report rating instruments

Investigating MCI subtypes and normal controls, Wadley *et al.* [61] found all MCI subgroups reported significantly greater IADL difficulty and worse everyday functioning scores than normal controls at baseline. Over a 3-year period, all MCI groups also showed a significantly steeper decline on the everyday-functioning composite score and IADL performance compared with the cognitively normal group.

One study comparing all three assessment modalities

In a study by Burton *et al.* [37], three different IADL measures were used that revealed differences between MCI subtypes and healthy controls on the Scales of Independent Behavior–Revised (on both the self- and informant-report version) and the performance-based Everyday Problems Test. No differences between groups emerged with the use of Lawton and Brody's IADL scale with either the self-report or the informant-report version.

Specific instrumental activities of daily living domains

Financial capacity performance-based instruments

Financial capacity is the best-studied IADL subdomain. The Financial Capacity Instrument (FCI) has been used in three studies [26,30,32]. The FCI assesses financial capacity in seven domains, including monetary skills, financial concepts and bank statement management. All three studies revealed that the overall financial capacity (total score) of patients with MCI was worse than that of healthy controls. The activity "bank statement management" was consistently affected across studies. Griffith *et al.* [26] additionally found group differences regarding bill payment and financial concepts. Moreover, Triebel *et al.* [32] reported longitudinal data showing that, at baseline, MCI participants were significantly worse than normal controls on all financial domains and on total scores. Furthermore, the MCI group had been divided into converters and nonconverters to dementia. At baseline, the MCI nonconverter group performed better than the converter group in the domains of financial conceptual knowledge, cash transactions, bank statement management, bill payment and both total scores. No differences were observed for the domains of basic

monetary skills, checkbook management, financial judgment and investment decision-making. Over a 1-year period, declines in the domain checkbook management and the total score were observed for the converters, but not for the nonconverters or controls [32].

Management of everyday technology

Performance-based instruments In 2010, Malinowsky *et al.* [53] used a standardized observation-based tool (Management of Everyday Technology Assessment) to evaluate ability to manage everyday technology (ET; for example, electronic household appliances, remote controls, cell phones) in patients with mild AD or MCI and controls. They found significant differences between all three groups. Patients with MCI performed worse in using technology than healthy controls did, but better than patients with dementia. In a more recent analysis of the same sample by the same work group [38], significant differences were observed only between healthy controls and patients with dementia when intrapersonal and environmental features were controlled for. They reasoned that what influences a person's ability to use ET—besides cognitive level or diagnosis—is within-person variability in intrapersonal characteristics and environmental influence (that is, the design of the ET and the context in which it is used).

Informant-rating instruments Muñoz-Neira *et al.* [54] added a technology subscale to a Spanish ADL questionnaire. They found significant group differences between healthy controls, patients with MCI and patients with dementia for the total score. Patients with AD had worse scores than patients with MCI and healthy controls on all seven subscales. Comparing patients with MCI and healthy controls, only the recreation and travel subscales differed significantly; no difference was observed for the technology subscale.

Self-report rating instruments Applying the Everyday Technology Use Questionnaire, Rosenberg *et al.* [56] investigated the perceived difficulty in use of everyday technologies in samples with AD, MCI and controls. They found significant differences between groups, as well as in the amount of technologies that were considered relevant in each group. Using the same instrument, Nygård *et al.* [55] could replicate the above-mentioned findings. Furthermore, they found a moderately strong association between engagement in everyday life activities and perceived difficulty in ET use in these three samples.

Driving capacity

Performance-based instruments Wadley *et al.* [51] investigated driving ability, which revealed that patients with MCI were significantly more likely than participants who were cognitively normal to be given "less than optimal" ratings for left-hand turns, lane control and the global driving rating. Furthermore, they tended to receive more "less than optimal" ratings on gap judgment and maintaining proper speed. No differences were found for right-hand turns or steering steadiness. The authors noted, however, that the magnitude of difference between MCI participants' driving performance and that of controls was small, and that, as a group, MCI drivers were not sufficiently impaired to have their driving ability rated as unsafe or unsatisfactory.

Self-report rating instruments O'Connor *et al.* [59] investigated 5-year trajectories of mobility indicators, including driving frequency and perceived driving difficulty. The study revealed that driving frequency had a steeper decline in the MCI group compared with healthy controls. Furthermore, driving in both normal and demanding situations was perceived as more difficult by patients with MCI than controls.

Shopping capacity performance-based instruments

Werner *et al.* [52] directly assessed the IADL domain of shopping by means of a virtual reality supermarket scenario (the Virtual Action Planning Supermarket). They found that patients with MCI covered a significantly higher mean distance, had longer pauses and accordingly took longer to complete their shopping than normal controls. However, the number of purchases, correct or wrong actions, stops and mean time to pay did not differ between groups.

Discussion

This review impressively illustrates that deficits in IADL are consistently present in MCI. Of the 37 included studies, 35 revealed deficits in global IADL or in specific IADL subdomains such as finances, shopping, keeping appointments, driving or ET use. Furthermore, compared with healthy controls, patients with MCI needed longer to complete tasks and tended to be less accurate. Effect sizes were predominantly moderate to large. In analyzing the MCI subtypes, we observed that the IADL deficits tended to be more pronounced in multiple-domains MCI than in single-domain MCI and in amnestic MCI than in nonamnestic MCI, respectively.

In general, patients with MCI had intermediate functional performance between healthy controls and patients with mild AD, particularly in more complex tasks with high cognitive demand. Financial capacity, particularly, was affected in a vast majority of studies. On the general IADL questionnaires, telephone use, responsibility for medication and keeping appointments were the domains most often affected. Nevertheless, there were studies that revealed no deficits in these domains [37,42].

Even when comparing studies in which researchers used the same instrument, such as the Seoul-IADL [36,41], only three matching domains emerged: telephone use, keeping appointments and using household appliances. Similar inconsistencies were observed for Lawton and Brody's IADL Scale [5]. In two studies in which this instrument was used, investigators did not find any differences between patients with MCI and persons who were cognitively normal [37,43], supporting the argument that this scale is not sensitive enough to detect subtle deficits in MCI. However, researchers in two other studies [44,45] used the same scale and identified impairments in patients with MCI regarding the domains of shopping, medication and finances. One possible explanation for these inconsistencies is the very heterogeneous operationalization of the MCI criteria. Some studies relied solely on a clinical decision, and others used cutoff scores to determine the magnitude of cognitive impairment, but even the cutoff scores varied between 1 SD and 1.5 SD below age- and education-adjusted norms. Furthermore, the mean MMSE scores of MCI subjects ranged from 23.1 [36] to 28.7 points [37], and mean MMSE scores of normal controls ranged from 26.5 [36] to 29.4 points [30]. The problem with studies including patients with MCI with very low MMSE scores is that IADL deficits may be due to already present, but not yet diagnosed, dementia. In a long-term study of patients with mild AD (MMSE score range, 20 to 26), 45% to 65% could not perform usual IADL tasks at baseline, and 70% to 85% of the remaining patients needed assistance with IADL after 3 years [81]. For future research, it would be helpful to conduct (sub)analyses with patients with MCI who have a MMSE score of 27 points or higher to ensure that they have not already converted to dementia. Another possibility is to use cutoff scores of 1 SD, instead of 1.5 SD, below age- and education-adjusted norms in neuropsychological tests [82]. Moreover, it should be taken into consideration that the MMSE is a rather insensitive measure for cognitive functioning, as it is not adjusted for age and education. In general, the use of MMSE cutoff scores to define MCI should be scrutinized.

In reviewing the selected articles, we found that the variety of assessment instruments applied to assess IADL in MCI was impressive; 31 different instruments were identified (see Table 1), which complicates comparisons among studies. Another problem is that few of these instruments were constructed and validated for IADL assessment in patients with MCI. The majority of the instruments used were originally designed for studies with patients with dementia, and thus the items are not calibrated to detect subtle differences from normal. Moreover, data on psychometric properties are mainly insufficient; for an overview of IADL scales in dementia where the need for validation studies is explicated, see the article by Sikkes *et al.* [83]. Measures specifically designed for MCI populations are required. This may be exemplified by the failure of the ADCS-ADL scale to reveal differences between patients with MCI and healthy controls [25], whereas the ADCS-MCI-ADL scales definitely detected differences [46,47]. The problem could be solved by constructing more sensitive item scoring for MCI-specific scales and/or by investigating in detail only those domains that have been shown to be impaired consistently in MCI, such as financial capacity. When the domain of financial capacity was thoroughly analyzed by an interview or a performance-based assessment procedure, differences between patients with MCI and control participants with cognitive impairment were persistently observed [26,32,39] and invariably revealed large effect sizes.

Furthermore, the majority of assessment instruments do not investigate computer skills or the handling of "new" technology in general. The instruments targeting ET use are examples of scales that focus on a particular domain that proved to be sensitive to subtle impairment, and significant differences were detected through both self-reports and observations [53-56].

Performance-based assessment methods seem to be a promising tool, especially for patients without proxies to provide information about the patient's IADL. Moreover, performance-based methods would overcome another methodological issue related to self- and/or informant-report measures. In three reviewed studies [15,25,44], healthy controls rated their IADL capacity themselves, whereas MCI subjects were rated by their proxies. This inconsistency could lead to biased results, as rating procedures differed. All assessment methods have their limitations. When using self-report, patients tend to over- or underestimate their abilities and may not have full insight into the impairments caused by the disease. Informant-based methods rely on the informant's knowledge about the patient, which might be affected by the amount of care provided. In addition, family members tend to misjudge the patient's capacity. Performance-based instruments also have limitations, such as a higher degree of training needed by assessors, a more time-consuming evaluation and an unfamiliar environment that might bias the functional performance [84].

Furthermore, this review revealed some main problems of MCI definition. The operationalization of MCI is not clearly specified, which leads researchers to define cutoff points and choose assessment instruments of their own. The new criteria for prodromal AD/MCI due to AD may overcome this problem by including biomarkers for the diagnosis of the condition [85]. Nevertheless, the differentiation between MCI and dementia, as described in the new National Institute on Aging and Alzheimer's Association criteria, rests on the determination of whether there is significant interference in the ability to

function at work or in usual daily activities [86]. Therefore, the identification of IADL deficits in MCI as an early phase of AD is absolutely essential for clinical practice. Regarding the effect sizes, the differences between MCI subjects and healthy controls are not only statistically significant but also clinically relevant and can be considered quite robust. Defining a threshold of functional impairment, however, remains a difficult task. MCI is primarily a neuropsychologically defined construct. To give recommendations on exact thresholds, IADL measures which are specifically designed for and/or validated in MCI populations are needed first. If this is achieved, future criteria for MCI could postulate mild deficits in IADL functioning (that is, more than 1.5 standard deviations below healthy controls) in at least one of the following domains: financial abilities, keeping appointments, task completion time, task accuracy or remembering recent events.

It appears evident on the basis of this review that patients with MCI with IADL deficits are more likely to convert to dementia than are patients with MCI without IADL restrictions [27,32]. In fact, the presence of acquired IADL disability not due to a concomitant physical condition seems to be in itself a valid marker of prodromal AD. Studies assessing structural brain functioning and IADL impairment in MCI simultaneously [87] can help to identify relevant biomarkers of IADL deficits and at-risk individuals. Failure to detect an individual's functional impairments might preclude training of these activities by occupational therapy or lead to neglecting needs and providing an inadequate amount of care from community-based services. Deterioration in IADL abilities, rather than cognition impairments, predicted a greater need of home help services in AD [88].

Conclusions

Although there was no uniform agreement about which IADL domains are typically—that is, characteristically and/or specifically—impaired in MCI and which types of instruments may detect those best, a clear tendency nevertheless emerged, with activities requiring higher cognitive processes being consistently affected. Also, the use of performance-based measures and technology-related items seems to be promising.

Future research should concentrate on both the thorough validation of established instruments and the development of new ones. As new instruments for IADL functioning in MCI are being developed, researchers should include items measuring the domains of financial capacities, keeping appointments, task completion time and task accuracy. Moreover, studies comparing the three assessment modalities—that is, self-report, informant-report rating and performance-based—in the same sample are needed. In the long run, this could lead to a more precise definition of functional impairment in MCI in terms of quantifiable cutoff scores.

