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Neuropsychiatrické symptomy jako časná manifestace Alzheimerovy nemoci

Neuropsychiatric symptoms as early manifestation of Alzheimer's disease

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V. Matušková, T. Nikolai, H. Marková, K. Čechová, J. Laczó, J. Hort, M. Vyhnálek

Neurologická klinika
2. LF UK a FN Motol, Praha
Mezinárodní centrum klinického výzkumu, FN u sv. Anny v Brně

✉
MUDr. Martin Vyhnálek, Ph.D.
Neurologická klinika
2. LF UK a FN Motol
V Úvalu 84
150 06 Praha
e-mail: martin.vyhnalek@fnmotol.cz

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Souhrn

Cíl: Neuropsychiatrické symptomy (NPS) jsou heterogenní skupina změn v osobnosti a chování, které lze pozorovat již v časných stadiích Alzheimerovy nemoci (AN). Mírná behaviorální porucha (mild behavioral impairment; MBI) je nová diagnostická kategorie popisující trvalé změny v osobnosti a chování s počátkem v pozdější fázi života. Na podkladě těchto kritérií byl vytvořen nový Dotazník mírné poruchy chování (Mild Behavioral Impairment Checklist; MBI-C) zaměřený na detekci NPS v časných stadiích AN. Cílem studie je představit námi adaptovanou českou verzi dotazníku MBI-C a studovat přítomnost a závažnost NPS na pilotním souboru pacientů. *Soubor a metodika:* Originální verze MBI-C byla adaptována do češtiny a administrována blízkým osobám 188 pacientů. Pacienti podstoupili komplexní neuropsychologické, neurologické vyšetření a zobrazení mozku a dle výsledků byli rozděleni do tří skupin: kognitivně zdraví (n = 69), amnestická mírná kognitivní porucha (amnestic mild cognitive impairment; aMCI) (n = 87) a demence při AN (n = 32). *Výsledky:* Pacienti s aMCI vykazovali v dotazníku MBI-C signifikantně vyšší skóre ve srovnání s kognitivně zdravými a zároveň nižší skóre než pacienti s demencí. Rozdíly byly patrné zejména v doménách nálady, motivace a kontroly impulzů. *Závěr:* Česká verze dotazníku MBI-C detekuje přítomnost NPS ještě před rozvojem syndromu demence a je dobře využitelná v klinické praxi.

Klíčová slova

neuropsychiatrické symptomy – Alzheimerova nemoc – mírná behaviorální porucha – mírná kognitivní porucha

Abstract

Aim: Neuropsychiatric symptoms (NPS) are a heterogeneous group of changes in personality and behavior that can be observed already in early stages of Alzheimer's disease (AD). Mild behavioral impairment (MBI) is a newly developed diagnostic category describing persistent changes in personality and behavior starting later in life. Based on these criteria, a new measure, the Mild Behavioral Impairment Checklist (MBI-C) has been developed, aimed at detecting NPS in early stages of AD. The aim of this study is to present the newly adapted Czech version of the MBI-C and to explore the presence of NPS in a pilot group of patients. *Patients and methods:* The original MBI-C has been adapted to Czech and administered to close informants of 188 patients. The patients were divided according to the results of a complex neuropsychological, neurological examination and brain imaging into 3 groups: cognitively normal (N = 69), amnestic mild cognitive impairment (aMCI; N = 87) and dementia due to AD (N = 32). *Results:* Patients with aMCI expressed in the MBI-C significantly more severe score compared to cognitively normal subjects and less severe compared to dementia patients. The differences were observed mainly in affective, motivation and impulse control domains. *Conclusion:* The Czech version of the MBI-C detects the presence of NPS even before the onset of dementia syndrome and is useful in clinical practice.

Key words

neuropsychiatric symptoms – Alzheimer´s disease – mild behavioral impairment – mild cognitive impairment

Úvod

V souvislosti se stárnutím populace stoupá incidence Alzheimerovy nemoci (AN). V minulosti bylo pravidlem diagnostikovat toto onemocnění ve stadiu demence. S vývojem nové medikace přímo zasahující do patofyziologie AN, u níž se předpokládá účinek zejména v časných stadiích tohoto onemocnění, se současná diagnostika zaměřuje na časná stadia. Demenci předchází prodromální stadium zvané mírná kognitivní porucha (mild cognitive impairment; MCI), která je definována existencí objektivizovatelného kognitivního deficitu u ještě soběstačného pacienta [1]. MCI je heterogenní koncept zahrnující postižení nervového systému různé etiologie. Ve stáří je MCI u většiny pacientů v příčinné souvislosti s časnými alzheimerovskými změnami – tzv. MCI při AN [2]. Stadiu MCI předchází stadium preklinické. V preklinickém stadiu jsou u pacienta již přítomny patologické změny v mozku detekovatelné pomocí biomarkerů, ale výkony při standardním neuropsychologickém vyšetření

Tab. 1. Kompletní diagnostická kritéria mírné behaviorální poruchy.

1. Změny v chování nebo osobnosti pozorované pacientem, pečovatelem nebo klinikem, s počátkem v pozdější fázi života (věk ≥ 50 let) a trvající nepřetržitě nebo nárazově alespoň po dobu 6 měsíců. Tyto příznaky reprezentují jasně pozorovatelnou změnu ve srovnání s obvyklým chováním nebo osobností pacienta alespoň v jedné z následujících domén:
   a) poruchy motivace (např. apatie, nedostatek spontaneity, lhostejnost);
   b) poruchy nálady (např. anxieta, dysforie, náladovost, euforie, iritabilita);
   c) poruchy kontroly impulzů (např. agitovanost, desinhibice, patologické hráčství, obsedantnost, perseverace, utilizační chování);
   d) nevhodné sociální chování (např. nedostatek empatie, ztráta náhledu, nedostatek sociálního taktu, psychická rigidita, zvýraznění předchozích osobnostních rysů);
   e) poruchy percepce a obsahu myšlení (např. bludy, halucinace).
2. Chování je dostatečně závažné na to, aby způsobilo alespoň minimální postižení alespoň v jedné z následujících oblastí:
   a) interpersonální vztahy;
   b) další aspekty sociálního fungování;
   c) schopnost podávat výkon na pracovišti;
   d) u pacienta obecně není narušena soběstačnost nebo fungování v běžném životě, je schopen fungovat s minimální pomocí nebo asistencí.
3. Ačkoliv komorbidity můžou být přítomny, změny v chování nebo osobnosti nelze připsat jiné současné psychiatrické poruše (např. generalizovaná úzkostná porucha, těžká deprese, manická nebo psychotické poruchy), traumatickému postižení nebo jiným onemocněním či fyziologickým účinkům látek nebo medikace.
4. Pacient nesplňuje kritéria syndromu demence (např. demence při Alzheimerově nemoci, frontotemporální demence, demence s Lewyho tělísky, vaskulární demence, jiná demence). Mírná kognitivní porucha může být diagnostikována současně s mírnou behaviorální poruchou.

jsou ještě v normě [3]. U části osob jsou však již přítomny subjektivní stížnosti na pokles v kognici, přičemž specifické stížnosti byly asociovány s vyšším rizikem rozvoje kognitivního deficitu [4]. Tato část osob v preklinickém stadiu AN je definována jako subjektivní kognitivní pokles (subjective cognitive decline; SCD) [5].

Kromě kognitivního deficitu lze však u AN pozorovat i změny v osobnosti a chování. Tato heterogenní skupina změn byla nazvána neuropsychiatrické symptomy (NPS) neboli behaviorální a psychologické symptomy. Zahrnuje např. poruchy nálady, motivace, vnímání a obsahu myšlení, změny chování, příjmu potravy a poruchy spánku. Ve stadiu demence jsou NPS častým příznakem a s postupnou progresí nemoci se obvykle zvýrazňují. Uvádí se, že u 70–90 % pacientů s demencí se vyskytuje alespoň jeden NPS, přičemž časté jsou jejich kombinace. Proto byly zařazeny i do nových konsenzuálních diagnostických kritérií demencí různé etiologie [6–8] a jsou také součástí českých doporučených postupů pro diagnostiku demence u AN a jiných demencí [9]. Tyto symptomy mohou způsobit nejen zhoršení soběstačnosti a kvality života pacientů, ale i zátěž pečovatelů, komplikace a nákladnost léčby a jsou nejčastějším důvodem institucionalizace [10].

V prodromálních a preklinických stadiích se NPS začaly zkoumat teprve nedávno a přítomnost alespoň jednoho příznaku byla pozorována u 35–75 % pacientů s MCI a u 18–30 % kognitivně zdravých starších osob v populaci [11–13]. Mezi nejčastější NPS v časných stadiích AN patří deprese, úzkost, apatie, iritabilita, agitace a poruchy spánku. Naopak bludy a halucinace jsou poměrně vzácné a vyskytují se až ve stadiu demence [14–19]. Nově vzniklé NPS prokazatelně zvyšují riziko rozvoje a progrese kognitivního deficitu u pacientů s MCI i u kognitivně zdravých starších osob [20–22]. Na rozsáhlé kohortě dobrovolníků studie Národního koordinačního centra pro Alzheimerovu nemoc (NACC) bylo recentně publikováno několik zajímavých zjištění:

1. Celkem 55 % kognitivně zdravých jedinců nad 60 let, kteří progredovali do MCI, vykazovalo NPS ještě před rozvojem kognitivního deficitu a dalších 24 % MCI rozvinulo NPS před rozvojem demence [23];
2. roční konverze pacientů s MCI a přítomností NPS do demence je 25 %, ve srovnání s 15 % pacientů s MCI dle populačních studií [24];
3. nižší přítomnost poruch nálady a jejich zlepšování v čase zvýšilo pravděpodobnost zpětného návratu z MCI do skupiny bez kognitivního deficitu [25].

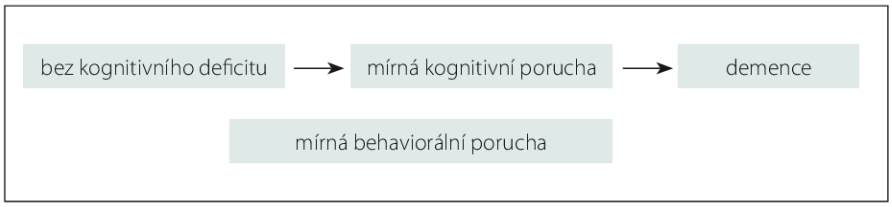
Dlouho se uvažovalo, že změny v chování a osobnosti jsou u neurodegenerativních onemocnění důsledkem kognitivního postižení. Výzkumy se ale v poslední době spíše přiklánějí k hypotéze, že nově vzniklé a přetrvávající NPS jsou, podobně jako kognitivní postižení, přímým důsledkem neuropatologických změn v mozku. Zatímco nově vzniklé NPS jsou asociovány s vyšším rizikem progrese kognitivního deficitu, přítomnost izolovaných depresivních příznaků [26,27] či jiné psychiatrické poruchy [28] v mládí nebyla asociována s vyšším rizikem rozvoje demence. Poruchy nálady se také s vyšší pravděpodobností vyskytují u osob s rizikovým genotypem ApoE4 [29]. U MCI navíc současná přítomnost ApoE4 a deprese či apatie zvyšuje riziko progrese do demence výrazněji, než by odpovídalo prostému aditivnímu efektu [22].