Abbreviations

AD: Alzheimer's disease; ADCS-ADL: Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory; ADCS-MCI-ADL-18: 18-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory adapted for patients with mild cognitive impairment; ADCS-MCI-ADL-24: 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory adapted for patients with mild cognitive impairment; ADL: Activities of daily living; ADL-PI: Activities of Daily Living-Prevention Instrument; am: Amnestic multiple domain; aMCI: Amnestic mild cognitive impairment; as: Amnestic single domain; BADL: Basic activities of daily living; Bayer-ADL: Bayer Activities of Daily Living Scale; CDR: Clinical dementia rating; DAD: Disability Assessment for Dementia; DAD-6: 6-item Disability Assessment for Dementia; DAFS: Direct Assessment of Functional Status; DHQ: Driving Habits Questionnaire; DOT: Day-Out Task; EPT: Everyday Problems Test; ETUQ: Everyday Technology Use Questionnaire; FAQ: Functional Activities Questionnaire; FC-ADL: Functional Capacities for Activities of Daily Living; FCI: Financial Capacity Instrument; FC-IADL: Functional Capacities for Instrumental Activities of Daily Living; IADL: Instrumental activities of daily living; 4-IADL: 4-item Instrumental Activities of Daily Living scale items chosen from Lawton and Brody; 9-IADL: 9-item Instrumental Activities of Daily Living scale; ICC: Intraclass correlation coefficient; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; KI-IADL: Knowledgeable Informant report about Instrumental Activities of Daily Living; L&B IADL: Lawton and Brody's Instrumental Activities of Daily Living; MCI: Mild cognitive impairment; md: Multiple domain; META: Management of Everyday Technology Assessment; MMSE: Mini Mental State Examination; nam: Nonamnestic multiple domain; naMCI: Nonamnestic mild cognitive impairment; nas: Nonamnestic single domain; NAT: Naturalistic action task; NC: Normal control; NIA-AA: National Institute on Aging and Alzheimer's Association; ns: nonsignificant; ROIL: Record of Independent Living; sd: Single domain; SD: Standard deviation; S-IADL: Seoul-Instrumental Activities of Daily Living; SIB-R: Scales of Independent Behavior–Revised; SR-IADL: Self-report Instrumental Activities of Daily Living; TADL-Q: Technology–Activities of Daily Living Questionnaire; TFLS: Texas Functional Living Scale; TIADL: Timed Instrumental Activities of Daily Living; UAB-DA: University of Alabama at Birmingham Driving Assessment; UCSD-UPSA: University of California San Diego Performance-Based Skills Assessment; VAPS: Virtual Action Planning Supermarket.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KJ conducted the literature search with support from MD, LH and LF and wrote the first draft of the manuscript. MEr, FP and LN added and analyzed literature regarding technology use. PJC, KP, EL and SAMS provided valuable input for restructuring parts of the manuscript. CW, RB, BD, MEw, EG, MGK, PM, JLM, MGMOR, JMO, ES, TS, RS, MT and BW were involved in revising the manuscript. All authors read and approved the final manuscript.

Acknowledgements

KJ received a scholarship from the Robert-Bosch Stiftung, Germany. MEw is supported by the European Commission Marie Curie Training Grant (PCIG12-GA-2012-334259) and the LMUexcellent Investment Fund. FP thanks LabEx DISTALZ (Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease) for their support. The work of SAMS is part of a fellowship project of Alzheimer Nederland, WE.15-2012-02. CW is currently receiving an ALF young researcher grant from Region Skåne, Sweden.

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Received: 13 June 2014 Accepted: 21 January 2015
Published online: 18 March 2015

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Manuskript 2

Jekel, K., Damian, M., Storf, H., Hausner, L., & Frölich, L. (in press). Development of a Proxy-Free Objective Assessment Tool of IADL in MCI Using Smart Home Technologies. *Journal of Alzheimer's Disease.*

Spezifikation des eigenen Beitrags

Die Erstautorin konzeptionierte die vorliegende Studie (unterstützt von LF und LH), rekrutierte die Probanden eigenständig, führte die Datenerhebung durch (zusammen mit MD und HS), wertete die Daten aus und erstellte das Manuskript.

Running head: Assessment of IADL in MCI Using Smart Home Technologies

Development of a Proxy-Free Objective Assessment Tool of IADL in MCI Using Smart Home Technologies

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Keywords: mild cognitive impairment, instrumental activities of daily living, performance-based measures, smart homes

ABSTRACT

Background: The assessment of activities of daily living (ADL) is essential for dementia diagnostics. Even in mild cognitive impairment (MCI), subtle deficits in instrumental ADL (IADL) may occur and signal a higher risk of conversion to dementia. Thus, sensitive and reliable ADL assessment tools are important. Smart homes equipped with sensor technology and video cameras may provide a proxy-free assessment tool for the detection of IADL deficits.

Objective: The aim of this paper is to investigate the potential of a smart home environment for the assessment of IADL in MCI.

Method: The smart home consisted of a two-room flat equipped with activity sensors and video cameras. Participants with either MCI or healthy controls (HC) had to solve a standardized set of six tasks, e.g. meal preparation, telephone use and finding objects in the flat.

Results: MCI participants needed more time (1384 vs. 938 seconds, $p < .001$) and scored less total points (48 vs. 57 points, $p < .001$) while solving the tasks than HC. Analyzing the subtasks, intergroup differences were observed for making a phone call, operating the television and retrieving objects. MCI participants showed more searching and task-irrelevant behavior than HC. Task performance was correlated with cognitive status and IADL questionnaires but not with participants' age.

Conclusion: This pilot study showed that smart home technologies offer the chance for an objective and ecologically valid assessment of IADL. It can be analyzed not only whether a task is successfully completed but also how it is completed. Future studies should concentrate on the development of automated detection of IADL deficits.

INTRODUCTION

For the definition of dementia, impairment in activities of daily living (ADL) is one of the key clinical criteria [1]. The assessment of ADL functioning is also important for patients suffering from mild cognitive impairment (MCI), as MCI patients with deficits in complex ADL functioning have a higher risk of conversion to dementia than MCI patients without ADL deficits [2-3]. In MCI, basic ADL functioning like eating or walking is preserved, but instrumental ADL (IADL) are often impaired. IADL requiring higher neuropsychological processes – like financial capacities, telephone use, finding things at home – are most at risk of decline [4]. Investigating functional and cognitive abilities in MCI participants, Bangen et al. found an association between IADL deficits and global cognitive functioning [5]. A study by Farias et al. revealed impairment of IADL domains that depend heavily on memory function [6].

In clinical practice, ADL functioning is usually assessed by informant-report measures like interviews or standardized questionnaires, less common is the use of self-report or direct performance-based measures. All of these measures have specific advantages and disadvantages: informant-report allows a quick evaluation of a broad range of everyday competences; however, a reliable proxy is not always available and evaluation can be prone to judgment biases [7-8]. Self-report also allows a quick evaluation of ADL functioning, however, patients with dementia lack awareness of their problems. In MCI there are inconsistent results regarding patients' self-assessment: some studies report preserved [9-10], others reduced awareness of deficits [11-12]. Using performance-based measures, a proxy is not necessary and judgment bias is a minor problem. Examples of existing performance-based measures are the "Revised Observed Tasks of Daily Living" [13] which assesses nine different IADL domains and has good psychometric properties or the "Financial Capacity Instrument" [14] which thoroughly analyzes financial abilities in 7 domains. However,

existing performance-based assessments are often time-consuming and mostly evaluate only a small range of ADL functioning, e.g. financial capacity [14]. Furthermore, the testing environment is quite artificial, which enhances internal validity but reduces ecological validity. A possible solution to this problem could be provided by smart home environments. A smart home is defined as „a physical world that is richly and invisibly interwoven with sensors, actuators, displays, and computational elements, embedded seamlessly in the everyday objects of our lives, and connected through a continuous network“ [15]. Smart homes have initially been developed to support people in their everyday life, monitor their health status, or detect falls. Research concentrated on activity recognition [16], detection of emergency situations or automation of processes [17]. The diagnostic value of smart homes, however, has only been recognized by few researchers so far who focus on the automated assessment of cognitive health [18]. Another stream of research concentrates on the development of fully automated video analyses to detect deficits in everyday functioning [19-21], however, they do not apply any additional sensor technology.

As smart homes are equipped with advanced technological devices and video cameras, those settings could be used to evaluate a person’s IADL functioning. The advantage of a smart home is that it offers a controllable, yet ecologically valid testing environment. Furthermore, rater bias could be thoroughly eliminated, as the technology offers the opportunity for a fully automated assessment, given the right algorithms. The aim of this study is to investigate the potential of smart home technologies for IADL assessment in MCI. Video analyses and sensor-based data will be recorded to find differences in IADL performance between patients with mild cognitive impairment and healthy controls. Furthermore, relationships between task performance and traditional ADL questionnaires will be analyzed.

METHOD

Participants

Participants aged 65 to 80 years were recruited at the memory clinic of the Central Institute of Mental Health in Mannheim, Germany. Mild Cognitive Impairment was determined using the Petersen clinical criteria [22]. Healthy controls were age- and gender-matched. All participants underwent a neuropsychological assessment to evaluate cognitive functioning. The assessment consisted of the CERAD-plus test battery [23], the Logical Memory task from the Wechsler-Memory Scale (Härting, 2000), the Clock Drawing Test [24] and the MMSE [25]. For the MCI group, participants had to be impaired in at least one cognitive domain (i.e., 1.5 SD below age- and education adjusted norms) and the MMSE had to be higher than 25 points. For the HC group, no cognitive deficits (i.e., all tests within age- and education-adjusted norms) were allowed. Patients with aberrant motor activity, or psychotic or major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Organization, 2000) were not included. For MCI participants, brain MRI scans were obtained via a 3.0-Tesla Magnetic Resonance Imaging (MRI) system (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). MRI data were analysed by experienced neuroradiologists using qualitative rating scales. Mediotemporal atrophy was assessed via the Scheltens' visual rating scale [26].

To control for depressive symptoms, the Geriatric Depression Scale (GDS; [27]) was administered to all potential participants. GDS scores of 6 and higher were an exclusion criterion. For the assessment of ADL functioning, participants' proxies completed the Barthel-ADL [28], the Bayer-ADL [29] and the ADCS-MCI-ADL-18 [30]. The Barthel-ADL assesses basic ADL functioning via 10 items, which include, among others, mobility, eating and continence. Maximum score is 100 points and indicates perfect ADL functioning. The Bayer-ADL consists of 25 items assessing basic and instrumental ADL functioning. Each item is rated on a 10 point scale, ranging from 1 (has never problems) to 10 (has always problems).

All answered items are summed up and divided by the number of answered items so that total scores range from 1 to 10. The ADCS-MCI-ADL consists of 18 items which mainly assess IADL functioning. The maximum score is 57 points and indicates completely intact ADL functioning.

The study was approved by the ethics committee of Heidelberg University, Germany. Informed consent was obtained from all participants and their proxies prior to enrolment.

IADL assessment in the smart home environment

The IADL assessment was conducted at the Fraunhofer Institute in Kaiserslautern, Germany. The smart home environment consisted of a 60 square meters two-room flat (see figure 1) equipped with (hidden) activity sensors and video cameras in every room.

-- figures 1 and 2 about here --

The flat was fully furnished and equipped with everyday objects like a television, book shelves, a kettle, armchairs and a telephone. Participants were told to imagine they moved into a holiday apartment and had to solve six tasks. Before the tasks started, participants had a 5 minute exploration phase to get familiar with the environment. The six tasks (see figure 3) were standardized and participants were handed over an instruction sheet for each task.

-- figure 3 about here --

Participants were instructed to do each task as quickly and accurately as they could. After task completion, participants were instructed to exit the apartment via the hallway door to get instructions for the next task.

Assessed parameters in the smart home environment

Task performance, i.e. IADL functioning, was assessed via different parameters. First of all, time to solve the single tasks was recorded via the activity sensors (when did participant start/stop the specific activity). Furthermore, the video material was analyzed to assess qualitative task performance. Two independent raters evaluated the different steps of task completion, interrater agreement was 98%. For example, task 4 (preparing a sandwich) consisted of 9 steps: 1) go into the kitchen, 2) get the bread, 3) toast the bread, 4) get a plate, 5) get a knife, 6) get the jam, 7) get the butter, 8) spread the toasted bread with jam and butter, 9) put the plate with the bread on the table. Correctly performed steps were evaluated with 1 point each, i.e. in task 4 a maximum of 9 points could be achieved. The 9 steps outlined above were mandatory to solve task 4 successfully and get the full score. However, to be scored as correct, the single steps to complete a task did not have to follow a specific order. This scoring procedure was chosen to enhance ecological validity, as there is a lot of individual variability in solving the tasks correctly. For all tasks together, the maximum score was 60 points.

Furthermore, task irrelevant behavior (e.g., stirring prepared cup of coffee while solving the television task) and searching behavior (e.g., opening cupboards to find a plate) were documented.

Feasibility questionnaire

After completion of all tasks, a semi-structured interview was conducted with each participant to evaluate feasibility of the IADL assessment in the smart home environment. The interview consisted of 14 questions, 9 of them had answer categories with a 5-point Likert Scale. Participants were asked whether the flat was “natural”, the tasks resembled everyday tasks, the tasks were easy to understand or whether they felt uncomfortable at any

time. Furthermore, they had to indicate things which could be improved and tasks they experience as difficult in their everyday life.

Statistical analyses

As data did not follow a normal distribution, non-parametric tests were applied for data analysis. For group comparisons, the Kolmogorov-Smirnov-Z test was applied, since it is recommended for small sample sizes and independent variables with few categories (Field, 2000). Furthermore, it provided more conservative results than the Mann-Whitney-U test. For correlation analyses, Kendall's tau (τ) was used, as it is recommended for small sample sizes with tied ranks (Field, 2009). Chi-square tests were applied for comparisons of categorical variables. Significance level for all analyses was set to $\alpha = .05$. All analyses were performed with SPSS 20.0.