I když se výzkum v této oblasti rychle rozvíjí, v praxi jsou NPS identifikovány často nepřesně nebo pozdě. MCI jako prodromální stadium se zaměřuje pouze na poruchy kognice a existenci NPS opomíjí. V praxi tak bývají nově vzniklé NPS ve stáří často považovány za počátek psychiatrického onemocnění, zejména depresivní poruchy [30]. To může vést k nesprávně stanovené diagnóze a oddalování správně cílené intervence. Analogický koncept, který by popisoval NPS ve stadiích předcházejících demenci, donedávna chyběl a v revidované formě byl publikován až v roce 2016 jako tzv. mírná behaviorální porucha (mild behavioral impairment; MBI) [31].

Mírná behaviorální porucha

Mírná behaviorální porucha je syndrom označující nově vzniklé změny v chování nebo osobnosti u starší populace s předpokladem neurodegenerativní etiologie. Iniciální pojetí mělo za cíl identifikovat časná stadia frontotemporální demence [32]. Avšak každá z demencí neurodegenerativní etiologie se může v časném stadiu manifestovat NPS. Proto byla kritéria rozšířena a v současnosti je MBI definována jako změny v chování nebo osobnosti udávané pacientem

nebo jeho okolím s počátkem v pozdější fázi života (věk ≥ 50 let) trvající po dobu alespoň 6 měsíců a nezpůsobené jinou současnou psychiatrickou poruchou, traumatickým poškozením mozku ani užíváním psychotropních látek nebo medikace (viz diagnostická kritéria v tab. 1). Změny by měly způsobovat alespoň minimální postižení v oblasti interpersonálních vztahů nebo podávání výkonu na pracovišti. Pacient je ale plně soběstačný, nesplňuje tedy kritéria demence. MBI může být diagnostikována současně s MCI, avšak může kognitivní deficit i předcházet (obr. 1) [31].



Obr. 1. Diagnostická kategorie mírné behaviorální poruchy.
Fig. 1. Diagnostic category of mild behavioral impairment.

Diagnostické nástroje měření neuropsychiatrických symptomů

Diagnostická kategorie MBI se snaží postihnout změny v chování a osobnosti ve stáří co nejčasněji a má potenciál přispět k zpřesnění diagnostického procesu neurodegenerativních onemocnění. Pro sledování NPS však existuje množství různých škál, což přispívá k výrazným rozdílům v udávaných prevalencích napříč studiemi.

Neuropsychiatrické symptomy lze v klinické praxi hodnotit několika způsoby – pozorováním a strukturovaným rozhovorem s pečovatelem a pacientem či za použití standardizovaných dotazníků a škál. Za zlatý standard mezi škálami NPS je obecně považován Neuropsychiatrický inventář (Neuropsychiatric Inventory; NPI), který má formu strukturovaného rozhovoru s pečovatelem [33]. Jeho zkrácená verze NPI-Q (Neuropsychiatric Inventory – Questionnaire) ve formě dotazníku pro pečovatele patří v zahraničí k výzkumně i klinicky nejužívanějším nástrojům [34]. Naopak rozšířením původního NPI vznikla verze pro expertního klinika – NPI-C [35]. V praxi se také setkáme s doménově specifickými nástroji určenými k hodnocení vlastního prožívání samotným pacientem, přičemž nejčastěji se hodnotí depresivní (Beckova škála deprese [BDI-II] [36], Geriatrická škála deprese [GDS-15] [37]) nebo úzkostná symptomatika (Beckova škála úzkosti [BAI] [38], Dotazník úzkosti a úzkostlivosti [STAI] [39]).

I když jsou výše zmíněné dotazníky validní a v praxi dobře etablované, většinou byly konstruovány a validovány na kohortě pacientů ve stadiu demence nebo u pacientů s psychiatrickým onemocněním. Nemusí tak být dostatečně senzitivní pro spektrum NPS obvyklé v časném stadiu neurodegenerace. Navíc posuzovaná doba trvání 1–4 týdny, která je u stávajících dotazníků obvyklá, může být příliš krátká na odlišení neurodegenerativní etiologie od přechodných narušení (např. poruchy přizpůsobení, vliv medikace či nedostatku spánku). Pro praxi je také důležitá časová úspornost administrace. Autoři konceptu MBI reflektovali tyto potřeby a na podkladě kritérií MBI vytvořili nástroj zaměřený přímo na detekci NPS ve stadiích předcházejících demenci – Dotazník mírné poruchy chování (Mild Behavioral Impairment – Checklist; MBI-C) [40].

Dotazník mírné poruchy chování

Dotazník mírné poruchy chování MBI-C byl publikován v roce 2017 pod záštitou neuropsychiatrické sekce mezinárodní Alzheimerovské společnosti. Jeho cílem je zachytit širší spektrum NPS v časovém horizontu 6 měsíců u pacientů v predementních stadiích (podrobný popis viz Metody).

Pouze dvě publikované studie se zabývaly prevalencí neuropsychiatrických příznaků a MBI u preklinických a prodromálních stadií za použití dotazníku MBI-C. U obou skupin zaznamenaly vysokou prevalenci NPS, alespoň 1 bod v dotazníku skórovalo 76 % pacientů s MCI a 55 % osob s SCD. Kompletní kritéria MBI však splňovalo pouze 14,2 % MCI [41] a 5,8 % SCD [42], protože NPS musí být dostatečně závažné, aby ovlivňovaly fungování v každodenních aktivitách. Design studií však neumožňuje zjistit, zda existují rozdíly ve skóre MBI-C mezi těmito diagnostickými skupinami.

Cíle této studie jsou: 1. představit námi nově přeloženou a adaptovanou oficiální českou verzi dotazníku MBI-C; 2. za pomoci dotazníku MBI-C sledovat přítomnost a závažnost NPS u klinicky a neuropsychologicky podrobně definovaného souboru osob bez kognitivního deficitu, s amnestickou formou MCI (aMCI) a demencí; 3. zjistit, zda je MBI-C schopen zachytit rozdíly v NPS v predementních stadiích; a 4. zjistit souvislost domény poruchy nálady v dotazníku MBI-C se sebeposuzujícími standardními dotazníky deprese a úzkosti.

Na základě znalostí o stoupající prevalenci a závažnosti NPS v závislosti na míře kognitivního deficitu předpokládáme, že dotazník MBI-C, který byl vyvinut k záchytu časných změn, zachytí rozdíly již v predementních stadiích (mezi kognitivně zdravými osobami a aMCI). Na základě předchozích výzkumů NPS očekáváme nejvýraznější rozdíly v doméně motivace a poruchy nálady.

Metody

Účastníci

Do studie bylo zahrnuto 188 osob starších 50 let (průměrný věk 71,33 let; směrodatná odchylka [standard deviation; SD] = 8,04) vyšetřených v rámci Czech Brain Aging Study (CBAS). CBAS je longitudinálně probíhající studie Kognitivního centra Neurologické kliniky 2. LF UK a FN Motol a programu Demence FNUSA – ICRC, jejímž hlavním cílem je identifikovat časné markery patologického stárnutí. Do studie CBAS jsou zahrnuty osoby odeslané praktickým lékařem nebo jiným specialistou pro stížnosti na kognici referované buďto samotným pacientem, jeho blízkou osobou nebo klinikem. Účastníci byli podrobně vyšetřeni (viz dále) a na základě neuropsychologického vyšetření klasifikováni do 3 skupin:

- Skupina s pravděpodobnou či možnou demencí při AN (smíšená prezentace s podílem vaskulárních změn) (AD; 32 osob) byla definována dle publikovaných kritérií [6].
- Skupina s MCI byla definována dle publikovaných kritérií [1] a zahrnovala osoby se subjektivními stížnostmi na kognici referovanými pacientem, blízkou osobou nebo klinikem, které měly objektivní postižení kognice ve standardním neuropsychologickém vyšetření, avšak v aktivitách denního života byly soběstačné. Postižení kognitivní domény znamenalo výkon v daném testu více než 1,5 SD pod věkově a vzdělanostně vázanou normou, zahrnuti byli pouze pacienti s postižením paměti, a to výlučně nebo v kombinaci s postižením jiné kognitivní domény (aMCI; 87 osob).

Tab. 2. Demografická a neuropsychologická charakteristika souboru.

	KZ n = 69 průměr (SD)	aMCI n = 87 průměr (SD)	AD n = 32 průměr (SD)	Rozdíly mezi skupinami
věk; rozsah	67,7 (0,77); 52–84	72,5 (0,84); 55–89	77,0 (1,16); 58–87	KZ < aMCI** < AD*
pohlaví Ž/M (% žen)	46/23 (66,7)	36/51 (41,4)	22/10 (68,8)	KZ > aMCI**; AD > aMCI**
MMSE; rozsah	29,1 (0,12); 26–30	26,5 (0,28); 19–30	19,4 (0,63); 14–25	KZ > aMCI** > AD**
vzdělání	16,3 (0,35)	15,3 (0,35)	13,9 (0,51)	KZ > AD**
GDS-15	2,0 (0,25)	3,1 (0,3)	3,6 (0,57)	KZ < aMCI*; KZ < AD*
BAI	8,6 (0,91)	8,6 (0,89)	7,8 (1,21)	–
LP (jednotky)	16,0 (0,46)	7,2 (0,58)	1,3 (0,43)	KZ > aMCI** > AD**
AVLT I–V	54,7 (0,95)	32,6 (0,87)	N/A	KZ > aMCI**
AVLT po 30 min	11,7 (0,25)	3,4 (0,32)	N/A	KZ > aMCI**
opakování čísel popředu (skóre)	9,4 (0,24)	8,8 (0,27)	7,6 (0,3)	KZ > AD**
opakování čísel pozadu (skóre)	6,8 (0,23)	5,6 (0,22)	4,3 (0,26)	KZ > aMCI** > AD**
TMT A (čas)	38,5 (1,26)	55,7 (3,12)	108,5 (11,6)	KZ < aMCI* < AD**
TMT B (čas)	82,4 (3,0)	136,7 (7,57)	239,9 (24,44)	KZ < aMCI** < AD**
BNT 30 (počet chyb)	1,7 (0,26)	5,4 (0,44)	10,4 (0,87)	KZ < aMCI ** < AD **
SVF – zvířata	25,9 (0,64)	17,9 (0,59)	10,1 (0,81)	KZ > aMCI ** > AD **
FVF (písmena N, K, P)	49,1 (1,40)	37,1 (1,34)	25,7 (2,65)	KZ > aMCI ** > AD **
ROCF kopie	31,0 (0,37)	26,5 (0,68)	21,5 (2,00)	KZ > aMCI ** > AD **
ROCF reprodukce po 3 min	18,4 (0,73)	8,5 (0,67)	2,5 (0,64)	KZ > aMCI **> AD **

*p < 0,05; **p < 0,01

AD – demence při Alzheimerově nemoci s možným podílem vaskulárních změn; aMCI – amnestická mírná kognitivní porucha; AVLT – Paměťový test učení; BAI – Beckova škála úzkosti; BNT – Bostonský test pojmenování; FVF – fonemická verbální fluence; GDS – Geriatrická škála deprese; KZ – kognitivně zdravé osoby; LP – logická paměť; M – muži; MMSE – Mini Mental State Examination; N/A – neměřeno; ROCF – Rey-Osterriethova komplexní figura; SD – standardní odchylka; SVF – sémantická verbální fluence; TMT – Test cesty; Ž – ženy

- Skupina s SCD (45 osob) na základě publikovaných kritérií [5] zahrnovala osoby se subjektivními stížnostmi na kognici, které v neuropsychologickém vyšetření skórovaly v rámci normy.

Dále bylo do studie zahrnuto 24 kognitivně zdravých dobrovolníků z Univerzity třetího věku nebo blízkých osob sledovaných pacientů neudávajících významnější subjektivní stížnosti na kognici, pro které by někdy vyhledali lékařskou pomoc, a jejichž výkon v neuropsychologickém vyšetření byl v rámci normy. Pro účely statistického vyhodnocení byly skupiny kognitivně zdravých dobrovolníků a SCD sloučeny do jedné skupiny „kognitivně zdraví" (KZ; 69 osob).

Do studie nebyly zahrnuty osoby s přítomností jiného psychiatrického či neurologického onemocnění (Parkinsonova nemoc, traumatické poškození mozku, CMP, dlouhodobé psychiatrické onemocnění [≥ 5 let], abúzus alkoholu), které by mohlo způsobit poruchy kognice či NPS.

Protokol vyšetření

Každý účastník absolvoval komplexní neurologické, neuropsychologické vyšetření a zobrazení mozku MR. Neuropsychologická baterie obsahovala skríningový test Mini Mental State Examination (MMSE) [43] a českou verzi testové baterie Uniform Data Set (UDS) [44] sestávající z následujících testů: Logická paměť WMS-R – oddálené vybavení příběhu A (LP), Opakování čísel WAIS-III (Wechslerova inteligenční škála pro dospělé), Test cesty A (Trail Making Test; TMT A) a Test cesty B (TMT B), Bostonský test pojmenování (zkrácená 30položková verze), sémantická verbální fluence (SVF; zvířata). Baterie UDS byla doplněna testy: fonemická verbální fluence (FVF s využitím písmen N, K, P) [45], Paměťový test učení (Auditory Verbal Learning Test; AVLT) [46] a Rey-Osterriethova komplexní figura (kopie a reprodukce po 3 min) [47]. Všichni účastníci dále vyplnili 2 sebeposuzovací škály ke zhodnocení depresivní a úzkostné symptomatologie: Geriatric Depression Scale (GDS-15) [37] a Beck Anxiety Inventory (BAI) [38]. Všechny diagnózy byly stanoveny na konsenzuálním diagnostickém sezení týmu neurologů a neuropsychologů.

Dotazník mírné poruchy chování MBI-C byl administrován blízkým osobám všech účastníků výzkumu. Dotazník obsahuje celkem 34 otázek, u kterých se hodnotí přítomnost symptomů jednoduchou formou ano/ne a jejich závažnost na třístupňové škále (1 – mírná změna, 2 – střední změna a 3 – výrazná změna). V souladu s kritérii MBI sleduje projevy pěti domén NPS – poruchy motivace (6 otázek zjišťujících zájem

a motivaci), poruchy nálady (6 otázek zaměřených na úzkostné a depresivní příznaky), poruchy kontroly impulzů (12 otázek zjišťujících kontrolu chování či impulzů, schopnost odložit uspokojení), nevhodné sociální chování (5 otázek zaměřených na dodržování sociálních norem, takt a empatii) a poruchy percepce a obsahu myšlení (5 otázek zaměřených na bludy a halucinace). Hodnotící osobou je primárně blízká osoba pacienta, přičemž přítomnost klinika není nutná.

Výstupem dotazníku je celkové skóre v rozsahu 0–102 bodů, které získáme prostým součtem všech odpovědí. Dále dotazník poskytuje 5 samostatných skórů dle jednotlivých hodnocených domén: poruchy motivace (0–18 bodů), poruchy nálady (0–18 bodů), poruchy kontroly impulzů (0–36 bodů), nevhodné sociální chování (0–15 bodů) a poruchy percepce a obsahu myšlení (0–15 bodů). Česká verze MBI-C byla přeložena z anglického originálu zkušeným klinikem a revidována kognitivními neurology a neuropsychology (MV, TN, HM, KČ). Zpětný překlad byl proveden nezávislým překladatelem, konzultován a schválen původním autorem dotazníku.

Do studie nebyly zahrnuty osoby, u nichž chyběly 4 a více z 34 položek v dotazníku (celkem 6 osob). Maximální odstup mezi jednotlivými vyšetřeními vč. vyplnění dotazníku byl 4 měsíce. NPS jsme považovali za přítomné, pokud osoba dosáhla alespoň 1 bod v jakékoliv doméně dotazníku.

Statistické zpracování dat

Meziskupinové rozdíly v demografických údajích jsme porovnali pomocí analýzy kovariance (analysis of covariance; ANCOVA), zastoupení pohlaví pomocí χ^2. Pro analýzu rozdílů v celkovém skóre MBI-C napříč jednotlivými skupinami jsme pro nesplnění předpokladu normálního rozložení použili logaritmované celkové skóre MBI-C a dále postupovali parametricky pomocí analýzy variance (analysis of variance; ANOVA) kontrolované pro věk a pohlaví účastníků. Pro analýzu rozdílů v jednotlivých doménových skórech MBI-C jsme použili neparametrický Kruskal-Wallisův test, post-hoc analýzy byly provedeny za použití Mann-Whitneyho U testu. Hladiny signifikance byly upraveny Holm-Bonferroniho korekcí pro vícenásobná porovnání. Spearmanovy korelace byly použity pro zjištění asociace mezi MBI-C doménou poruchy nálady a sebeposuzovacími škálami GDS-15 a BAI (rovněž s úpravou hladin signifikance Holm-Bonferroniho korekcí pro vícenásobná porovnání). Velikosti efektu jsou uvedeny jako η^2 (eta-squared) nebo korelační koeficient r, přičemž za malý efekt považujeme η^2 = 0,02–0,13 nebo r = 0,1–0,3; za středně velký efekt považujeme η^2 = 0,13–0,26 nebo r = 0,3–0,5 a za velký efekt považujeme η^2 > 0,26 nebo r > 0,5. Všechny analýzy byly provedeny v programu SPSS (verze 20) (IBM, Armonk, NY, USA).

Výsledky

Demografická a neuropsychologická charakteristika souboru

Celkem bylo do studie zařazeno 188 osob, z toho 87 osob s aMCI, 32 osob s AD a 69 osob KZ. Jednotlivé diagnostické skupiny se významně lišily v zastoupení pohlaví (nižší zastoupení žen ve skupině aMCI oproti KZ a AD; $p < 0,01$), ve věku (skupina AD byla nejstarší; $p < 0,05$) a vzdělání (skupina AD měla oproti KZ průměrně nižší vzdělání; $p < 0,05$). Dle očekávání se skupiny dále vzájemně lišily ve skóre MMSE a ve výkonech napříč všemi neuropsychologickými testy. Osoby ve skupině KZ vykazovaly dle sebeposouzení nižší úroveň depresivní symptomatiky (GDS-15) než aMCI a AD. Naopak v sebeposouzení úzkostné symptomatiky (BAI) jsme nezjistili žádné rozdíly mezi diagnostickými skupinami. Blízkou osobou vyplňující dotazník MBI-C byli nejčastěji partneři/partnerky (69 %) nebo děti účastníků (23 %) a v 79% uváděli každodenní kontakt s účastníkem. Vztah ani intenzita kontaktu se napříč skupinami nelišily. Detailní charakteristika souboru je uvedena v tab. 2.

Výskyt neuropsychiatrických příznaků dle MBI-C

Administrace dotazníku trvala méně než 5 min, více než 95 % dotazníků bylo vyplněno správně bez přítomnosti administrátora. Alespoň 1 NPS (tj. alespoň 1 bod v dotazníku MBI-C) jsme pozorovali u 50,7 % KZ osob, u 78,2 % osob s aMCI a u 97 % osob s AD. Nejčastějšími doménami MBI u skupiny KZ byly poruchy nálady (37,7 %) a kontroly impulzů (37,7 %). U skupiny aMCI byly nejčastější poruchy kontroly impulzů (61,4 %), nálady (60,7 %) a motivace (51,2 %). U skupiny AD byly rovněž nejčastěji uváděny poruchy kontroly impulzů (89,3 %), nálady (71,9 %) a motivace (71,9 %). Poruchy sociálního chování a percepce a obsahu myšlení byly u KZ vzácné (13 a 6 %) a objevovaly se častěji u aMCI (24 a 16 %) a AD (29 a 30 %).

Rozdíly v MBI-C mezi diagnostickými skupinami

V analýze ANCOVA kontrolované pro věk a pohlaví se skupiny výrazně lišily v celkovém skóre MBI-C ($F [2,181] = 23,85$; $p < 0,001$; partial $\eta^2 = 0,21$), bez významného ovlivnění této variability věkem ($F [1,181] = 1,69$; $p = 0,20$) nebo pohlavím účastníků ($F [1,181] = 1,02$; $p = 0,31$). V souladu s naším očekáváním dosahovala skupina KZ průměrného nejnižšího skóre MBI-C, skupina AD nejvyššího skóre a skupina aMCI skórovala mezi těmito dvěma skupinami. V jednotlivých doménách jsme napříč diagnostickými skupinami našli statisticky významné rozdíly v poruchách motivace ($\chi^2 [2] = 33,59$; $p < 0,001$) nálady ($\chi^2 [2] = 19,98$; $p < 0,001$), kontroly impulzů ($\chi^2 [2] = 32,14$; $p < 0,001$) a percepce a obsahu myšlení ($\chi^2 [2] = 11,39$; $p < 0,01$). KZ a aMCI se lišily v poruchách motivace ($U = 1912,5$; $p < 0,001$), nálady ($U = 2076$; $p = 0,001$) a kontroly impulzů ($U = 1946,5$; $p = 0,001$). U skupiny aMCI bylo oproti KZ naznačeno vyšší skóre i v poruchách percepce a obsahu myšlení ($p = 0,046$), po úpravě Holm-Bonferroniho korekcí ale tento rozdíl zanikl. Skupiny aMCI a AD se rovněž signifikantně lišily v poruchách motivace ($U = 1004,5$; $p = 0,019$), nálady ($U = 1030,5$; $p = 0,046$) a kontroly impulzů ($U = 677,5$; $p = 0,001$). Skupiny KZ a AD se signifikantně lišily v poruchách motivace ($U = 453$; $p < 0,001$), nálady ($U = 579$; $p < 0,001$), kontroly impulzů ($U = 308,5$; $p < 0,001$) a také percepce a obsahu myšlení ($U = 774,5$; $p = 0,001$). V doméně nevhodného sociálního chování jsme nenašli žádné významné rozdíly, což je důsledkem nízkého skóre ve všech skupinách. Celkové i doménové skóre v dotazníku MBI-C napříč diagnostickými skupinami jsou shrnuty v tab. 3. Jednotlivé rozdíly celkového skóre ilustruje obr. 2, rozdíly doménových skórů obr. 3.