RESULTS

Sample characteristics

The sample consisted of 11 MCI patients (mean age = 74.6 years, SD = 4.9) and 10 HC (mean age = 73.4 years, SD = 4.4). Clinical and demographic data of the sample are depicted in table 1. The majority of participants was female (MCI = 73%, HC = 70%). As groups were matched for age and gender, no group differences were observed for these variables. Furthermore, no group differences emerged for years of education, GDS score and the Barthel-ADL. Significant intergroup differences were found for the MMSE score (MCI: M = 27.5 points, SD = 1.0; HC: M = 29.6 points, SD = 0.5), the CERAD subtests, the Bayer-ADL score (MCI: M = 2.9, SD = 1.0; HC: M = 1.3, SD = 0.4) and the ADCS-MCI-ADL score (MCI: M = 45.4, SD = 4.4; HC: M = 54.1, SD = 2.8). For MCI participants, structural neuroimaging data, i.e. brain MRI scans, were available: 9 of 11 MCI participants (82%) showed clinically significant mediotemporal atrophy.

-- table 1 about here --

Performance in the smart home environment

Significant intergroup differences were observed for the performance of the IADL tasks in the smart home environment (see table 2 for details). The MCI group needed more time to complete the six tasks than the HC group (1384 vs. 938 seconds, $p < .001$). Looking at the single tasks, the MCI group needed more time than the HC group to complete task 1 ‘placing objects’, task 3 ‘making a phone call’, task 5 ‘operating the TV’ and task 6 ‘retrieving the objects’. No intergroup differences regarding time emerged for task 2 ‘making coffee’ and task 4 ‘preparing a sandwich’. In terms of total points, i.e. correctly performed

steps to solve all tasks, the MCI group differed significantly from the HC group (48 points vs. 57 points, $p < .001$). Looking at the single tasks, the MCI group obtained significantly fewer points than the HC group in task 3 ‘making a phone call’, task 5 ‘operating the TV’ and task 6 ‘retrieving the objects’. Furthermore, the MCI group showed more searching and task-irrelevant behavior than the HC group.

-- table 2 about here --

Correlation analyses

Correlation analyses revealed that neither IADL performance in the smart home nor ADL questionnaire scores were correlated with participants’ age (see table 3 for details).

-- table 3 about here --

Total time to perform the six tasks was significantly negatively correlated with the MMSE scores, $\tau = -.64$, $p < .01$. Total points were significantly positively correlated with the MMSE scores, $\tau = .85$, $p < .01$. Furthermore, total time was negatively correlated with total points, $\tau = -.49$, $p < .01$. Looking at the ADL questionnaires, significant correlations for both the Bayer-ADL and the ADCS-MCI-ADL with total time to solve the tasks and total points emerged. Regarding single items, the item ‘telephone use’ of the Bayer-ADL was significantly correlated with task 3 ‘making a phone call’, both for time ($\tau = .43$, $p < .01$), total points ($\tau = -.52$, $p < .01$) and number of dial attempts ($\tau = 47$, $p < .01$). Comparable results were observed for the corresponding item of the ADCS-MCI-ADL. The item ‘finding objects at home’ of the ADCS-MCI-ADL was correlated with the time to complete task 6 ‘retrieving

the objects' (τ = -.35, p < .05), task 6 total points (τ = .63, p < .01) and the number of retrieved objects in task 6 (τ = .60, p < .01).

Table 4 depicts correlations between selected CERAD-subtests and completion time of the single tasks. Generally, all reported correlations are negative: the smaller the z-score in the CERAD-subtests (indicating worse performance), the more time was needed for task completion. Task 3 'making a phone call' and task 6 'retrieving the objects' were significantly correlated with all CERAD-subtests. The fewest correlations were found for task 2 'making coffee' which showed moderate correlations with Trail Making Test A and B. Completion time of each of the 6 tasks was moderately correlated with Trail Making Test B.

-- table 4 about here --

Feasibility

The participants evaluated the smart home environment and the tasks as realistic (4.24 points, SD = .99, on a 5-point Likert scale, and 4.81 points, SD = .41, respectively). Moreover, they did not feel uncomfortable while solving the tasks (M = 1.2 points, SD = 0.5) or experienced the scenario as too long (M = 1.1 points, SD = 0.3). 52.4% evaluated task 6 'retrieving the objects' as the most difficult task, 14.3% considered task 3 'making a phone call' the most difficult.

DISCUSSION

The present study investigated the potential of smart home technologies to assess instrumental activities of daily living in MCI. Results show that the new assessment tool detected differences between MCI participants and healthy controls. First of all, MCI participants needed more time to complete the tasks than healthy controls. This is in line with findings of Wadley et al. who observed reduced speed in MCI participants while solving IADL-related tasks [31]. Analyzing the subtasks in our sample, significant intergroup differences were observed for placing and retrieving objects, making a phone call and operating the TV, whereas no differences regarding completion time emerged for making coffee and preparing a sandwich. The latter two tasks could be considered as not highly cognitive demanding: while they required the use of electronic devices (i.e., kettle and toaster, respectively) the participant only had to operate the on/off switch, not multiple steps as in the TV or telephone tasks. Research on IADL in MCI mainly comes to the conclusion that IADL requiring complex neuropsychological processes, e.g. financial capacity or operating technological devices, are affected early in the course of the disease [4, 32]. Reppermund et al. conducted a factor analysis by which they subdivided the Bayer-ADL items in items with high or low cognitive demand. Only the high cognitive demand items (e.g., observing important dates, doing two things at a time) reliably differentiated MCI patients from healthy controls [33].

In the present study, MCI participants not only needed more time to complete tasks, but also made more errors (i.e., scored fewer total points) than healthy controls. Looking at the subtasks, differences were observed for using the telephone, operating the TV and retrieving the objects. This means that qualitative task performance only differed in three of six tasks, partially supporting the findings of Wadley et al. who evidenced reduced speed in MCI patients but qualitatively intact IADL functioning [31]. Investigating IADL performance

in a naturalistic setting, Seelye et al. also observed that MCI participants made more errors than healthy controls while solving tasks but profited from indirect prompting [34].

Correlation analyses in the present study revealed moderate to strong relationships between “traditional” ADL questionnaires and the IADL assessment in the smart home environment. This underlines the usefulness of the newly developed method, as it reflects proxies’ evaluation. As the study aimed to develop a “proxy-free” assessment, the significant correlations are promising. Furthermore, the Trail Making Test B (a measure of executive functioning) was significantly correlated with completion time in each of the 6 tasks. This underlines the importance of intact executive functioning for task completion. Another interesting finding is that tasks 3 and 6, which were experienced as most difficult by participants, were significantly correlated with performance in *all* CERAD-subtests.

One major shortcoming of the present study is the small sample size. This is due to the fact that IADL evaluation in smart homes is an innovative field of research and cost-intensive. To some extent, logistic reasons were also responsible for the small sample size as participants had to be transported to the testing site which had the monitoring technology installed. However, the sample was very carefully chosen: MCI patients were matched to the healthy controls regarding age and gender. Only participants without any mobility constraints or major depression were included. The majority of MCI patients had clinically significant mediotemporal atrophy indicating underlying AD pathology. Moreover, MCI participants had an average MMSE of 27.5 points which is quite high compared to other studies investigating intergroup differences between MCI and healthy controls (see Jekel et al., 2015 for an overview). Nevertheless, significant IADL deficits were observed for the MCI group. The biggest strength of the study can be seen in the ecologically valid IADL assessment. While performance-based assessments are most often conducted in quite artificial laboratory settings, our study provided participants with a fully furnished two-room flat. Thus, participants were able to profit from environmental cues which facilitate ADL performance.

To make the setting even more naturalistic, future studies could incorporate distracters (e.g., a second person) and interruptions (e.g., a ringing phone which has to be answered) or tasks requiring multi-tasking abilities (e.g., listening to the radio and remembering the songs while making a sandwich).

By means of the sensor data and video recording, it was possible to unobtrusively observe and analyze *how* participants solved the tasks. Interestingly, in tasks 2 (making coffee) and 4 (preparing a sandwich) no significant intergroup differences emerged; however, MCI patients showed more searching and task-irrelevant behavior while solving the tasks. This could be a first indicator for cognitive decline and important for early detection of MCI. The chance to monitor *how* participants solve IADL-related tasks is an important advantage of smart home environments. However, in clinical routine settings, traditional IADL questionnaires are – at least for the moment – the method of choice, as they are inexpensive and do not involve logistic challenges.

Another shortcoming of the study is that it partially relied on an observer-rating of IADL performance. After successful pilot testing, the development of fully automated video and sensor data analyses should be intensified. Research groups already showed that automatic video monitoring systems can successfully detect differences in ADL performance (see König et al., 2015). Future research should concentrate on the validation of the tasks in a bigger sample and promote a fully-automated IADL assessment via sensors and video recordings. Besides, longitudinal studies exploring IADL performance of community-dwelling elders at baseline and their risk of conversion to dementia in the following years would be of interest. A first step into this direction has already been taken by Kaye et al. who unobtrusively collected in-home activity data in the homes of 265 elderly participants. The authors intend to use their assessment technology for the detection of incident cognitive and functional decline [35]. Similarly, it seems possible to implement the smart home

technologies of our study at care facilities to identify IADL deficits and provide individual assistance.

CONCLUSIONS

In sum, this study demonstrates the big potential of smart home technologies for the assessment of IADL functioning. Smart homes offer an ecologically valid environment, in which – via sensor-based technology in combination with video recording – more information about a patient's IADL can be gathered than via questionnaires. Future research should be conducted with a larger sample to validate tasks and concentrate on a fully-automated assessment of IADL functioning.

Study funding

KJ received a scholarship from the Robert-Bosch Stiftung, Germany.

Contribution of the authors

All listed authors made important contributions to the paper. KJ set up the experimental design, collected and analyzed the data and wrote the first draft of this paper. MD and HS supported the data collection. LH and LF were involved in designing the study and revising the final version of this manuscript.

Figure 1. Layout of the smart home.

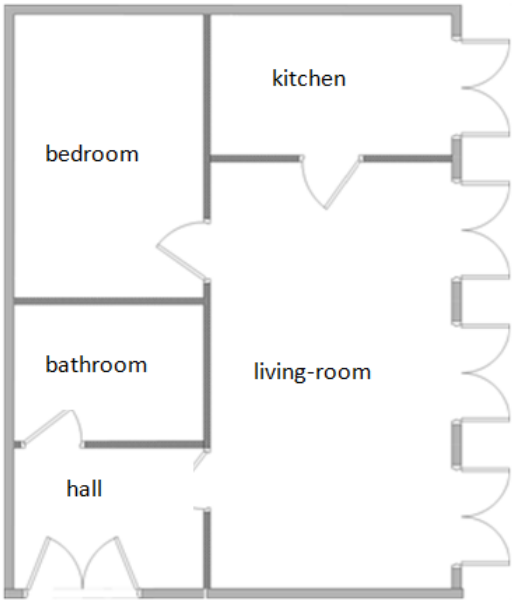

Figure 2. Living-room and kitchen of the smart home.

Figure 3. Tasks. Participants were instructed to …

1. … unpack 10 objects from a suitcase and bring them to prespecified places in the flat
2. … boil water in the kettle and make a hot coffee
3. … make a phone call and take a note from the telephonee
4. … prepare a sandwich with butter and jam
5. … switch on the TV, choose a channel and switch off the TV again
6. … retrieve the 10 objects and pack them into the suitcase again

Table 1. Characteristics and group comparisons for MCI and HC.

Characteristics	MCI group *n* = 11	HC group *n* = 10	*p*
Age in years, mean (SD)	74.6 (4.9)	73.4 (4.4)	.512
Female, n (%)	8 (73%)	7 (70%)	.890
Education, years, mean (SD)	10.2 (3.0)	11.5 (3.2)	.349
GDS, mean (SD)	3.1 (1.9)	2.7 (2.0)	.654
MMSE, mean (SD)	27.5 (1.0)	29.6 (0.5)	**.001**
Barthel-ADL, mean (SD)	96.4 (4.5)	97.0 (3.5)	.863
Bayer-ADL, mean (SD)	2.9 (1.0)	1.3 (0.4)	**.001**
ADCS-MCI-ADL, mean (SD)	45.4 (4.4)	54.1 (2.7)	**.001**
CERAD Word List learning, mean (SD)	-2.0 (0.6)	0.9 (0.8)	**.001**
CERAD Constructional Praxis, mean (SD)	-1.0 (0.8)	0.9 (0.8)	**.002**
CERAD Word List Recall, mean (SD)	-1.8 (0.3)	0.6 (0.5)	**.001**
Trail Making Test A, mean (SD)	-0.8 (0.7)	0.0 (0.4)	**.037**
Trail Making Test B, mean (SD)	-0.9 (0.6)	0.1 (0.4)	**.008**
Mediotemporal atrophy, n (%)	9 (82%)	-	-

MCI = Mild Cognitive Impairment, HC = Healthy Controls. Significant p-values < 0.05 are represented in bold characters. Geriatric Depression Scale (GDS) scores range from 0 to 15, with higher scores indicating depressive symptoms. Mini Mental State Examination (MMSE) scores range from 0 to 30, with higher scores indicating better cognitive functioning. Barthel-ADL scores range from 0 to 100, with higher scores indicating better ADL functioning. Bayer-ADL scores range from 1 to 10, with higher scores indicating worse ADL functioning. ADCS-MCI-ADL scores range from 0 to 57, with higher scores indicating better ADL functioning. CERAD and Trail Making Test mean scores are age- and education adjusted z-scores.