Korelace s dotazníky depresivní a úzkostné symptomatiky

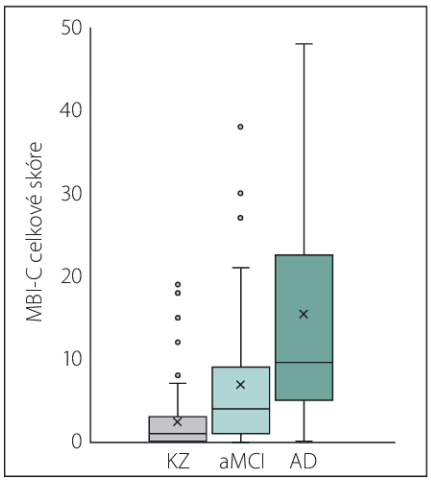
Skóre v doméně poruch nálady pozitivně korelovalo se sebeposuzujícím dotazníkem depresivní symptomatologie GDS-15 ve skupině KZ (Rho = 0,41; $p = 0,001$), aMCI (Rho = 0,41; $p < 0,001$) i ve skupině AD (Rho = 0,36; $p = 0,047$). Pozitivní korelace MBI-C s dotazníkem úzkosti BAI jsme rovněž pozorovali ve skupině KZ (Rho = 0,32; $p = 0,007$) a aMCI (Rho = 0,44; $p < 0,001$), ale ne ve skupině AD (Rho = 0,27; $p = 0,17$).

Tab. 3. Rozdíly ve skórech MBI-C mezi diagnostickými skupinami.

MBI-C	KZ n = 69 M (SD) rozsah	aMCI n = 87 M (SD) rozsah	AD n = 32 M (SD) rozsah	ANCOVA / K-W	Velikost efektu
celkové skóre (0–102)	2,44 (0,49) 0–19	6,80 (0,87) 0–38	15,41 (2,67) 0–59	F (188) = 23,85; p < 0,001	partial η_2 = 0,21
poruchy motivace (0–18)	0,43 (0,15) 0–8	1,90 (0,29) 0–13	4,16 (0,92) 0–18	χ^2 (2) = 33,59; p < 0,001	r_1 = –0,35* r_2 = –0,22* r_3 = –0,55*
poruchy nálady (0–18)	0,80 (0,17) 0–7	2,04 (0,31) 0–16	3,91 (0,83) 0–16	χ^2 (2) = 19,98; p < 0,001	r_1 = –0,26* r_2 = –0,19* r_3 = –0,41*
poruchy kontroly impulzů (0–36)	0,97 (0,27) 0–9	2,25 (0,33) 0–13	5,11 (1,05) 0–20	χ^2 (2) = 32,14; p < 0,001	r_1 = –0,27* r_2 = –0,32* r_3 = –0,56*
nevhodné sociální chování (0–15)	0,19 (0,07) 0–3	0,43 (0,12) 0–8	0,94 (0,35) 0–9	χ^2 (2) = 5,03; p = 0,08	r_1 = –0, 01 r_2 = –0,01 r_3 = –0,02
poruchy percepce a obsahu myšlení (0–15)	0,07 (0,04) 0–2	0,21 (0,05) 0–2	1,17 (0,43) 0–9	χ^2 (2) = 11,39; p < 0,01	r_1 = –0,15 r_2 = –0,18 r_3 = –0,34*

*velikost efektu při výsledku signifikantním na úrovni p upravené Holm-Bonferroniho korekcí

η_2 – velikost efektu pouze příslušnosti ke skupině na variabilitu celkového skóre MBI-C, vyjádřena jako eta squared; AD – demence při Alzheimerově nemoci s možným podílem vaskulárních změn; aMCI – amnestická mírná kognitivní porucha; ANCOVA – analýza kovariance; K-W – Kruskal-Wallisův test; KZ – kognitivně zdraví; M – průměr; MBI-C – dotazník mírné behaviorální poruchy; n – počet; r_1 – velikost efektu pro data KZ vs. aMCI; r_2 – velikost efektu pro data aMCI vs. AD; r_3 – velikost efektu pro data KZ vs. AD; SD – standardní odchylka



Obr. 2. Celkové skóre MBI-C.
AD – pravděpodobná či možná demence při Alzheimerově nemoci; aMCI – amnestická mírná kognitivní porucha; KZ – kognitivně zdravé osoby; MBI-C – Dotazník mírné behaviorální poruchy

Fig. 2. MBI-C total score.
AD – probable or possible dementia due to Alzheimer's disease; aMCI – amnestic mild cognitive impairment; KZ – cognitively healthy persons; MBI-C – Mild Behavioral Impairment Checklist

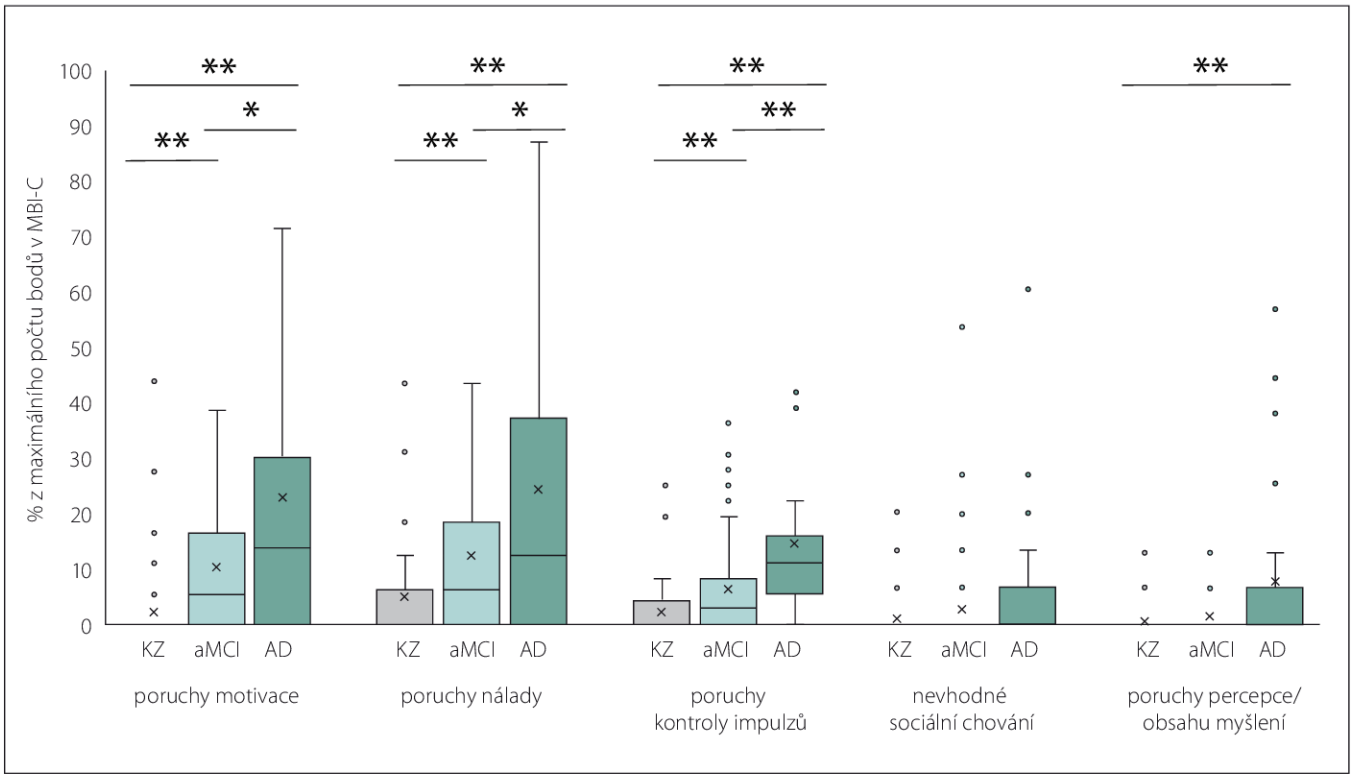
Diskuze

Představili jsme diagnostická kritéria MBI a námi adaptovanou českou verzi dotazníku MBI-C jako nový nástroj pro zachycení NPS v predementních stadiích. Dotazník vyplnily blízké osoby našich účastníků, především jejich partneři. Zjistili jsme, že MBI-C je schopen dobře detekovat přítomnost NPS v predementích stadiích. Rozdíly byly patrné nejenom v doméně poruch motivace a nálady, ale i v doméně kontroly impulzů.

Dle našeho očekávání se celkové skóre v dotazníku zvyšovalo napříč skupinami se vzrůstajícím kognitivním deficitem. Tyto výsledky jsou konzistentní se zjištěním klinických [48] i populačních studií [12,49], i když ty používaly ke zkoumání prevalence zejména Neuropsychiatrický inventář (NPI) jako zlatý standard měření NPS.

Námi zjištěná přítomnost a závažnost NPS hodnocena MBI-C u aMCI je ve shodě s nedávným zjištěním [41]. Ve skupině KZ jsme však pozorovali značně velký rozsah celkových skórů MBI-C, který může být způsoben sloučením zdravých dobrovolníků a osob s SCD. I když u SCD není přítomen objektivní kognitivní deficit, příznaky úzkosti a deprese jsou u nich častější než u kognitivně zdravých osob bez stížností [50]. Je ale důležité poznamenat, že NPS se vyskytují i u zdravého stárnutí a jejich prevalence a závažnost nejsou doposud dobře prozkoumány.

Rozdíly mezi KZ a aMCI byly nejvíce patrné v doménách poruch motivace, nálady a kontroly impulzů. Obdobné výsledky byly publikovány v běžné populaci při použití NPI [49]. U klinické populace se nálezy různí, dle NPI se objevily rozdíly mezi SCD a MCI pouze v poruchách motivace a nálady [48]. V poslední době se ukazuje, že nově vzniklé poruchy nálady jako deprese či úzkost a poruchy motivace zvyšují riziko rozvoje kognitivního deficitu a progrese do demence [17,19,26,27]. Naproti tomu doména kontroly impulzů je poměrně heterogenní doménou a napříč studiemi je zkoumána nejednotně. Symptomy agitovanosti či impulzivity, které jsou její součástí, jsou však také častou nekognitivní prezentací v časných stadiích AN [14,48], přítomnost agitovanosti zvyšuje riziko progrese z MCI do demence [22]. V naší studii se u aMCI nej-



Obr. 3. Relativní doménová skóre MBI-C (v procentech z maximálního počtu bodů).

AD – pravděpodobná či možná demence při Alzheimerově nemoci; aMCI – amnestická mírná kognitivní porucha; KZ – kognitivně zdravé osoby; MBI-C – Dotazník mírné behaviorální poruchy

Fig. 3. MBI-C relative domain scores (percentage of the maximum domain score).

AD – probable or possible dementia due to Alzheimer´s disease; aMCI – amnestic mild cognitive impairment; KZ – cognitively healthy persons; MBI-C – Mild Behavioral Impairment Checklist

častěji vyskytovaly podrážděnost (33 %), netrpělivost (31 %), tvrdohlavost/rigidita myšlení (32 %) a hádavost (26 %). Naproti tomu u KZ jsme pozorovali hlavně symptomy podrážděnosti a netrpělivosti, oproti aMCI však v mnohem menším zastoupení (13 a 17 %).

V doménách nevhodného sociálního chování a poruchách percepce a obsahu myšlení se skóre KZ a aMCI nelišilo. Nejedná se o překvapivý výsledek, protože poruchy sociálního chování jsou časným příznakem zejména frontotemporální demence [7,15], která byla vylučujícím kritériem v naší studii. U časných stadií AN je toto chování vzácné [11,15]. Rovněž bludy a halucinace bývají častěji spojovány s prodromálními stadii onemocnění s Lewyho tělísky [16]. U AN se obvykle vyskytují zejména v pozdějších stadiích demence, přičemž bludy často předchází halucinace [10,14]. Poruchy percepce a obsahu myšlení byly u naší skupiny AD častější než u KZ, a to zejména v položkách popisujících bludy; mezi skupinami aMCI a AD jsme naopak rozdíly nezaznamenali. Nutno však zmínit, že naše studie zahrnovala pouze pacienty ve stadiu lehké demence. Pacienti ve stadiu středně těžké a těžké demence nebyli do této studie zařazeni.

Doména poruch nálady v MBI-C středně silně korelovala se sebeposuzujícími škálami depresivní (GDS-15) a úzkostné symptomatiky (BAI) u KZ a aMCI, což podporuje její validitu u těchto skupin.

Výsledky této studie je nutné interpretovat v kontextu jejích silných stránek i limitací. Silnou stránkou studie je podrobně vyšetřený soubor pacientů i kognitivně zdravých osob. Vyšetření zahrnovalo komplexní neuropsychologické, neurologické vyšetření i neurozobrazovací metody. Jedná se o jednu z prvních studií srovnávající pomocí MBI-C úroveň NPS mezi osobami s demencí, aMCI a normální kognicí. Za limit studie považujeme nerovnoměrný počet osob napříč skupinami. I navzdory nižšímu počtu jsme však byli schopni najít statisticky významné rozdíly srovnatelné s podobnými studiemi. Nutno také uvést, že pouhé hodnocení přítomnosti počtu a závažnosti NPS pomocí MBI-C neumožňuje stanovit, kolik lidí ze souboru osob bez demence splnilo kritéria MBI.

Co se týče samotného dotazníku, jeho výhodou oproti nejpoužívanějšímu NPI je delší posuzovaný časový úsek trvání symptomů (6 vs. 1 měsíc), což umožňuje vyloučit přechodná narušení, a tedy s větší pravděpodobností detekovat prodromální stadium demence [31].

Závěr

Námi adaptovaná česká verze dotazníku MBI-C detekuje přítomnost změn v chování a osobnosti ještě před rozvojem syndromu demence. Dotazník je zároveň krátký a jednoduše administrovatelný i bez přítomnosti klinika. Z těchto důvodů se ukazuje jako slibný nástroj pro použití při podezření na přítomnost NPS u pacientů v preklinických a prodromálních stadiích AN. Jeho validace vůči zlatému standardu je cílem budoucích studií.

Pro klinickou praxi je dotazník MBI-C aktuálně volně dostupný ke stažení na oficiální stránce www.mbitest.org [51].

Etické principy

Studie byla provedena v souladu s Helsinskou deklarací z roku 1975 (a jejími revizemi z let 2004 a 2008) a etickými standardy Etické komise 2. LF UK a FN Motol. Všichni účastníci podepsali informovaný souhlas schválený Etickou komisí 2. LF UK a FN Motol č. rozhodnutí: EK-701/16.

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Konflikt zájmů

Autoři deklarují, že v souvislosti s předmětem studie nemají žádný konflikt zájmů.

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Mild Behavioral Impairment Is Associated With Atrophy of Entorhinal Cortex and Hippocampus in a Memory Clinic Cohort

*Veronika Matuskova[1,2], Zahinoor Ismail[3,4,5,6], Tomas Nikolai[1,2], Hana Markova[1,2], Katerina Cechova[1,2], Zuzana Nedelska[1,2], Jan Laczó[1,2], Meng Wang[4,5], Jakub Hort[1,2] and Martin Vyhnalek[1,2]**

[1] Memory Clinic, Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czechia, [2] International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czechia, [3] Department of Psychiatry, Cumming School of Medicine, Calgary, AB, Canada, [4] Department of Clinical Neurosciences, Cumming School of Medicine, Calgary, AB, Canada, [5] Department of Community Health Sciences, Cumming School of Medicine, Calgary, AB, Canada, [6] Hotchkiss Brain Institute and O'Brien Institute for Public Health, University of Calgary, Calgary, AB, Canada

Objectives: Mild behavioral impairment (MBI) is a syndrome describing late-onset persistent neuropsychiatric symptoms (NPS) in non-demented older adults. Few studies to date have investigated the associations of MBI with structural brain changes. Our aim was to explore structural correlates of NPS in a non-demented memory clinic sample using the Mild Behavioral Impairment Checklist (MBI-C) that has been developed to measure MBI.

Methods: One hundred sixteen non-demented older adults from the Czech Brain Aging Study with subjective cognitive concerns were classified as subjective cognitive decline ($n = 37$) or mild cognitive impairment ($n = 79$). Participants underwent neurological and neuropsychological examinations and brain magnetic resonance imaging (MRI) (1.5 T). The Czech version of the MBI-C was administered to participants' informants. Five *a priori* selected brain regions were measured, namely, thicknesses of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and entorhinal cortex (ERC) and volume of the hippocampus (HV), and correlated with MBI-C total and domain scores.

Results: Entorhinal cortex was associated with MBI-C total score ($r_S = -0.368$, $p < 0.001$) and with impulse dyscontrol score ($r_S = -0.284$, $p = 0.002$). HV was associated with decreased motivation ($r_S = -0.248$, $p = 0.008$) and impulse dyscontrol score ($r_S = -0.240$, $p = 0.011$).

Conclusion: Neuropsychiatric symptoms, particularly in the MBI impulse dyscontrol and motivation domains, are associated with medial temporal lobe atrophy in a clinical cohort of non-demented older adults. This study supports earlier involvement of temporal rather than frontal regions in NPS manifestation. Since these regions are typically affected early in the course of Alzheimer's disease (AD), the MBI-C may potentially help further identify individuals at-risk of developing AD dementia.

Keywords: entorhinal cortex, hippocampus, mild behavioral impairment-checklist, mild cognitive impairment, neuropsychiatric symptoms, subjective cognitive decline, magnetic resonance imaging

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****Correspondence:***
Martin Vyhnalek
martin.vyhnalek@fnmotol.cz

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INTRODUCTION

Neuropsychiatric symptoms (NPS) are a common feature in early stages of various neurodegenerative diseases (Desmarais et al., 2018; Fischer and Agüera-Ortiz, 2018; Ismail et al., 2018; Sherman et al., 2018; Bateman et al., 2020) and can precede the onset of dementia by several years (Singh-Manoux et al., 2017; Tapiainen et al., 2017). NPS may emerge before detectable cognitive decline and are associated with a higher risk of clinical progression to mild cognitive impairment (MCI) or dementia (Sugarman et al., 2018; Wise et al., 2019). There is compelling evidence linking various NPS, such as depression, anxiety, apathy, agitation, and irritability, to accumulation of beta-amyloid, a hallmark of Alzheimer's disease (AD) (Bensamoun et al., 2016; Ng et al., 2017; Gatchel et al., 2019; Goukasian et al., 2019; Johansson et al., 2020), but these symptoms can also occur in physiological aging (Bunce et al., 2012) or can be related to other pathologies, such as cerebrovascular disease (Tiel et al., 2015). Thus, their clinical interpretation is often challenging.

To improve the detection of early stages of neurodegenerative diseases, a new neurobehavioral syndrome, named mild behavioral impairment (MBI), has been recently proposed by the Alzheimer's Association Working Group (Ismail et al., 2016). MBI describes new-onset and persistent NPS in non-demented older adults (reflecting a change from baseline patterns of behavior), as an at-risk state for incident cognitive decline and dementia. MBI can emerge not only in persons with MCI but also in cognitively normal (CN) older adults, in whom MBI is associated with a greater risk of incident cognitive decline and dementia (Taragano et al., 2018; Matsuoka et al., 2019; Ismail et al., 2021). MBI (assessed with the Neuropsychiatric Inventory) was highly prevalent in both clinical and community-based cohorts of non-demented older adults (Mortby et al., 2018; Sheikh et al., 2018).

To verify the presence of MBI and to address the need for a more sensitive and specific NPS scale in preclinical and prodromal stages of neurodegenerative diseases, a new instrument, the Mild Behavioral Impairment Checklist (MBI-C) (Ismail et al., 2017a), has been developed. The MBI-C serves as a global and domain-specific NPS measure including early symptom presentations. Its factor structure has been validated in older adults with normal cognition (Creese et al., 2020), as have its psychometric properties to capture MBI in subjective cognitive decline (SCD) (Mallo et al., 2018b) and MCI (Mallo et al., 2018a) populations. Thus, the MBI-C may provide a more precise alternative to routinely used NPS measures that have been mostly developed to assess NPS in the dementia stage. A large population-based study of non-demented older adults using the MBI-C reported at least one symptom in more than half of the participants, with affective and impulse dyscontrol symptoms being the most commonly reported (Creese et al., 2019).

Recent studies have demonstrated a link between higher MBI-C score and increased beta-amyloid pathology (a higher global and regional beta-amyloid PET uptake) in CN older adults (Lussier et al., 2020). The presence of MBI in non-demented ADNI participants predicted a higher increase in a plasma neurofilament light protein over 2 years compared to the participants without MBI, bringing evidence for the link between MBI and subsequent neurodegeneration (Naude et al., 2020). Furthermore, MBI has demonstrated an association with AD risk genes (Andrews et al., 2018; Creese et al., 2021). Thus, it seems that MBI also identifies a potential at-risk group for incident cognitive decline and AD dementia. However, studies that explored structural neuroimaging correlates of MBI in older adults at-risk for AD dementia are scarce.

Using the informant version of the MBI-C, we aimed to examine the associations between regional brain atrophy on magnetic resonance imaging (MRI) and NPS severity in a memory clinic cohort of clinically and neuropsychologically well-defined non-demented older adults. Five brain regions were selected based on their previously reported associations with NPS [thicknesses of the orbitofrontal cortex and anterior cingulate cortex (Rosenberg et al., 2015; Boublay et al., 2016)] and with early AD pathology [posterior cingulate cortex, entorhinal cortex, and hippocampal volume (Braak et al., 2006)]. To measure NPS severity, MBI-C total score and five MBI-C domain scores were used. We hypothesized that in this cohort of individuals at risk of developing AD dementia, (1) participants with higher MBI burden would have more pronounced atrophy, above and beyond demographics (age, sex, and years of education) and global cognitive status; and (2) across the MBI domains, more pronounced regional atrophy would be associated particularly with more severe affective, decreased motivation, and impulse dyscontrol symptoms, which are the NPS known to be present in early stages of AD (Bensamoun et al., 2016; Ng et al., 2017; Gatchel et al., 2019; Johansson et al., 2020).