Table 2. Comparison of IADL performance between groups.

Parameters assessed	MCI group *n* = 11 M (SD)	HC group *n* = 10 M (SD)	*p*
Time in seconds			
Total	1384.3 (179.1)	938.1 (88.2)	**.000**
Task 1 – placing objects	309.7 (70.1)	229.9 (58.1)	**.029**
Task 2 – making coffee	194.0 (90.7)	156.3 (38.7)	.493
Task 3 – making a phone call	240.9 (60.3)	126.7 (30.8)	**.002**
Task 4 – preparing a sandwich	225.0 (55.7)	175.5 (28.8)	.098
Task 5 – operating the TV	167.0 (60.2)	104.9 (29.1)	**.032**
Task 6 – retrieving objects	247.6 (92.4)	144.8 (46.4)	**.041**
Points			
Total	48.0 (3.7)	56.8 (1.7)	**.000**
Task 1 – placing objects	10.8 (1.5)	11.6 (1.0)	.559
Task 2 – making coffee	6.9 (1.0)	7.9 (0.3)	.980
Task 3 – making a phone call	4.5 (1.2)	7 (0.0)	**.002**
Task 4 – preparing a sandwich	8.5 (0.8)	8.7 (0.7)	.999
Task 5 – operating the TV	7.7 (1.1)	8.9 (0.3)	**.032**
Task 6 – retrieving objects	9.5 (1.2)	12.7 (1.3)	**.000**
Searching behaviour	7.6 (5.4)	2.2 (2.0)	**.029**
Task-irrelevant behaviour	2.7 (1.5)	0.3 (0.5)	**.002**

MCI = Mild Cognitive Impairment, HC = Healthy Controls. Significant p-values < 0.05 are represented in bold characters.

Table 3. Correlations between IADL performance in the smart home and MMSE, age, ADL questionnaires.

	Total Points	MMSE	Bayer-ADL	ADCS-MCI-ADL	Age
Total Time	-.49**	-.64**	.47**	-.58**	.10
Total Points		.85**	-.68**	.70**	-.12
MMSE			-.67**	.66**	-.12
Bayer-ADL				-.80**	-.03
ADCS-MCI-ADL					-.07

**$p < .01$; *$p < .05$; N = 21.

Table 4. Correlations between completion time of the smart home tasks and CERAD-subtests.

time / z-scores	Task 1 Placing objects	Task 2 Making coffee	Task 3 Making a phone call	Task 4 Preparing a sandwich	Task 5 Operating the TV	Task 6 Retrieving objects
CERAD Word List Learning	-.52**	-.12	-.49**	-.32*	-.32*	-.41*
CERAD Constructional Praxis	-.30*	-.23	-.40**	-.29*	-.39**	-.43**
CERAD Word List Recall	-.33*	-.01	-.50**	-.23	-.18	-.35*
Trail Making Test A	-.26	-.36*	-.37**	-.44**	-.25	-.37**
Trail Making Test B	-.42**	-.33*	-.41**	-.35*	-.31*	-.38**

**$p < .01$; *$p < .05$; N = 21.

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Manuskript 3

Damian, M., Hausner, L., **Jekel, K.**, Richter, M., Frölich, L., Almkvist, O., Boada, M., Bullock, R., De Deyn, P. P., Frisoni, G. B., Hampel, H., Jones, R. W., Kehoe, P., Lenoir, H., Minthon, L., Olde Rikkert, M. G., Rodriguez, G., Scheltens, P., Soininen, H., Spiru, L., Touchon, J., Tsolaki, M., Vellas, B., Verhey, F. R., Winblad, B., Wahlund, L. O., Wilcock, G., & Visser, P. J. (2013). Single-Domain Amnestic Mild Cognitive Impairment Identified by Cluster Analysis Predicts Alzheimer's Disease in the European Prospective DESCRIPA Study. *Dementia & Geriatric Cognitive Disorders, 36,* 1-19.

Spezifikation des eigenen Beitrags

Die Drittautorin unterstützte MD bei der methodischen Konzeptionierung des vorliegenden Manuskripts, beteiligte sich an der statistischen Analyse der Daten sowie an der Erstellung und Überarbeitung des Textes.

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2013;36:1–19
DOI: 10.1159/000348354
Accepted: January 8, 2013
Published online: May 3, 2013
© 2013 S. Karger AG, Basel
1420–8008/13/0362–0001$38.00/0
www.karger.com/dem

Original Research Article

Single-Domain Amnestic Mild Cognitive Impairment Identified by Cluster Analysis Predicts Alzheimer's Disease in the European Prospective DESCRIPA Study

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Dement Geriatr Cogn Disord 2013;36:1–19
DOI: 10.1159/000348354
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Key Words
Mild cognitive impairment · Alzheimer's disease · Mild cognitive impairment subtypes · Conversion to Alzheimer's disease

Abstract
Background/Aims: To identify prodromal Alzheimer's disease (AD) subjects using a data-driven approach to determine cognitive profiles in mild cognitive impairment (MCI). ***Methods:*** A total of 881 MCI subjects were recruited from 20 memory clinics and followed for up to 5 years. Outcome measures included cognitive variables, conversion to AD, and biomarkers (e.g. CSF, and MRI markers). Two hierarchical cluster analyses (HCA) were performed to identify clusters of subjects with distinct cognitive profiles. The first HCA included all subjects with complete cognitive data, whereas the second one selected subjects with very mild MCI (MMSE ≥28). ANOVAs and ANCOVAs were computed to examine whether the clusters differed with regard to conversion to AD, and to AD-specific biomarkers. ***Results:*** The HCAs identified 4-cluster solutions that best reflected the sample structure. One cluster (aMCIsingle) had a significantly higher conversion rate (19%), compared to subjective cognitive impairment (SCI, $p < 0.0001$), and non-amnestic MCI (naMCI, $p = 0.012$). This cluster was the only one showing a significantly different biomarker profile ($A\beta_{42}$, t-tau, APOE ε4, and medial temporal atrophy), compared to SCI or naMCI. ***Conclusion:*** In subjects with mild MCI, the single-domain amnestic MCI profile was associated with the highest risk of conversion, even if memory impairment did not necessarily cross specific cut-off points. A cognitive profile characterized by isolated memory deficits may be sufficient to warrant applying prevention strategies in MCI, whether or not memory performance lies below specific z-scores. This is supported by our preliminary biomarker analyses. However, further analyses with bigger samples are needed to corroborate these findings.
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Introduction

Subjects with mild cognitive impairment (MCI) have an increased risk for Alzheimer's disease (AD) [1]. Previous studies have shown that specific subtypes of MCI are more likely to progress to AD-type dementia. However, there is still disagreement concerning the conversion rates of these subtypes, which in turn leads to the question of whether it is justified to label one of these subtypes the prodromal stage of AD [2, 3].

Previous approaches to define prodromal AD by specific cognitive subtypes had several problems. According to Petersen [4], MCI can be differentiated into amnestic (aMCI) versus non-amnestic (naMCI) subtypes, which can further be divided into the subtypes 'single domain' and 'multiple domains', depending on which and how many cognitive domains are impaired [1, 4]. However, as neither specific tests nor specific cut-off scores are prescribed to define cognitive impairment, Petersen's criteria are often operationalized in many different ways. In a Consensus Conference in Stockholm in 2003, these criteria were therefore revised by Winblad et al. [5]. The Stockholm MCI criteria standardized the definition of objective cognitive impairment by setting the cut-off point at –1.5 SD, minimizing the risk for false-positive diagnoses (in contrast to –1.0 SD). However, this cut-off point remains an arbitrary criterion. Defining MCI subtypes using pre-specified cut-offs leads to subtypes that are more theoretical entities than empirical groups with homogeneous cognitive profiles. Depending on the specific cut-off point, the distribution of the subjects across the subtypes can vary considerably [6, 7]. This is all the more evident when bearing in mind that often subjects fall into one subtype because they curtly 'miss' the alternative one. Hence, one cannot expect the

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resulting subtypes to be 'real' syndromes with a specific underlying pathology and, in turn, liability to progress to dementia, not to mention AD.

Visser and Verhey [8] examined 320 non-demented patients of a memory clinic and diagnosed MCI according to 5 sets of MCI criteria: ageing-associated cognitive decline [9], age-associated memory impairment [10], aMCI [4], and mild functional impairment [11]. After 5 years, 18% of the patients had progressed to AD, but the conversion rate strongly depended on the applied criteria and ranged from 20 (ageing-associated cognitive decline) to 38% (aMCI). The authors concluded that none of the present MCI concepts is fully predictive of AD conversion. Different biomarkers have been identified as useful in detecting prodromal AD, but they are still not universally available in routine clinical practice [12]. Hence, there is still a pressing need for further neuropsychological characterization of individuals with MCI who are most likely to convert to AD or other types of dementia [13].

The present study intended to identify a data-driven typology of MCI subtypes using hierarchical cluster analysis (HCA) and to validate the empirical clusters longitudinally, based on their rates of conversion to AD and on the basis of AD-specific biomarkers, in order to identify one cluster that could be regarded as the pre-clinical stage of AD. Unlike defining MCI subtypes using pre-specified cut-offs, cluster analysis determines the grouping of MCI subjects on the basis of the data at hand. We started from the assumption that isolating maximally different neuropsychological clusters by HCA would help identify one cluster that, in combination with a higher rate of conversion to AD and an AD-specific biomarker profile, could be labelled as the prodromal AD profile.

Materials and Methods

Study Design, Setting and Participants

The study was part of the DESCRIPA project, a 5-year multi-centre prospective cohort study conducted within the network of the European Alzheimer's Disease Consortium [14]. A cohort of 881 subjects with objective or subjective cognitive impairment (SCI, age ≥55) were assessed in 20 European memory clinics between March 2003 and March 2007. Subjects with subjective, but no objective cognitive impairment were included as MCI (not as healthy control subjects), as they have a higher risk of cognitive decline compared to subjects without subjective (and objective) impairment [15, 16]. Subjects with dementia or any somatic, metabolic, psychiatric or neurological disorder that may cause cognitive impairment were excluded. No healthy controls were included in the study. The study protocol was approved by the local Medical Ethics Committee of each centre. All participants and/or their authorized representatives gave their informed consent. For the following analyses, we selected only subjects with complete neuropsychological tests at baseline (see below) and at least 1 follow-up (n = 485).

Measurements

Clinical Assessment

All subjects underwent a standard battery of examinations, including clinical history, medical/neurological examinations, laboratory tests, MRI, neuropsychological examinations and clinical rating scales (CDR, neuropsychiatric scales, depression scales and ADL scales). Diagnoses were made on the basis of a clinical consensus. Both the clinical phenotype (syndrome) and the presumed aetiology were recorded. All subjects were invited for annual follow-up assessments for up to 5 years. Dementia was diagnosed according to DSM-IV [17] and AD according to NINCDS-ADRDA criteria [18] by the diagnostic team at each centre. Outcome measures included cognitive variables and progression to AD. Sixteen (80%) of the involved clinics also obtained biological data (CSF $A\beta_{42}$, t-tau, p-tau, APOE ε4 genotype, medial temporal lobe atrophy, MTA, and/or white matter lesions, WML). Data were collected by investigators who were blinded to the results of the CSF and blood analyses, as well as to the imaging results. The study methods are described in detail in Visser et al. [14, 19].

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Neuropsychological Examination

Because the participation of the centres in the DESCRIPA study was intended not to interfere with their routine practice, the neuropsychological tests used in this study varied among centres. However, all centres assessed the following cognitive domains: memory, language, executive function, attention and visuo-construction. For each cognitive domain, a primary test was selected at each centre that was the same as, or similar, to the tests that were used at the other centres [14]. The primary tests to assess memory were the learning and delayed recall measure of the Rey auditory verbal learning test [20, 6 centres], and the word list of the Consortium to Establish a Registry for AD (CERAD) test battery [21, 3 centres]. The primary test to assess language was the 1-min verbal fluency test for animals [22, all centres]. The primary test to assess speed/attention and executive function was the trail-making test (TMT), parts A and B [23, all centres]. The primary tests to assess visuo-construction were the copy subtest of the Rey-Osterrieth complex figure [24, 7 centres], or the copy of the CERAD figures [21, 2 centres]. If patients had missing data in these primary tests, alternative tests were used, which were selected beforehand for each primary test [14, 19]. All centres administered the MMSE [25]. Raw test scores were transformed to standardized scores wherein the age, education and gender of the subjects were taken into consideration. The standardization of the test scores was performed using normative data routinely used at each centre. In order to be able to merge the data from the different centres, further analyses were performed using z-scores. The relevant methods have been detailed elsewhere [14, 26–29]. For the analyses reported in this paper, the 6 'key' cognitive scores were selected, as a relatively big portion of the sample (485 of the 881 subjects) had data in these variables. These variables were either single measures of a cognitive domain (e.g. the variable 'tmt-a' assessing speed and attention on the basis of the TMT-A score alone), or were composite variables containing information from tests selected as primary, or alternative tests (e.g. 'learning', assessing episodic memory on the basis of CERAD, ADAS-cog and word lists of other tests).