MATERIALS AND METHODS

Participants

A total of 116 participants with subjective cognitive concerns were included in this study. Participants were recruited from the Czech Brain Aging Study (CBAS), an ongoing longitudinal memory clinic-based study aimed at detecting early changes associated with pathological brain aging (Sheardova et al., 2019). Participants with subjectively perceived cognitive complaints were referred to our memory clinic by general practitioners or other specialists. All participants underwent standard neurological and laboratory evaluations, comprehensive neuropsychological examination, and 1.5-T brain magnetic resonance imaging (MRI) within 3 months from the initial visit. Based on the neuropsychological examination, the participants were classified as either SCD or MCI. SCD ($n = 37$) was diagnosed using the SCD-Initiative Workgroup criteria (Jessen et al., 2014) and included persons with (1) subjectively perceived cognitive decline compared to a previously normal status, unrelated to an acute event, and (2) no objective cognitive impairment in the neuropsychological assessment based on age-, gender-, and education-adjusted norms. Subjective cognitive complaints were assessed by an experienced neuropsychologist in a semi-structured interview. MCI ($n = 79$) was diagnosed

according to the NIA-AA 2011 criteria (Albert et al., 2011) and included persons with the following: (1) subjectively perceived cognitive decline compared to a previously normal status; (2) neuropsychologically confirmed objective cognitive impairment below 1.5 SD on at least two tests within a domain in at least one of five established cognitive domains; (3) preservation of independence in functional abilities; and (4) the absence of dementia. Both amnestic ($n = 66$; aMCI) and non-amnestic ($n = 13$; naMCI) MCI were included. All the diagnoses were made by consensus involving cognitive neurologists and neuropsychologists. The exclusion criteria were as follows: (1) a diagnosis of dementia; (2) the presence of other neurologic or psychiatric diseases [e.g., Parkinson's disease, traumatic brain injury, stroke, alcohol or substance abuse, severe brain vascular burden (Fazekas scale ≥ 2 on MRI), current major psychiatric disorder, or a history of major psychiatric disorder as confirmed by clinical interviews]. The demographic characteristics of the participants are presented in **Table 1**.

All participants provided written informed consent according to the Declaration of Helsinki and the study was approved by the Ethics Committee of Motol University Hospital.

TABLE 1 | Demographic, neuropsychological and volumetric characteristics of the participants.

Characteristics	SCD $n = 37$ $M \pm SD$	MCI $n = 79$ $M \pm SD$	All $n = 116$ $M \pm SD$
Age[a]	66.37 ± 6.71	71.05 ± 8.41**	69.56 ± 8.18
Female, *n* (%)[b]	22 (59.5)	35 (44.3)	57 (49)
MMSE, score[a]	29.30 ± 0.88	26.82 ± 2.51**	27.61 ± 2.42
Education[a]	16.55 ± 3.21	14.82 ± 3.16**	15.38 ± 3.26
RAVLT 1-5, score[a]	55.41 ± 7.44	35.05 ± 11.60**	41.78 ± 14.14
RAVLT delayed recall, score[a]	12.03 ± 2.29	4.69 ± 3.73**	7.12 ± 4.79
LM delayed recall, score[a]	15.46 ± 3.91	8.08 ± 5.52**	10.43 ± 6.12
WAIS-III Digit span, score[a]	16.27 ± 3.23	13.67 ± 3.71**	14.50 ± 3.75
TMT A, time to completion (s)[a]	36.35 ± 7.11	55.72 ± 29.53**	49.49 ± 26.23
TMT B, time to completion (s)[a]	76.30 ± 21.25	166.64 ± 81.63**	137.58 ± 80.25
BNT-30, mistakes after a semantic cue[a]	1.62 ± 1.79	5.00 ± 3.91**	3.92 ± 3.73
C-VF animals, score[a]	26.43 ± 5.46	18.25 ± 5.38**	20.86 ± 6.60
P-VF, score[a]	52.08 ± 11.79	36.68 ± 12.98**	41.59 ± 14.48
PST—colors, time to completion (s)[a]	28.33 ± 6.68	42.64 ± 18.17**	38.00 ± 16.78
ROCF copy, score[a]	31.24 ± 3.11	26.70 ± 5.87**	28.16 ± 5.55
ROCF recall, score[a]	19.35 ± 6.38	9.40 ± 6.17**	12.60 ± 7.77
ERC, mm[a]	3.30 ± 0.43	2.91 ± 0.46**	3.03 ± 0.48
HV, mm^3[a]	3,935.83 ± 434.98	3,381.10 ± 607.54**	3,558.04 ± 614.01
ACC, mm[a]	2.74 ± 0.18	2.73 ± 0.21	2.73 ± 0.20
PCC, mm[a]	2.37 ± 0.11	2.33 ± 0.21	2.33 ± 0.18
OFC, mm[a]	2.52 ± 0.12	2.40 ± 0.21**	2.44 ± 0.19
AMG, mm^3[a]	1,407.97 ± 182.21	1,281.90 ± 232.91*	1,322.12 ± 225.10

**Difference from SCD group at $p < 0.05$; **difference from SCD group at $p < 0.01$. [a]t-test; [b]chi-square. SCD, subjective cognitive decline; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; LM, logical memory; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trial Making Test; BNT (30), Boston Naming Test—30-item version; C-VF, category verbal fluency; P-VF, phonemic verbal fluency—letters N, K, and P; PST, Prague Stroop Test; ROCF, Rey–Osterrieth complex figure; ERC, entorhinal cortex thickness; HV, hippocampal volume; ACC, anterior cingulate cortex thickness; PCC, posterior cingulate cortex thickness; OFC, orbitofrontal cortex thickness; AMG, amygdala volume; M, mean; SD, standard deviation.*

Neuropsychological Assessment

The neuropsychological battery included the Mini-Mental State Examination (MMSE) as a screening of global cognitive function and the following tests to assess five (Albert et al., 2011) cognitive domains: (1) memory by the Rey Auditory Verbal Learning Test (RAVLT), Logical Memory from the Wechsler Memory Scale-Third Edition (LM), and Rey–Osterrieth Complex Figure Test (ROCFT recall after 3 min); (2) executive function by the Trail Making Test B (TMT B), phonemic verbal fluency—letters N, K, and P (P-VF) and Prague Stroop test—colors (PST); (3) language by the Boston Naming Test 30-item version (BNT) and category verbal fluency—animals (C-VF); (4) attention and working memory by the Trial Making Test A (TMT A) and Digit Span Forward and Backward (DS) from the Wechsler Adult Intelligence Scale-Third Edition; and (5) visuospatial function by the Rey–Osterrieth Complex Figure Test (ROCFT copy) (Nikolai et al., 2018). All scores are presented in **Table 1**.

Neuropsychiatric Assessment

The Czech version of the MBI-C (Matuskova et al., 2020) was completed by a participant's close informant (a partner, a descendant, or another relative). The MBI-C is a newly developed instrument specifically designed to assess neuropsychiatric symptoms before the onset of dementia (Ismail et al., 2017a). It comprises of 34 items evaluating five behavioral domains in line with the recently proposed MBI diagnostic criteria (Ismail et al., 2016): (1) decreased motivation (six questions assessing cognitive, emotional, and behavioral apathy); (2) affective dysregulation (six questions evaluating depressive and anxiety symptoms); (3) impulse dyscontrol (12 questions assessing symptoms of agitation, aggression, impulsivity, and abnormal reward salience); (4) social inappropriateness (five questions describing tact, empathy, and sensitivity); and (5) abnormal perception and thought content (five questions regarding suspiciousness, grandiosity, and hallucinations). Each question requires an answer regarding presence (yes/no) and severity of the symptoms (1—mild, 2—moderate, 3—severe). The symptoms should represent a change from the person's usual behavior and persist over the last 6 months. The total score as well as five domain scores were calculated as a sum of the corresponding item severity ratings resulting in the MBI-C total score (0–102), decreased motivation score (0–18), affective dysregulation score (0–18), impulse dyscontrol score (0–36), social inappropriateness score (0–15), and abnormal perception and thought content score (0–15). *Z* scores were calculated for the MBI-C total score and all the domain scores for the whole cohort. Participants with four or more missing items on the MBI-C were excluded. In case of three or fewer missing items, both total and domain scores were calculated without these items. All scores are presented in **Table 2**.

TABLE 2 | MBI-C scores of the participants.

MBI-C, score (range)[a]	SCD *n* = 37 *M* ± SD	MCI *n* = 79 *M* ± SD	All *n* = 116 *M* ± SD
Total (0–102)	2.65 ± 4.27 (0–18)	5.38 ± 5.66 (0–27)**	4.51 ± 5.39 (0–27)
Decreased motivation (0–18)	0.46 ± 1.12 (0–5)	1.48 ± 2.01 (0–8)**	1.16 ± 1.83 (0–8)
Affective dysregulation (0–18)	0.97 ± 1.57 (0–7)	1.75 ± 2.14 (0–9)*	1.50 ± 2.00 (0–9)
Impulse dyscontrol (0–36)	1.00 ± 2.15 (0–9)	1.77 ± 2.28 (0–9)*	1.53 ± 2.26 (0–9)
Social inappropriateness (0–15)	0.19 ± 0.52 (0–2)	0.25 ± 0.59 (0–3)	0.23 ± 0.57 (0–3)
Abnormal perception/thought (0–15)	0.03 ± 0.16 (0–1)	0.11 ± 0.39 (0–2)	0.09 ± 0.34 (0–2)

**Difference from SCD group at p < 0.05; **difference from SCD group at p < 0.01. [a]Mann–Whitney U test.SCD, subjective cognitive decline; MCI, mild cognitive impairment; MBI-C, Mild behavioral impairment checklist; M, mean; SD, standard deviation.*

MRI Acquisition and Processing

Brain scans were performed on a 1.5-T scanner (Siemens AG, Erlangen, Germany) using the T1-weighted three-dimensional high-resolution magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with TR/TE/TI = 2,000/3.08/1,100 ms, flip angle 15°, 192 continuous partitions, slice thickness = 1.0 mm, and in-plane resolution = 1 mm. Scans were visually checked by an image analyst to ensure appropriate data quality and by a neuroradiologist to exclude participants with a major pathology interfering with cognitive functioning such as cortical infarctions, tumor, subdural hematoma, and hydrocephalus.

Volumetric segmentation and cortical reconstruction were performed using the FreeSurfer image analysis software (version 5.3), which is documented and freely available[1]. FreeSurfer is a popular and widely used algorithm and has been described in detail and well documented in prior publications (Fischl and Dale, 2000; Fischl et al., 2002, 2004a,b; Ségonne et al., 2004; Han et al., 2006; Jovicich et al., 2006; Reuter et al., 2010). Cortical thicknesses in four regions were selected based on previously reported associations with NPS (orbitofrontal cortex, OFC; anterior cingulate cortex, ACC) (Rosenberg et al., 2015; Boublay et al., 2016) or with early AD pathology (posterior cingulate cortex, PCC; entorhinal cortex, ERC) (Braak et al., 2006). Regional thickness from the left and right hemispheres was averaged. We also included hippocampal volumes (HV), adjusted for the total estimated intracranial volume (eTIV) using the proportion method (O'Brien et al., 2011), and right and left HV were averaged. Volumetric characteristics are presented in **Table 1**. Subsequently, we performed an exploratory analysis with amygdala volume, adjusted for the total estimated intracranial volume (eTIV). These results are presented in the **Supplementary Material** (part 2).

Statistical Analysis

To explore the differences between SCD and MCI groups, we performed *t*-tests for normally distributed data. Due to a non-normal distribution, Mann–Whitney *U* tests were used to compare MBI total and domain scores between the groups. Chi-square test was used to examine differences in sex proportion. All subsequent analyses were performed within the whole sample (SCD + MCI). Because of a non-normal, right-skewed distribution of the MBI-C scores, the associations of the MBI-C total score and five domain scores with the ROIs were assessed using covariate-adjusted Spearman rank correlations. In the first model, the correlations were adjusted for age, sex, and years of education. In the second model, we included additional adjustment for MMSE. Furthermore, we performed complementary analyses excluding naMCI participants (resulting in $n = 103$). The analyses were corrected for multiple comparisons using the Holm–Bonferroni correction (corrected for the number of tests performed per each MBI score). All the analyses were performed using SPSS version 20.

RESULTS

Participants' demographic, neuropsychological, and MRI characteristics are presented in **Table 1**. MBI-C scores are presented in **Table 2**. Most of the informants that completed the MBI-C were participants' spouses/partners (70%) or descendants (22%). Overall, 70% of the cohort reported at least one symptom (scored ≥ 1) in the MBI-C (54% of SCD and 78.5% of MCI). Symptoms of affective dysregulation and impulse dyscontrol were the most common, while abnormal perception/thought content were the least common (see **Table 2**).

In the entire cohort, MBI-C total score was weakly associated with ERC thickness, controlling for age, sex, and education. Within MBI-C domains, impulse dyscontrol score was moderately associated with ERC thickness and weakly associated with HV, the former remaining significant after additional controlling for MMSE. Decreased motivation score was weakly associated with HV; however, this association disappeared after additional controlling for MMSE.

Moreover, HV was weakly associated with MBI-C total score, and OFC thickness was weakly associated with MBI-C total score, impulse dyscontrol, and decreased motivation; the two former associations survived additional controlling for MMSE. However, all these associations disappeared after correcting for multiple comparisons. No other associations were observed. All results are presented in **Table 3**. Excluding naMCI participants ($n = 13$) from the analyses did not substantially change the results (see part 1 in the **Supplementary Material**).

[1]http://surfer.nmr.mgh.harvard.edu/

TABLE 3 | Associations of cortical thickness and volume measures with MBI-C total and domain scores.

	Spearman r_S, p value adjusted for age, sex, and education						Spearman r_S, p value adjusted for age, sex, education, and MMSE					
	MBI-C total score	**MBI-C Motivation**	**MBI-C Affectivity**	**MBI-C Impulse dyscontrol**	**MBI-C Social**	**MBI-C Perception/ thought**	**MBI-C total score**	**MBI-C Motivation**	**MBI-C Affectivity**	**MBI-C Impulse dyscontrol**	**MBI-C Social**	**MBI-C Perception/ thought**
ERC†	−0.284, 0.002*	−0.138, 0.146	−0.154, 0.103	−0.368, < 0.001*	−0.130, 0.169	−0.125, 0.187	−0.238, 0.012	−0.087, 0.361	−0.110, 0.248	−0.337, < 0.001*	−0.137, 0.151	−0.132, 0.165
HV††	−0.225, 0.016	−0.248, 0.008*	−0.060, 0.527	−0.240, 0.011*	−0.182, 0.053	0.031, 0.744	−0.168, 0.077	−0.199, 0.035	−0.002, 0.985	−0.196, 0.038	−0.195, 0.040	0.033, 0.731
ACC†	−0.018, 0.851	0.065, 0.497	−0.011, 0.907	−0.051, 0.589	−0.171, 0.070	−0.123, 0.196	−0.023, 0.813	0.062, 0.518	−0.015, 0.877	−0.056, 0.560	−0.171, 0.071	−0.123, 0.198
PCC†	−0.058, 0.544	−0.013, 0.889	−0.014, 0.887	−0.150, 0.113	−0.078, 0.409	−0.122, 0.197	−0.051, 0.590	−0.007, 0.942	−0.008, 0.935	−0.146, 0.125	−0.078, 0.411	−0.122, 0.199
OFC†	−0.214, 0.023	−0.201, 0.033	−0,127, 0.182	−0.206, 0.028	−0.125, 0.186	−0.099, 0.295	−0.197, 0.038	−0.185, 0.051	−0.110, 0.247	−0.191, 0.043	−0.126, 0.186	−0.100, 0.294

†*Cortical thickness (averaged between left and right hemisphere);* ††*volume (averaged between left and right hemisphere) adjusted for eTIV (proportion method);* **significant after applying Holm–Bonferroni correction for multiple comparisons. MBI-C, mild behavioral impairment checklist; ERC, entorhinal cortex thickness; HV, hippocampal volume (eTIV); ACC, anterior cingulate cortex thickness; PCC, posterior cingulate cortex thickness; OFC, orbitofrontal cortex thickness.*

Following our finding that MBI was mostly associated with the two medial temporal lobe (MTL) structures, we wanted to further explore the associations with the amygdala, a key MTL structure involved in neuropsychiatric manifestations. In the exploratory analysis, we found that the amygdala was not associated with any of the MBI-C scores (see part 2 of the **Supplementary Material**).

DISCUSSION

To the best of our knowledge, this is the first study using the MBI-C to examine the relationships between regional brain atrophy and NPS in a well-characterized sample of non-demented memory clinic participants enrolled in the Czech Brain Aging Study. We assessed the association between atrophy in five *a priori* selected brain regions and MBI-C severity. We found that MBI-C total score as well as impulse dyscontrol and decreased motivation domain scores were associated with atrophy in two medial temporal lobe (MTL) regions, i.e., the ERC and hippocampus.

Medial temporal lobe regions (known to be affected early in AD) have traditionally been associated with cognitive functions, especially episodic memory and spatial navigation (Braak et al., 2006; Laczó et al., 2017; Berron et al., 2020). However, evidence suggests that their anterior parts belong to a distinct functional subsystem (Ranganath and Ritchey, 2012), which is involved in the regulation of motivational and emotional behavior (Fanselow and Dong, 2010). Disruption of this integrity may therefore also manifest with various NPS. This is supported by several recent studies. It has been shown that accumulation of tau pathology in the ERC and inferior temporal lobe (Gatchel et al., 2017b) and lower HV (Donovan et al., 2015) are associated with depressive symptoms in CN older adults. The hippocampus is also among the structures associated with apathy in non-demented older adults (Johansson et al., 2020) and with agitation in MCI and AD (Trzepacz et al., 2013). Our findings are therefore consistent with prior reports describing MBI as a manifestation of neurodegeneration (Ismail et al., 2016) and, in some, a manifestation of early AD. The latter is also supported by research linking MBI to AD pathology in cognitively normal older adults (Lussier et al., 2020; Johansson et al., 2021).

We found impulse dyscontrol domain to be the most strongly associated with MTL atrophy. This complies with a very recent finding that impulse dyscontrol was associated with tau deposition in the ERC and hippocampus in preclinical AD (Johansson et al., 2021). Also, an ADNI machine learning study found that baseline presence of these symptoms was an important input feature for cognitive category classification (CN, MCI, and dementia) at 40 months (Gill et al., 2020). In a mixed cohort of CN, MCI, and AD dementia, impulse dyscontrol was associated with lower white matter integrity and lower thickness of the parahippocampal gyrus (Gill et al., 2021). Impulse dyscontrol is a heterogeneous domain, including symptoms such as agitation, disinhibition, abnormal reward salience, or impaired oral intake (Ismail et al., 2016; Saari et al., 2021). In our study, the items mostly endorsed by the informants included agitation, argumentativeness, impatience, and rigidity (items 1, 2, 5, and 7), which were also found to be the most prevalent in a similar cohort (Saari et al., 2021) and were previously designated as an "agitation" cluster (Creese et al., 2019). Neurodegenerative changes in MTL may thus manifest as this cluster of agitation symptoms, possibly as a result of impaired inhibition of emotional responses in stressful interpersonal situations (Sturm et al., 2013). In line with a recent network analysis of impulse dyscontrol domain in SCD and MCI, they may represent a cluster of impulsive behaviors observed in social settings rather than generalized impulsivity or compulsive behavior (Saari et al., 2021).

Lower HV in our study was also associated with apathy (decreased motivation domain), although to a lesser extent.

This is in accordance with apathy being consistently reported as one of the most prevalent symptoms in non-demented older adults and associated with AD pathology (Sherman et al., 2018; Johansson et al., 2020).

Medial temporal lobe also comprises the amygdala, a key structure that regulates emotional behavior. It has been suggested that in early AD, amygdala atrophy is comparable to hippocampal atrophy (Poulin et al., 2011). We thus conducted an exploratory analysis to see whether there is an association between MBI-C scores and amygdala volume. None of the MBI-C scores were associated with amygdala volume, which is in line with a previous study (Poulin et al., 2011) and suggests that, from the main MTL structures explored here, MBI symptoms are specific to ERC and hippocampal atrophy.

Interestingly, we found no associations between atrophy in our selected regions and symptoms of depression and anxiety (affective dysregulation domain) although these were among the most prevalent in our cohort, are among the most commonly reported in non-demented older adults (Ismail et al., 2018), and have been associated with an increased risk of progression to AD dementia (Pietrzak et al., 2015; Gallagher et al., 2018; Gatchel et al., 2019). There may be several explanations for these findings. First, depressive and anxiety symptoms may not be specific to neurodegenerative changes in regions included here. Instead, they may be caused by other pathological changes, including serotonin or noradrenaline deficiency (Šimić et al., 2017) or comorbid white matter pathology (Puzo et al., 2019). Furthermore, there is substantial overlap between key symptoms of depression and apathy, and they may often co-occur (Nobis and Husain, 2018). In a study in CN older adults using GDS-derived clusters of symptoms, only apathy/anhedonia but not anxiety/concentration were associated with both reduced HV volume and posterior cortical hypometabolism (Donovan et al., 2015). Another longitudinal study of older adults reported that anhedonia, but not dysphoria, is a risk factor for conversion to dementia (Lee et al., 2019). In the MBI-C, these symptoms are also part of decreased motivation domain. The use of different NPS instruments may thus be another possible reason for these differences. Altogether, previous findings along with ours may thus not be conflicting, but rather describe a broader array of symptoms that emerge early in the course of AD.

We found no associations between PCC thickness and MBI-C scores, although PCC is involved in NPS pathophysiology in early AD. PCC hypometabolism was associated with higher apathy scores both cross-sectionally and over time across the AD clinical spectrum (Gatchel et al., 2017a). Individuals with preclinical AD with more severe NPS displayed metabolic dysfunction in PCC at baseline and 2-year follow-up (Ng et al., 2017). The discrepancy between positive findings from metabolic studies and the absence of a relationship in our study could be explained by the fact that, in AD, metabolic changes in this region precede atrophy (Rodriguez-Oroz et al., 2015).