Cerebrospinal Fluid

CSF was collected to measure $A\beta_{42}$, t-tau and p-tau with single-parameter ELISA kits. The operators analysing the CSF data were blinded to all clinical information. In order to provide reference data for the prevalence of a CSF AD profile, 93 healthy controls were selected from another study [19]. All CSF values were expressed as z-scores and corrected for age and gender if appropriate, based on the reference population of the healthy control subjects [14]. The z-scores of $A\beta_{42}$, t-tau and p-tau were inverted such that for all measures a more negative z-score indicated a more severe reduction (as was expected for $A\beta_{42}$) and a more positive z-score indicated more elevated concentrations (as was expected for t- and p-tau). Of the 487 subjects included in this investigation, CSF data were available for 182 subjects from 8 study sites.

Genetics

The APOE ε4 genotype was determined by PCR of genomic DNA, extracted from EDTA anti-coagulated blood using the PCR technique [27]. Data for APOE ε4 were available for 546 subjects from 16 study sites.

Imaging

In some of the centres, subjects underwent a neuroimaging examination, i.e. either CT or MRI, according to the routine protocol of the specific centre. Although the scanners and protocols at different sites varied, the imaging data were collected and analysed centrally [27]. For the analyses presented here, 2 imaging variables were selected: MTA and WML. Both were rated with qualitative rating scales [24, 25], using a 5-point visual rating scale to assess MTA, and the Age-Related White Matter Changes Scale to assess WML. MTA and WML data were available from 10 sites for 370 and 372 subjects, respectively. Subjects with and without data for the neuropsychological or biomarker variables did not differ from each other with regard to age, gender and education. As the most important conclusions were those drawn from the analyses pertaining to the clusters, the only differences tested were those within each cluster.

Whereas the cluster analyses included 485 subjects with complete data sets in the cognitive variables used to build the clusters, only 114, 331 and 246 of the original 881 subjects had data in the CSF, APOE ε4 and imaging variables, respectively. The analyses reported here included different portions of the complete sample, as the sample size would have been reduced to only 71 subjects if only subjects with complete data sets in all of the above-mentioned variables had been selected.

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Statistical Procedures

Hierarchical Cluster Analysis

HCA was performed to investigate whether the heterogeneous MCI cohort could be differentiated into more homogeneous subgroups. To sort the subjects into different clusters, the 6 neuropsychological variables were entered into the analysis in order to build groups of subjects with possibly homogeneous but distinct cognitive profiles. The hierarchical method was chosen because – unlike partitioning methods – it does not start from a specific predefined grouping of the elements, but determines the grouping on the basis of the data at hand. The clustering of cognitively similar subjects into one group was reached using an agglomerative algorithm, where the starting point was the finest partitioning of the elements: at the beginning of the clustering procedure each subject constituted its own cluster and subsequently the algorithm put those subjects and clusters together to which had the most similar cognitive profile, i.e. which minimized the distance or the heterogeneity measure.

Due to the metric level of the z-transformed neuropsychological scores, the distance measure 'squared euclidean distance' was chosen, as several linkage algorithms are based on this measure. The Ward method was used because other grouping methods have several drawbacks or are very difficult to understand. A simulation study by Bergs [30] showed that, compared to the other algorithms, Ward's method offers good partitions, puts the elements in the 'correct' groups and signals the correct number of clusters. The Ward algorithm summarizes those elements or clusters which augment the heterogeneity measure (here the variance criterion) in a minimal degree, so that Ward's method is also suitable to build maximally homogeneous groups. To help determine the optimal number of clusters, the horizontal hierarchical tree plot was used to visualize the course of the used heterogeneity measure during the agglomeration process.

Two HCA were performed: the first HCA included all 485 subjects with complete cognitive data sets; the second HCA was run selecting subjects with baseline MMSE ≥28, i.e. with very mild MCI. We chose MMSE ≥28 because in subjects with 'normal' educational level (in general at least 8 years), and age ≥65, the corresponding z-scores are still in the normal range [31]. By this selection we could also rule out a possible confounding effect of the overall severity of cognitive impairment on cluster building.

Logistic Regression Analysis

To investigate whether sub-classifying MCI subjects enhances the prediction of AD compared to the plain use of cognitive test scores, logistic regression analyses (LRA) were computed, using the variable 'conversion to AD' as the binary dependent variable (converted vs. not converted at follow-up) and the cluster and cognitive variables as predictor (independent) variables. Different sets of predictors were included as independent variables in order to compare their suitability to predict conversion to AD.

Three sets of predictors were chosen. The first set contained the 6 aforementioned cognitive variables only. The second set included these cognitive variables plus the cluster variable cluster_485. This variable resulted from the cluster analysis that included all 485 subjects and contains information about the cluster membership of these subjects (e.g. if subject 1 has a '2' in this variable, this means that this subject was classified into cluster 2, whose label will be described in the results section). The third set of predictors included the cognitive variables, the cluster variable cluster_485, and the cluster variable cluster_313. The last-mentioned variable resulted from the cluster analysis that included only the 313 subjects with very mild MCI, i.e. MMSE ≥28. By including this variable as a predictor, the LRA automatically excluded all subjects with missing data in this variable. Hence, the results of the analyses run with the third set of predictors apply only to the 313 subjects with MMSE ≥28.

For each of the 3 sets of predictors, two stepwise ('stepforward') LRA were computed. In the first ones, all predictors were forced into the model in order to determine: (1) the predictive validity of the model including all available cognitive information and (2) the order from the best to the least predicting variable. To allow all available variables into the model, the inclusion p values were set at 1. In the second analyses, the inclusion p values were set at 0.05 so that each variable was expected to increment the prediction by a minimum degree in order to be included in the model. These second analyses were run in order to determine at which point the algorithm stops including further variables because they do not enhance the predictive accuracy, demonstrating which predictors are necessary and sufficient to predict AD. The second analyses are denoted with an inverted comma (e.g. model 1', model 2', etc.). In order to compare the predictive value of the different models, sensitivity, specificity, and positive and negative predictive values were computed. Because these predictive values are affected by the prevalence of the disease at hand, the (positive and negative) likelihood ratios were also reported.

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To validate the MCI clusters identified by the HCAs, ANOVAs and ANCOVAs were computed in order to examine whether the clusters differed from each other in their biomarker profiles. The analyses were computed using the biomarkers as dependent variables, and the variable 'MCI clusters' as the independent variable. Because the biomarkers MTA and WML were age dependent, ANCOVAs were computed including age as a covariate.

To examine demographic, clinical and neuropsychological differences between the clusters, genders or other groups, additional analyses were conducted: To test for differences between two independent groups, we performed Student's t tests (for continuous variables). In cases where the variances differed between the compared groups, the corrected t and d.f. values are reported. Paired-sample t tests were conducted to compare the means of 2 variables in one sample. ANOVAs were performed to test for differences between more than two groups. In case of significant group differences, the ANOVAs were followed by Games-Howell post hoc analyses, as this type of post hoc test takes into account small and/or unequal sample sizes. When post hoc tests indicated significant differences between 2 clusters, or 2 cluster pairs only, the reports were limited to the (significant) p values. Differences between the distributions of categorical, non-dichotomous variables were tested with Pearson's χ^2 tests. For dichotomous variables, Fisher's exact tests were computed (here, only p values are reported). To test correlations between nominal variables, the phi coefficient and odds ratio (OR) were computed. For ordinal variables, or when dichotomous or ordinal variables were correlated with metric variables, Kendall's tau-b was used. When multiple hypotheses were tested on a set of data, the Bonferroni correction was used to avoid cumulating α-errors: when n hypotheses were tested, each individual hypothesis was tested at a statistical significance level of 0.05/n or 0.01/n. All tests were two-sided. All analyses were performed using the Statistical Package for the Social Sciences (SPSS 19 and IBM SPSS 20).

Results

Descriptives

As only subjects with complete neuropsychological tests at baseline and at least 1 follow-up (n = 485) were included in the analyses, 396 subjects had to be excluded. The baseline characteristics of the included (n = 485) and excluded (n = 396) subjects are shown in table 1.

The included subjects were comparable to the excluded subjects in terms of gender (p = 0.631) and rate of conversion to AD (p = 0.149). However, they differed significantly in terms of age [t(878) = 4.125, p < 0.0001], baseline MMSE [t(703) = –5.589, p < 0.0001], and education [t(879) = 2.509, p = 0.012]. Both age and education were higher in the excluded subjects (age = 71.5 years, education = 10.7 years) compared with the included subjects (age = 69.3 years, education = 10.0 years), whereas baseline MMSE was lower in the former (27.0) than in the latter (27.8). Hence, the included subjects were less cognitively impaired (MMSE) and younger, but less educated than the excluded subjects.

Whereas the mean time to AD and the rate of conversion to AD did not differ significantly between the two groups [t(157) = –0.208, p = 0.835 and p = 0.149, respectively], mean follow-up time differed significantly between the included and the excluded subjects [t(370) = 8.359, p < 0.0001].

Demographic Variables and Conversion to AD

Of the 485 subjects considered in the first HCA, 91 (18.8%) had developed AD at one of the follow-up visits. The risk of conversion to AD increased with age [r(485) = 0.203, p < 0.0001] but was not associated with gender [phi(485) = 0.058, p = 0.205; OR(485) = 1.353, 95% CI = 0.847–2.163] or education [r(485) = –0.022, p = 0.563]. Figure 1 shows the cognitive profiles of the 'converters' and the 'non-converters'. The x-axis depicts the cognitive variables (separately for converters and non-converters) and the y-axis shows the mean values of their z-scores.

At baseline, converters (mean MMSE = 26.4, SD = 2.39) and non-converters (mean MMSE = 28.1, SD = 1.56) differed from each other not only in the magnitude of the cognitive deficits [t(107) = 6.738, p < 0.0001] but also in the pattern of relative strengths and weak-

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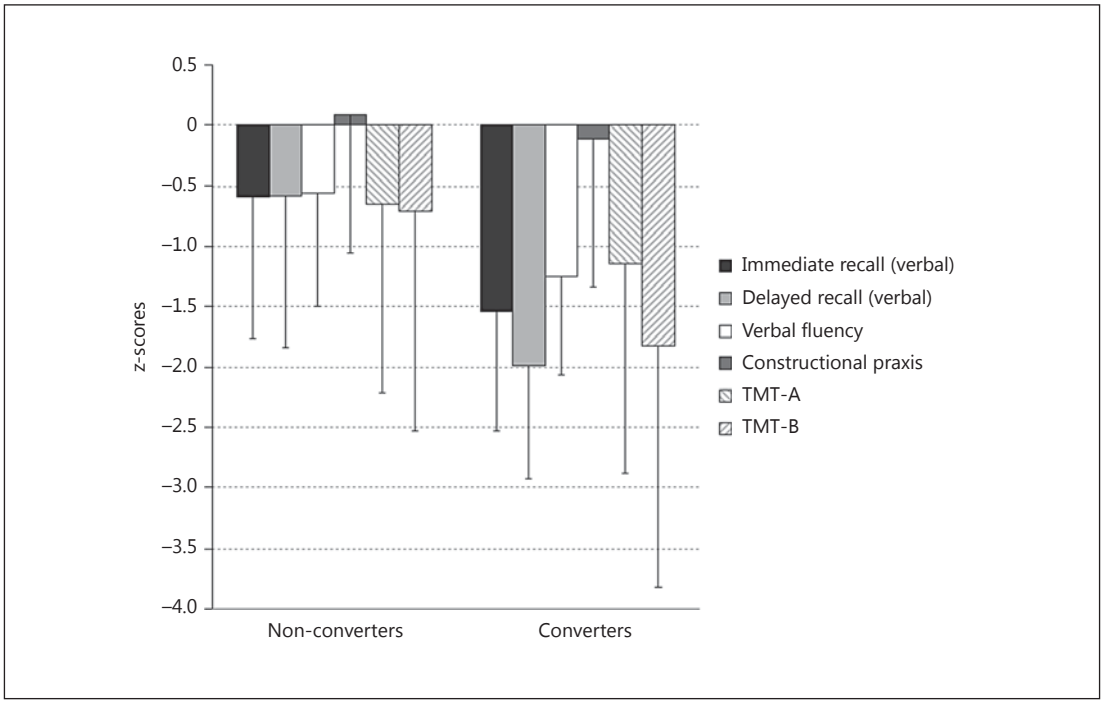

Fig. 1. Cognitive profiles of 'converters' vs. 'non-converters'. The z-scores on the y-axis indicate the cognitive performance of subjects who remained non-demented vs. those who converted to AD at follow-up. Usually, z-scores ≤–1.5 or ≤–1.0 are used to define impaired test performance.

Table 1. Baseline characteristics and status at follow-up

		Included subjects (n = 485)			Excluded subjects (n = 396)		
Immediate recall	z-scores	–0.76	1.20	485[1]	–1.09	1.18	343[1]
Delayed recall		–0.85	1.32	485[1]	–1.34	1.29	298[1]
Verbal fluency		–0.69	0.95	485[1]	–1.04	1.05	351[1]
Constructional praxis		0.05	1.16	485[1]	0.12	1.14	277[1]
TMT-A		–0.74	1.61	485[1]	–0.61	1.76	271[1]
TMT-B		–0.92	1.91	485[1]	–1.03	2.08	257[1]
MMSE		27.8	1.87	482[1]	27.0	2.48	387[1]
Age, years		69.35	7.60	485[1]	71.5	7.94	395[1]
Female, n, %		275	56.7	485[1]	231	58.3	395[1]
Education, years		10.04	4.17	485[1]	10.7	4.27	396[1]
Status at follow-up, n %	not demented	394	81.2		223	85.1	
	AD	91	18.8	485[1]	59	14.9	396[1]
Follow-up time, years		2.79	0.81	394[1]	2.10	1.06	223[1]
Time to AD, years		1.80	0.94	94[1]	1.83	1.02	65[1]

Data are expressed as mean and SD unless otherwise specified. For the cognitive variables, z-scores are listed, indicating the number of SDs from the average of a healthy control population. [1] Number of subjects without missing data in the respective variable.

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Table 2. Baseline cognitive scores and status at follow up: HCA sample and clusters (n = 485)

		SCI (n = 224)		aMCIatex (n = 62)		aMCIexec (n = 32)		aMCIsingle (n = 167)	
Immediate recall	z-scores	0.02	0.93	−0.92	1.03	−1.69	1.12	−1.58	0.86
Delayed recall		0.12	0.90	−0.86	1.02	−1.45	1.11	−2.02	0.81
Verbal fluency		−0.19	0.91	−0.96	0.84	−1.24	0.78	−1.14	0.75
Constructional praxis		0.16	1.11	−0.44	1.32	−0.17	1.29	0.13	1.10
TMT-A		−0.03	0.97	−3.99	0.90	−0.68	0.99	−0.49	1.06
TMT-B		−0.09	1.30	−3.12	1.74	−4.77	0.46	−0.47	1.17
MMSE		28.5	1.43	27.02	2.08	26.69	2.16	27.3	1.90
Age, years		67.98	7.45	70.418	5.64	71.26	7.63	70.416	8.14
Female, n, %		121	54.0	45	72.6	23	71.9	86	51.5
Education, years		10.79	4.20	6.98	3.29	8.69	4.04	10.43	3.90
Status at follow-up, n, %	not demented	216	96.4	47	75.8	17	53.1	114	68.3
	AD	8	3.6	15	24.2	15	46.9	53	31.7
Follow-up time, years		2.89	0.82	2.49	0.58	2.76	0.56	2.72	0.87
Time to AD, years		1.43	0.53	1.80	0.56	1.60	0.74	1.63	0.75

Data are expressed as mean and SD unless otherwise specified. For the cognitive variables, z-scores are listed, indicating the number of SDs from the average of a healthy control population.

nesses. Both groups performed relatively well in constructional praxis. However, only converters were significantly more impaired in delayed versus immediate recall [$t(90) = 4.920$, $p < 0.0001$] and in TMT-B versus TMT-A [$t(90) = 2.996$, $p < 0.004$], a pattern of impairment typical for demented subjects.

Differentiating MCI Clusters

The horizontal hierarchical tree plot showed that the value of the heterogeneity measure escalated after building 4 clusters. Thus, a 4-cluster solution was regarded as the best choice.

The HCA sorted the 485 subjects into the following 4 clusters: 224 (46.2%) were classified into cluster 1, 62 (12.8%) into cluster 2, 32 (6.6%) into cluster 3 and 167 (34.4%) into cluster 4. Table 2 lists the baseline scores of the clusters on the 6 cognitive variables, the mean MMSE scores, demographics, cluster-specific rates of conversion to AD, mean time to conversion, and mean follow-up duration in the 4 clusters.

Figure 2 specifies the cognitive profiles of the 4 clusters.

Based on the neuropsychological variables entered into the HCA, the 4 clusters can be characterized as follows:

- Cluster 1 (n = 224) had subjective cognitive impairments with very mild (if any) objective deficits, so that it can be best labelled with 'SCI'.
- Cluster 2 (n = 62) had severe deficits in psychomotor speed, moderate deficits in executive functioning and mild memory deficits, so that it can be best labelled with 'inattentive, dysexecutive aMCI' (aMCIatex).
- Cluster 3 (n = 32) had prominent deficits in executive functioning, mild-to-moderate memory deficits and mild deficits in verbal fluency. This group was the most impaired group and can be best described with 'dysexecutive aMCI' (aMCIexec).
- Cluster 4 (n = 167) showed deficits in immediate verbal recall that were comparable to those in cluster 3, but with more pronounced impairment in delayed memory, without executive or attentional deficits. This cluster can be referred to as 'aMCI, single domain' (aMCIsingle).

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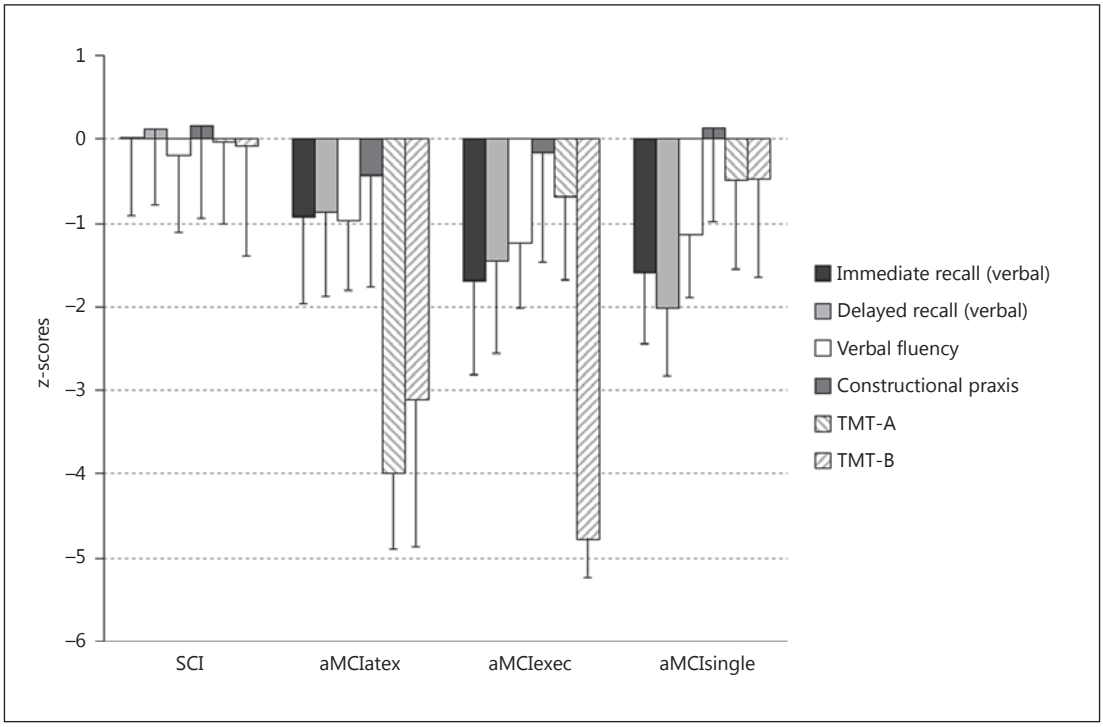

Fig. 2. Cognitive profiles of the 4 clusters identified in the complete sample (n = 485). The z-scores on the y-axis indicate the cognitive performance of the SCI, aMCIatex, aMCIexec and aMCIsingle clusters. Usually, z-scores ≤–1.5 or ≤–1.0 are used to define impaired test performance.

After Bonferroni correction (a = 0.05/6 = 0.008), the clusters differed in terms of age [F(3, 478) = 4.759, p = 0.003], baseline MMSE [F(3, 478) = 24.914, p < 0.0001] and education [F(3, 478) = 16.657, p < 0.0001]. Whereas age differed significantly between SCI on the one hand and aMCIatex and aMCIsingle on the other (p = 0.030 and p = 0.013, respectively), baseline MMSE differed between SCI and each of the 3 other clusters (p < 0.0001). As to differences in education, there was a tendency of the least impaired clusters (SCI and aMCIsingle) to have more years of education than the more impaired clusters (aMCIatex and aMCIexec). However, differences in education were significant only between aMCIatex and the SCI and aMCIsingle clusters (both p < 0.0001). As for age at first visit, the cluster with the lowest mean age (67.9 years) was the least impaired SCI cluster. However, the order from the 'youngest' to the 'oldest' cluster (SCI, aMCIatex, aMCIsingle and aMCIexec) was neither consistent with the overall degree of cognitive impairment (MMSE) or the number of impaired cognitive functions, nor did these differences reach significance level. As for gender distribution, the significant inter-cluster difference [$\chi^2(3) = 11.868$, p = 0.008] was due to the differences of SCI versus aMCIatex (54.0 vs. 72.6% females, p = 0.009) and aMCIsingle versus aMCIatex (51.5 vs. 72.6% females, p = 0.004). After Bonferroni correction (p = 0.05/6 = 0.0083) only the latter difference remained significant. Severity of depressive symptoms was highest in aMCIatex and differed significantly from severity in SCI [t(90) = –2.327, p = 0.022] and in aMCIsingle [t(95) = 2.235, p = 0.028]. However, after Bonferroni correction (p′ = 0.0083), neither of these differences remained significant.

In which neuropsychological variables the clusters differed significantly from one another is reported in table 3.

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Table 3. Complete sample clusters: differences in the cognitive variables (Games-Howell post hoc tests)

MCI clusters (n = 485)		Cognitive variables											
		immediate recall		delayed recall		verbal fluency		constructional praxis		TMT-A		TMT-B	
I	J	I–J	p	I–J	p	I–J	p	I–J	p	I–J	p	I–J	p
aMCIatex	aMCIexec	0.768	0.011	0.589	0.069	0.273	0.404	–0.276	0.767	–3.317	<0.0001	1.656	<0.0001
	aMCIsingle	0.661	<0.0001	1.157	<0.0001	0.175	0.478	–0.570	0.016	–3.505	<0.0001	–2.642	<0.0001
aMCIexec	aMCIsingle	–0.106	0.957	0.568	0.043	–0.098	0.912	–0.295	0.627	–0.188	0.767	–4.298	<0.0001

I–J = Mean difference; Bonferroni-corrected significance level: 0.05/6 = 0.008.

Conversion to AD, Mean Time to Conversion, and Mean Follow-Up Duration

The cluster-specific rates of conversion to AD, mean time to conversion and mean follow-up duration in the 4 clusters are reported in table 2. The highest conversion rate was found in the aMCIexec cluster (46.9%), which differed significantly from that of the aMCIatex cluster (24.2%, p = 0.036). However, after Bonferroni correction (0.05/3 = 0.016) this difference was no longer significant. Because significantly lower conversion rates were self-evident in subjects with just SCI, only the rates of the clusters with objective cognitive impairment were compared with one another. The clusters did not differ with regard to the mean time to AD either [F(3, 84) = 0.489, p = 0.691], whereas the average follow-up time was significantly longer in the SCI than in the aMCIatex cluster (p = 0.001). Whereas time to AD was computed selecting subjects who converted to AD, follow-up time was examined only in subjects who did not convert, in order to avoid comparing it between groups with different conversion rates (and hence different follow-up times, as converters dropped out of the study earlier).

Differentiating MCI Clusters of Subjects with MMSE ≥28

A second HCA was conducted to test if the stability of the clusters could also be demonstrated in subjects with very mild MCI. In order to test if a cognitive profile predicting AD can be identified at a very early stage of MCI, only subjects with a baseline MMSE ≥28 (n = 313) were selected for the second HCA. This HCA generated, again, 4 clusters whose cognitive profiles are shown in figure 3.

Based on the cognitive performance of the subjects, the 4 new clusters are characterized as follows:

- Cluster 1 (n = 86, mean MMSE = 29.1, SD = 0.73; mean age = 66.3, SD = 7.74) had no objective cognitive deficits, hence this cluster was labelled 'SCI' (SCI28+).
- Cluster 2 (n = 116, mean MMSE = 28.8, SD = 0.70; mean age = 68.5, SD = 7.94) had moderate deficits in immediate verbal recall, even more pronounced impairment in delayed recall, and minimal impairment in verbal fluency. This cluster was labelled 'aMCI, single domain' (aMCIsingle28+).
- Cluster 3 (n = 51, mean MMSE = 28.7, SD = 0.83; mean age = 71.0, SD = 6.62) had prominent deficits in executive functioning, almost similar impairment in attention and psychomotor speed, and minimal impairment in verbal fluency and memory. This group was labelled 'attentional and executive impairment with secondary memory deficits' (atexMCI28+).
- Cluster 4 (n = 60, mean MMSE = 29.0, SD = 0.75; mean age = 68.6, SD = 7.09) showed no memory deficits but mild impairment in constructional praxis, executive functioning and verbal fluency. This cluster was labelled 'naMCI' (naMCI28+).

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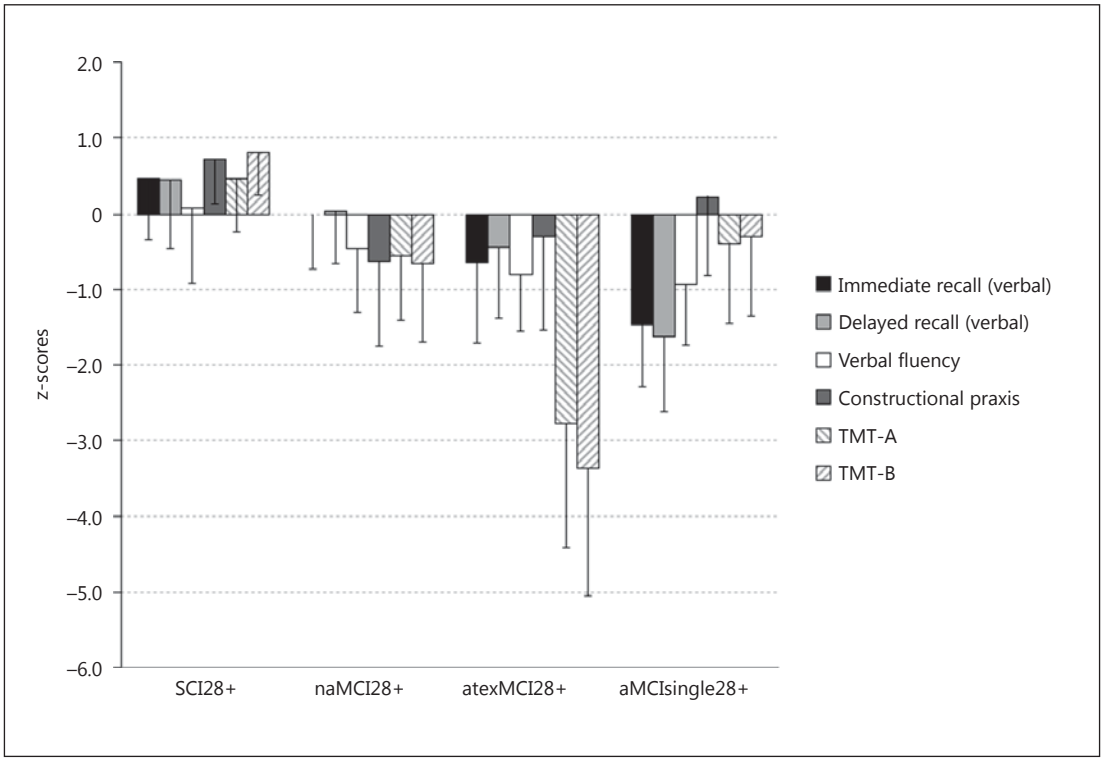

Fig. 3. Cognitive profiles of the 4 clusters identified in the very mild MCI (MMSE ≥28) sample (n = 313). The z-scores on the y-axis indicate the cognitive performance of the SCI28+, naMCI28+, atexMCI28+ and aMCIsingle28+ clusters. Usually, z-scores ≤–1.5 or ≤–1.0 are used to define impaired test performance.

After Bonferroni correction (a = 0.05/6 = 0.008), the clusters did not differ with regard to baseline MMSE except for the difference between SCI28+ and aMCIsingle28+ (p = 0.003). The clusters SCI28+ and atexMCI28+ differed significantly with regard to age (p = 0.001) and education (p < 0.0001). Education differed also between aMCIsingle28+ and atexMCI28+ (p < 0.0001), with aMCIsingle28+ being more educated than atexMCI28+. Severity of depressive symptoms differed between the clusters too [F(3, 250) = 2.707, p = 0.046]. Games-Howell post hoc comparisons indicated that the inter-cluster difference in depressive symptoms was only attributable to the difference SCI28+ versus atexMCI28+ (p = 0.045). In contrast to aMCIsingle28+, where delayed recall was slightly more impaired than immediate recall (t = 1.70; d.f. = 115; p = 0.092), an opposite tendency was present in atexMCI28+ (t = –1.568; d.f. = 50; p = 0.123), although both results were not significant. In summary, atexMCI28+ was the cluster with the lowest education level and the highest severity of depressive symptoms. There were no differences in gender distribution [$\chi^2(3) = 1.438$, p = 0.697].

In which neuropsychological variables the 'very mild MCI' clusters differed significantly from one another is reported in table 4.

Conversion to AD, Mean Time to Conversion, and Mean Follow-Up Duration in the MMSE ≥28 Clusters

In the subset of subjects with milder cognitive impairment (MMSE ≥28), the highest conversion rate was found in the aMCIsingle cluster (19%), which differed significantly

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Table 4. MMSE 28+ clusters: differences in the cognitive variables (Games-Howell post hoc tests)

MCI Clusters 28+ (n = 313)		Cognitive variables											
		immediate recall		delayed recall		verbal fluency		constructional praxis		TMT-A		TMT-B	
I	J	I–J	p	I–J	p	I–J	p	I–J	p	I–J	p	I–J	p
aMCIsingle28+	atexMCI28+	–0.819	<0.0001	–1.184	<0.0001	–0.130	0.753	0.514	0.058	2.375	<0.0001	3.077	<0.0001
	naMCI28+	–1.46	<0.0001	–1.668	<0.0001	–0.476	0.003	0.854	<0.0001	0.159	0.702	0.358	0.147
atexMCI28+	naMCI28+	–0.638	0.003	–0.484	0.016	–0.346	0.118	0.341	0.445	–2.217	<0.0001	–2.719	<0.0001

I–J = mean difference; Bonferroni-corrected significance level: 0.05/6 = 0.008.

from the conversion rate of naMCI (5%, p = 0.012, Bonferroni-corrected significance level: 0.05/3 = 0.016). Time to AD did not differ between the clusters [F(3, 26) = 0.446, p = 0.722], whereas the average follow-up time was significantly longer in SCI28+ than in atexMCI28+ (p = 0.004).

Predicting Conversion to AD: Does Sub-Classifying MCI Subjects Improve the Diagnostic Accuracy of the Cognitive Scores?

In order to determine whether knowledge of the subtype or cluster of an MCI subject has an additional benefit to the prediction of conversion to AD compared to the plain use of the subjects' cognitive scores, 6 LRA were performed, using different combinations of potentially predicting variables. The 6 resulting models are presented in table 5.

According to the LRA that included the cognitive variables only (models 1 and 1'), conversion to AD at follow-up was correctly predicted in 84.5% of the cases. Specificity amounted to 96.4% and sensitivity to 33.0% (model 1). In model 1', where the LRA algorithm stopped including further variables if they did not enhance the predictive accuracy, the variables of delayed recall, TMT-B and verbal fluency were identified as the best predictors. The variables of verbal immediate recall, constructional praxis and TMT-A did not contribute to the prediction of conversion to AD (p = 0.275, p = 0.828 and p = 0.849, respectively). While the predictive accuracy of the 6 cognitive variables (model 1) remained virtually unaffected by the exclusion of the redundant cognitive variables (model 1', see table 6) in both models, high specificity values are derogated by low sensitivity values.

To examine whether the clustering of the MCI sample improves prediction of AD, the models 1 and 1' were supplemented by two further models (models 2 and 2'): in model 2, the 6 aforementioned cognitive variables plus the cluster_485 variable were included. In model 3, these model 2 predictors were supplemented by the cluster_313 variable.

In model 2, the order of the included variables shows that the cluster_485 variable was slightly more predictive than the redundant variables identified in model 2'. However, the contribution of the cluster_485 variable was not significant (p = 0.292), so that the predictive accuracy of this set of predictors does not significantly improve, compared to models 1 and 1'.

In contrast, model 3, which also included the cluster_313 variable, showed another picture: here, the LRA algorithm selected the cluster_485 variable as the best predictor, followed by the variables of delayed recall, TMT-B and immediate recall. In model 3' the algorithm excluded all variables but cluster_485 (best predictor) and delayed recall (second-best predictor). However, in model 3' sensitivity is significantly reduced compared to model 3. On the basis of these 2 'best' variables, AD was predicted for only 1 subject who, at least in the 4 years of follow-up, did not progress to AD.

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Table 5. LRA to predict conversion to AD

	Predictors	β	SE (β)	Wald	d.f.	p	Expected (β), OR
Model 1	delayed recall	–1.085	0.182	35.648	1	<0.0001	0.338
	TMT-B	–0.224	0.082	8.932	1	0.003	0.784
	verbal fluency	–0.465	0.181	6.614	1	0.010	0.628
	immediate recall	0.192	0.176	1.191	1	0.275	1.211
	constructional praxis	–0.026	0.120	0.047	1	0.828	0.974
	TMT-A	–0.018	0.094	0.036	1	0.849	0.982
	constant	–3.458	0.327	112.141	1	<0.0001	0.031
Model 1’	delayed recall	–0.957	0.138	48.39	1	<0.0001	0.384
	TMT-B	–0.236	0.069	11.65	1	0.001	0.790
	verbal fluency	–0.461	0.180	6.58	1	0.010	0.631
	constant	–3.471	0.320	118.024	1	<0.0001	0.031
Model 2	delayed recall	–0.990	0.201	24.212	1	<0.0001	0.372
	TMT-B	–0.258	0.082	9.885	1	0.002	0.773
	verbal fluency	–0.415	0.186	4.968	1	0.026	0.661
	immediate recall	0.218	0.178	1.509	1	0.219	1.244
	cluster_485	0.173	0.164	1.112	1	0.292	1.188
	TMT-A	–0.036	0.096	0.142	1	0.707	0.965
	constructional praxis	–0.032	0.120	0.072	1	0.788	0.968
	constant	–3.782	0.468	65.411	1	<0.0001	0.023
Model 2’	delayed recall	–0.957	0.138	48.390	1	<0.0001	0.384
	TMT-B	–0.236	0.069	11.650	1	0.001	0.790
	verbal fluency	–0.461	0.180	6.578	1	0.010	0.631
	constant	–3.471	0.320	118.024	1	<0.0001	0.031
Model 3	cluster_485	0.787	0.286	7.600	1	0.006	2.198
	delayed recall	–0.823	0.287	8.242	1	0.004	0.439
	TMT-B	–0.225	0.137	2.700	1	0.100	0.798
	immediate recall	0.592	0.287	4.261	1	0.039	1.807
	cluster_313	0.363	0.391	0.861	1	0.353	1.438
	TMT-A	0.096	0.173	0.311	1	0.577	1.101
	constructional praxis	–0.064	0.195	0.106		0.745	0.938
	verbal fluency	0.026	0.291	0.008	1	0.928	1.027
	constant	–5.797	1.451	15.956	1	<0.0001	0.003
Model 3’	cluster_485	0.554	0.230	5.798	1	0.016	1.740
	delayed recall	–0.512	0.241	4.502	1	0.034	0.599
	constant	–4.292	0.627	46.933	1	<0.0001	0.014

Overall model evaluation		–2LL	R^2	χ^2	d.f.	p
Model 1	n = 485	348.499	0.353	119.784	6	<0.0001
Model 1’		349.812	0.350	118.471	3	<0.0001
Model 2	n = 485	347.371	0.356	120.913	7	<0.0001
Model 2’		349.812	0.350	118.471	3	<0.0001
Model 3	n = 313	153.028	0.305	49.152	8	<0.0001
Model 3’		162.124	0.252	40.056	2	<0.0001

R^2 = Nagelkerke’s R^2.

PPV and NPV = Positive and negative predictive value, respectively; LR+ and LR– = positive and negative likelihood ratio, respectively.

Model 1: All 6 cognitive variables ‘forced’ into the model by setting P(IN) and P(OUT) = 1.

Model 1’: Only the best predicting cognitive variables ‘allowed’ into the model, P(IN) = 0.05, P(OUT)= 0.10.

Model 2: All 6 cognitive variables plus the cluster_485 variable ‘forced’ into the model.

Model 2’: Only the best predicting variables of model 2 allowed into the model.

Model 3: All 6 cognitive variables plus both cluster variables (cluster_485 and _313) forced into the model.

Model 3’: Only the best predicting variables of model 3 allowed into the model.

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Table 6. Diagnostic accuracy of different LRA models

	Diagnostic accuracy, %	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR–
Model 1	84.5	33.0	96.4	68.2	86.2	–0.346	–0.332
Model 1’	84.5	31.9	96.7	69.0	86.0	–0.333	–0.319
Model 2	84.9	35.2	96.4	69.6	86.6	–0.369	–0.355
Model 2’	84.5	31.9	96.7	69.0	86.0	–0.333	–0.319
Model 3	91.1	12.9	99.6	80.0	91.2	–0.131	–0.119
Model 3’	89.8	0	99.6	0	90.1	0	–0.010

PPV and NPV = Positive and negative predictive value, respectively; LR+ and LR– = positive and negative likelihood ratio, respectively.

Model 1: All 6 cognitive variables ‘forced’ into the model by setting P(IN) and P(OUT) = 1.

Model 1’: Only the best predicting cognitive variables ‘allowed’ into the model, P(IN) = 0.05, P(OUT)= 0.10.

Model 2: All 6 cognitive variables plus the cluster_485 variable ‘forced’ into the model.

Model 2’: Only the best predicting variables of model 2 allowed into the model.

Model 3: All 6 cognitive variables plus both cluster variables (cluster_485 and _313) forced into the model.

Model 3’: Only the best predicting variables of model 3 allowed into the model.

In summary, in all 3 sets of predictors high specificity values were derogated by very low sensitivity values, showing that they are accurate only in identifying non-converters, but not subjects who later convert to AD. However, model 3 contains both the cognitive and cluster variables that can be regarded as the combination of variables with the highest predictive accuracy (91.1%) and the lowest decrement in sensitivity (12.9%) and positive predictive value (80%).

It has to be mentioned that these results (models 3 and 3’) only apply to the 313 subjects who were included in the respective LRAs, as all other subjects with missing data in the cluster_313 variable (i.e. subjects with MMSE <28) were automatically excluded. Hence, the last-mentioned results apply only to subjects with MMSE ≥28, i.e. very mild MCI.

Inter-Cluster Differences in Biomarkers

Table 7 shows the results of the ANOVAs and ANCOVAs computed to test for significant inter-cluster differences in the biomarkers.

ANOVAs and ANCOVAs were computed separately for the two HCA samples. In both samples, the aMCIsingle subtype (aMCIsingle28+) was the only one which differed significantly from the SCI cluster. However, while in the complete sample aMCIsingle was associated with abnormalities in $A\beta_{42}$, t-tau and MTA, in the very mild MCI sample it was associated with a significantly ‘abnormal’ MTA only. In the very mild MCI sample, CSF markers did not differ from those of the cognitively healthy SCI subjects. Interestingly, APOE ε4 differed significantly between aMCIsingle28+ and the naMCI group, but only in the very mild MCI subjects.

Discussion

HCA subdivided an MCI cohort into 4 groups with maximally different cognitive profiles which differed in their rates of conversion to AD: (1) SCI, (2) mainly attentional with additional executive and amnestic impairment (aMCIatex), (3) mainly executive impairment (aMCIexec) and (4) mainly amnestic impairment (aMCIsingle). The highest rate of conversion

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Table 7. Inter-cluster differences in biomarkers

Biomarkers	Complete sample (n = 485)		MMSE28+ sample (n = 313)	
	differing clusters	p	differing clusters	p
$A\beta_{42}$	SCI vs. aMCIsingle	0.014	n.s.	n.s.
t-tau	SCI vs. aMCIsingle	0.044	n.s.	n.s.
p-tau	n.s.	n.s.	n.s.	n.s.
APOE ε4	n.s.	n.s.	naMCI28+ vs. aMCIsingle28+	0.039
MTA	SCI vs. aMCIsingle	<0.0001	SCI vs. aMCIsingle28+	<0.0001
WML	n.s.	n.s.	n.s.	n.s.

To test for inter-cluster differences in the biomarkers $A\beta_{42}$, t-tau, p-tau and APOE ε4, ANOVAs were computed. ANCOVAs were computed to test for inter-cluster differences in MTA and WML, as these variables were not age-corrected and age had to be entered as a covariate.

to AD was found in the aMCIexec cluster (46.9%), followed by aMCIsingle (31.7%), aMCIatex (24.2%) and SCI (3.6%).

Because the cluster with the highest rate of conversion (aMCIexec) also had the lowest baseline MMSE, an additional HCA was run selecting subjects with baseline MMSE ≥28, i.e. very mild MCI, to rule out a possible confounding effect of the overall severity of cognitive impairment on cluster building. This second HCA identified the following 4 clusters: (1) SCI (SCI28+), (2) mainly amnestic impairment (aMCIsingle28+), (3) mainly executive and attentional deficit plus slight memory impairment (atexMCI28+) and (4) mainly constructional, non-amnestic impairment (naMCI28+). Because of the MMSE ≥28 criterion, the corresponding rates of conversion to AD were much lower than those found in the complete sample clusters (1.2, 19, 9.8 and 5%, respectively). Nevertheless, 2 of these 28+ clusters (SCI28+ and aMCIsingle28+) had similar cognitive profiles to those found in the original HCA, with an interesting difference: whereas aMCIexec was the high-risk cluster of the complete sample HCA solution, aMCIsingle28+ was the high-risk cluster in the MMSE28+ cluster solution. Hence, examining only subjects with very mild MCI, single-domain aMCI was identified as the most probable prodromal AD phenotype in spite of its lower degree of deficit multiplicity and its similar severity of global cognitive impairment (mean MMSE) compared to atexMCI28+. Thus, the number and severity of impaired cognitive domains do not seem to matter as much as the degree of memory impairment. In fact, executive functioning was much more impaired in the atexMCI28+ than memory in the aMCIsingle28+ cluster. Still, the highest conversion rate (19%) was found in the latter, which had the highest memory impairment. Hence, in the earliest stages of cognitive impairment, prominent memory impairment is crucial and sufficient to enhance the risk of conversion, so that single-domain aMCI might be labelled the earliest cognitive phenotype of AD. In the atexMCI28+ cluster, impaired memory performance can partly be explained by the pronounced attentional and executive deficits, which are cognitive features more typical for depressive subjects than for degenerative brain processes. In fact, atexMCI28+ was the cluster with the most severe depressive symptoms. Furthermore, only the aMCIsingle28+ cluster showed a tendency to the dementia-specific pattern of more impaired delayed recall and less impaired immediate recall [32].

According to most of the studies on conversion rates of MCI subtypes, single-domain aMCI is less likely to convert to AD compared to multiple-domain aMCI, because the memory component specific for AD and the multiplicity of cognitive deficits indicating the severity of brain destruction interact, which results in a higher risk of progression to dementia [3, 33–40]. This is in line with our results in the total cohort, but was not confirmed in the very mildly

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impaired cohort. This supports the suggestion of Hughes et al. [41] that multiple-domain aMCI represents a more advanced disease state.

In the complete sample, the aMCIsingle cluster was associated with an AD-specific biomarker profile: decreased $A\beta_{42}$, increased t-tau, and MTA, compared to subjects with only SCI. The biomarker differences might have been even more pronounced if healthy controls had been included in the study, as Visser et al. [19] could show in another study. In the MMSE ≥28 sample, CSF markers could not differentiate between any of the clusters, probably because CSF markers become abnormal very early, even in subjects who will in their lifetime never express symptoms of AD dementia, and do not change appreciably as the disease progresses [42]. WML did not differentiate between any of the clusters, whereas APOE ε4 differed between aMCIsingle and naMCI. However, MTA was the only biomarker which consistently and highly significantly differentiated between SCI and aMCIsingle both in the complete and in the MMSE ≥28 sample. This is in line with the hypothetical model of dynamic AD biomarkers of Jack et al. [42], stating that the direct substrate of memory impairment is hippocampal atrophy (as measured by MRI) and not, for example, Aβ deposition.

The results of this study have to be seen in light of some limitations. As the study population was recruited from memory clinics, the results may not be generalized to other settings or to the general population. As the number of included cognitive tests was limited because of the multi-centre and naturalistic nature of the study, the study findings are specific to the tests that were selected. In addition, this study was carried out without a healthy control group, as the included subjects with no objective cognitive impairment all had subjective concerns and, hence, a higher risk of developing cognitive deficits and converting to dementia compared to truly healthy controls [15, 16]. Another problem of this and other studies comparing the conversion risk of aMCI versus naMCI subtypes could also have led to biased results: identifying clusters with memory impairment as the most susceptible ones to convert to AD could reflect a tautological problem. In order to diagnose dementia, i.e. to decide whether a subject has converted to dementia or not, memory impairment is, by definition, a necessary prerequisite. Hence, subjects with a baseline cognitive profile corresponding to naMCI are less probable to be judged as 'converted' (to dementia or AD) at follow-up, because they have to develop memory deficits in the first place. However, if only amnestic forms of MCI are taken into consideration, this problem concerns both multiple- and single-domain aMCI. Actually, it affects multiple-domain aMCI in particular, as memory impairment has to be accompanied by deficits in at least one additional cognitive domain in order to fulfil dementia criteria. Because single- and not multiple-domain aMCI was found to be the most susceptible to convert to AD, the aforementioned tautology does not explain this specific result. However, tautology problems have to be taken into consideration as a source of bias affecting results pertaining to the comparison between amnestic and non-amnestic clusters. Another limitation of this study is the lack of a measure of 'cued recall' like, for example, the Free and Cued Selective Reminding test, which has been found to correlate with CSF biomarkers of AD more strongly than CERAD delayed recall measures [43] and to accurately predict MTA, as semantic cuing draws upon hippocampal and entorhinal structures [44]. Furthermore, the study is limited by the fact that the MCI clusters were built on the basis of their cognitive profiles only, even if they could be correlated with AD-specific biomarkers afterwards. Finally, in all logistic regression models, sensitivity values were low (range = 0–35.2%), while accuracy (84.5–91.1%) and specificity (96.4–99.6%) of the various variables and clusters predicting incident AD were high. Hence, the cognitive variables used in the analyses were accurate in identifying subjects *not* at risk of developing AD, but they were not sensitive to detect those who *are* at risk. This is consistent with the results of Stephan et al. [45], who found that 'no MCI-derived threshold accurately identified an at-risk group with a 2-year progression rate greater than 20%'.

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To our knowledge, this is the first prospective study investigating the conversion rates of MCI subtypes defined on an empirical basis using HCA. This method was chosen to find homogeneous groups having in common not only performance below specific cut-off points (as it is often the case when building MCI subtypes), but 'real' underlying cognitive profiles. According to analyses where a *theoretical* sub-classification of MCI subjects (using 1.5 SD as the cut-off) was compared with the *empirical* one (using cluster analyses as presented in this paper), the theoretically specified subtype with the highest conversion rate to AD was multiple-domain aMCI. In clinical routine, where the aforementioned cut-off is used to define impairment, this cognitive profile would, at least in neuropsychological terms, already meet criteria for dementia and identify subjects at risk too late. In fact, some subjects in this theoretical subtype had particularly low baseline MMSE values.

In summary, our results are consistent with those of other investigators finding that amnestic forms of MCI are at higher risk of progressing to dementia or AD compared to non-amnestic forms of MCI [35]. Considering only subjects with baseline MMSE values ≥28, i.e. subjects with very mild MCI, single-domain aMCI was identified as the most susceptible form to progress to AD. This is consistent with our biomarker analyses and with the notion of hippocampal damage leading to isolated memory deficits. Furthermore, our results confirm that delayed recall measures and MTA are the most useful markers of conversion to AD [46], and that today imaging data still seem to be better immediate predictors of conversion to AD than CSF markers [47]. According to the model of the AD pathological cascade in the study of Jack et al. [42], MRI markers are more predictive of conversion to AD than CSF markers, as they are the last to become abnormal and the most proximate pathological substrate of cognitive symptoms.

The results of this study are also of clinical relevance. The pattern of cognitive weaknesses and strengths of MCI subjects is predictive of AD, whether or not they perform below specific cut-off z-scores. Prodromal AD should already be taken into consideration in the presence of isolated memory impairment, even if the subject's performance has not yet crossed specific cut-off points. This is supported by our preliminary biomarker analyses. However, further analyses are needed to corroborate this finding.

Acknowledgements

This work was supported by the 6th FP of the EU (www.descripa.eu), and the EVO grant from Kuopio University Hospital and Academy of Finland (H.S.).

Appendix

Clusters of the complete sample (n = 485)	
SCI	Subjective cognitive impairment
aMCIatex	Inattentive, and dysexecutive amnestic MCI
aMCIexec	Dysexecutive amnestic MCI
aMCIsingle	Single-domain amnestic MCI
Clusters of the MMSE ≥28 sample (n = 313)	
SCI28+	Subjective cognitive impairment (MMSE ≥28)
aMCIsingle28+	Single-domain amnestic MCI (MMSE ≥28)
atexMCI28+	Inattentive, and dysexecutive MCI with mild memory deficits (MMSE ≥28)
naMCI28+	Non-amnestic MCI (MMSE ≥28)

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