We also did not observe any associations between ACC or OFC thickness and MBI-C scores. This is in contrast with previous research on various NPS that have identified consistent abnormalities mainly within ACC and frontal regions (Rosenberg et al., 2015; Boublay et al., 2016). There may be several explanations for this. First, our study involved persons in early stages of cognitive impairment (i.e., mean MMSE in MCI group was 26.82 $\pm$ 2.51) compared to previous research mostly focusing on persons with AD dementia (Rosenberg et al., 2015; Boublay et al., 2016). This is also supported by no significant differences in ACC and OFC thicknesses between our SCD and MCI groups (see **Table 1**). Similarly, previous studies exploring structural correlates of apathy in CN and MCI individuals also reported no (Guercio et al., 2015) or weaker (Johansson et al., 2020) associations with atrophy in ACC or frontal regions (compared to temporal regions) and concluded that these associations may only be evident in later stages of AD. Our findings are consistent with this hypothesis. Furthermore, inconsistent findings may stem from different study cohorts. In non-demented older adults referred for progressive behavioral symptoms, MBI was associated with isolated frontal atrophy and a higher risk of progression to behavioral variant of frontotemporal dementia at 4 years (Orso et al., 2020). Cognitive complaints were an exclusion criterion in that study, as opposed to our study, in which they represented the main reason for referral to our clinic. This may have accounted for different regional atrophy being associated with MBI, possibly resulting from a distinct underlying pathology. Finally, we found several associations with OFC that disappeared after correction for multiple comparisons. Together with the fact that OFC is heavily connected with the hippocampus and other MTL structures and their interaction is important for selecting appropriate behavioral responses based on changing social cues (Catenoix et al., 2005; Ranganath and Ritchey, 2012; Ross et al., 2013), we may hypothesize that MBI-C symptoms may also reflect impaired MTL-OFC interaction.

We acknowledge several limitations to our study. First, a memory clinic setting limits the generalizability of our results to a general population, as neuropsychiatric symptoms are more frequent in clinical versus community samples (Ismail et al., 2017b). Another issue to consider is the lack of beta-amyloid and tau biomarkers, which limits our ability to attribute the structural changes we observed truly to AD pathology, notwithstanding the fact that all participants presented to clinic with cognitive concerns. Furthermore, some MBI-C domains (social inappropriateness and abnormal perception/thought) had very low mean scores and a limited range of scores. Thus, the opportunity to detect associations may be low. Finally, it would be pertinent to examine MBI symptoms also in SCD and MCI groups separately since detecting MBI may be particularly useful in persons with no cognitive impairment in terms of identifying at-risk individuals (Ismail et al., 2020). The modest sample size in our study did not allow us to perform the analysis in these subgroups, and we addressed this issue by controlling the analyses for age and global cognition, represented by MMSE. On the other hand, even though we recognize these two separate groups in our sample, we consider them a cognitive continuum of non-demented older adults presenting with subjective cognitive concerns that urged them to seek medical help. They underwent the same recruiting process as they were recruited from the same CBAS cohort. Including both groups also improved our ability

to detect associations with volumetric measures of brain atrophy, which may be more challenging to capture in SCD only.

CONCLUSION

In summary, using the MBI-C, designed to assess a broad spectrum of early and persistent NPS in predementia stages, we found symptoms of apathy and impulse dyscontrol to be associated with medial temporal lobe atrophy, but not with frontal lobe atrophy. This study suggests that there is a wider group of neuropsychiatric symptoms emerging early in the course of neurodegeneration and supports earlier involvement of temporal rather than frontal regions in their manifestation. Our findings also support MBI-C as a valid tool for detecting NPS in a clinical cohort of non-demented older adults, which may be potentially useful in further detection of individuals at-risk of developing AD dementia. A research implementing longitudinal study design and AD biomarkers is ongoing.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the policy of the Czech Brain Aging Study (CBAS), which allows sharing of the data only after previous approval. Requests to access the datasets should be directed to MV, martin.vyhnalek@fnmotol.cz.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Second Faculty of Medicine, Charles University and Motol University Hospital. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MV, VM, and ZI participated in the design of the study and data interpretation and drafted the manuscript. VM, HM, KC, TN, MV, JL, and JH were involved in data acquisition and interpretation. ZN was involved in MRI data acquisition and processing. VM and MW performed the statistical analyses. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.643271/full#supplementary-material

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Contribution of Memory Tests to Early Identification of Conversion from Amnestic Mild Cognitive Impairment to Dementia

Martin Vyhnalek[a,b,*], Dylan J. Jester[c,d,e], Ross Andel[a,b,c], Hana Horakova[a,b], Tomas Nikolai[a,b], Jan Laczó[a,b], Veronika Matuskova[a,b], Katerina Cechova[a,b], Katerina Sheardova[b] and Jakub Hort[a,b]
[a]*Memory Clinic, Department of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital, Prague, Czech Republic*
[b]*International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic*
[c]*School of Aging Studies, University of South Florida, Tampa, FL, USA*
[d]*Department of Psychiatry, University of California San Diego, La Jolla, CA, USA*
[e]*Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla, CA, USA*

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Abstract.
Background: Memory tests using controlled encoding and cued recall paradigm (CECR) have been shown to identify prodromal Alzheimer's disease (AD), but information about the effectiveness of CECR compared to other memory tests in predicting clinical progression is missing.
Objective: The aim was to examine the predictive ability of a memory test based on the CECR paradigm in comparison to other memory/non-memory tests for conversion to dementia in patients with amnestic mild cognitive impairment (aMCI).
Methods: 270 aMCI patients from the clinical-based Czech Brain Aging Study underwent a comprehensive neuropsychological assessment including the Enhanced Cued Recall test (ECR), a memory test with CECR, two verbal memory tests without controlled encoding: the Auditory Verbal Learning Test (AVLT) and Logical memory test (LM), a visuospatial memory test: the Rey-Osterrieth Complex Figure test, and cognitive testing based on the Uniform Data Set battery. The patients were followed prospectively. Conversion to dementia as a function of cognitive performance was examined using Cox proportional hazard models.
Results: 144 (53%) patients converted to dementia. Most converters (89%) developed dementia due to AD or mixed (AD and vascular) dementia. Comparing the four memory tests, the delayed recall scores on AVLT and LM best predicted conversion to dementia. Adjusted hazard ratios (HR) of immediate recall scores on ECR, AVLT, and LM were similar to the HR of categorical verbal fluency.
Conclusion: Using the CECR memory paradigm in assessment of aMCI patients has no superiority over verbal and non-verbal memory tests without cued recall in predicting conversion to dementia.

Keywords: Alzheimer's disease, memory, mild cognitive impairment, verbal fluency

INTRODUCTION

Assessment of memory impairment is a key neuropsychological approach when predicting conversion to Alzheimer dementia (AD dementia) in

*Correspondence to: Martin Vyhnalek, Department of Neurology, Charles University, Second Faculty of Medicine, and Motol University Hospital, V Úvalu 84, 150 06 Prague, Czech Republic. Tel.: +420 224 436 800; E-mail: martin.vyhnalek@fnmotol.cz.

patients with mild cognitive impairment (MCI), subjective cognitive decline, and in cognitively healthy older adults [1, 2]. Various neuropsychological tests are used in the diagnosis of AD, though practice differs across countries and within countries in relation to specialization of the clinical sites [3]. There is a need for consensus as some guidelines recommend the use of memory tests with a controlled encoding paradigm [4–6] whereas others do not [7, 8]. Controlled learning/encoding with semantic cues diminishes the interference of attention, strategy, and working memory during the encoding part of the test, based on the encoding specificity principle [9].

Patients with MCI are at increased risk of progression to dementia and those with memory impairment (amnestic MCI – aMCI) are at particularly high risk of converting to AD dementia [10]. It was suggested that memory recall deficit in memory tests with controlled encoding that is not normalized or significantly improved with cueing or recognition is specific for hippocampal impairment [11, 12]. Keeping with the current knowledge of localization of neuropathological changes in early AD, the so-called hippocampal type of memory impairment was postulated to be the core neuropsychological marker of prodromal AD [4, 13].

The most widely used test with the controlled encoding and cued recall (CECR) paradigm is the Free and Cued Selective Reminding Test (FCSRT), which includes free and total recall subtests [14]. The FCSRT uses category cues at both acquisition and retrieval in an attempt to ensure semantic encoding and enhance recall.

The hippocampal type of memory impairment was found to be highly specific and sensitive when predicting aMCI conversion to dementia in a longitudinal study with the FCSRT [15]. An additional study demonstrated the utility of FCSRT in a population-based cohort of older adults where free and total recall showed good specificity, sensitivity, and negative predictive value in predicting dementia; however, positive predictive values were low, and many subjects with poor free and total recall scores in the FCSRT remained free of dementia at 5 years [16]. In another longitudinal aging study, a decline in free recall was detected 7 years before the diagnosis of dementia [17].

One cross-sectional study brought indirect evidence for the superiority of FCSRT measures for discrimination between AD and non-AD etiology of MCI: both free and cued FCSRT recall were more closely related to a cerebrospinal fluid (CSF) biomarker signature indicative of AD in comparison to two free recall measures without a controlled encoding paradigm (Logical memory, CERAD test), though only delayed recalls were compared [18].

Apart from the FCSRT, other studies have been conducted demonstrating the relation of other memory tests with dementia conversion, though inclusion of the CECR paradigm and comparison of several memory tests in one battery is rare and consensus on which memory tests best predict conversion is unclear. One longitudinal study of patients with aMCI with 3 years follow-up found the TAVEC – Verbal Learning Test of the Complutense University (a test using free and cued recall – Spanish version of the Californian Verbal Learning Test) to be the best predictor of conversion to dementia in MCI patients compared to other tests in the battery; however, no other verbal memory test was used to allow direct comparison [19].

To the best of our knowledge, only one prior longitudinal study compared a memory test based on the CECR paradigm with a wordlist memory test based on uncontrolled learning and free recall. A short 6-item test was found to be superior to a 10-item version of the Auditory Verbal Learning Test (AVLT) in predicting conversion to AD dementia at 18 months follow-up [20]. Another longitudinal study used a modified 15-word version of the FCSRT, in which controlled encoding was not implemented, and found free recall in this test to be superior to a memory test using story recall [21].

Besides the memory tests using a list of words such as the AVLT or FCSRT, tests using story recall have been recommended in clinical practice and research to identify patients likely to convert to dementia. Among them, the Logical memory test (LM) in particular has been widely used in the United States, where it has been a part of the UDS [2, 22] and the PACC (preclinical AD cognitive composite) battery [23, 24]. This suggests the need of comparing the LM to tests using the CECR paradigm.

In summary, the clinical utility of memory tests with the free and cued paradigm has been demonstrated in numerous previous studies; however, there is no conclusive evidence of superiority of tests using CECR over other memory tests (without this paradigm) among older adults without dementia.

Recently, attention has been drawn to non-memory domains. In particular, semantic fluency has been identified as an independent predictor of the presence of AD pathology in cognitively normal older adults. Addition of category fluency to the PACC cognitive

battery provided unique information about early cognitive decline not currently captured by the episodic memory, executive function, and global cognition components, and was suggested to improve detection of early Amyloid-beta-related cognitive decline [24, 25]. Moreover, recent work by the Czech Brain Aging Study has suggested that a dysnomic form of aMCI may exist, and that patients with dysnomic or severe multi-domain aMCI are more likely to progress to dementia [26].

In our previous cross-sectional study, we examined the potential of the Enhanced Cued Recall (ECR) test, which is an alternative version of the FCSRT based on the same paradigm, to reflect the hippocampal atrophy in nondemented older adults. We compared it with two other frequently used memory tests, the AVLT—a test with 15 words without this procedure, and the nonverbal Rey–Osterrieth complex figure test (ROCFT) and we found no superiority of the ECR test over the AVLT [27].

Building on previous research, the aim of this longitudinal clinical based study was to compare the potential of four memory tests (ECR, AVLT, ROCF, and LM) and other, non-memory tests to predict the conversion to dementia in aMCI patients. We expected that the ECR test using the CECR paradigm would be superior to other memory and non-memory tests to predict conversion to dementia.

METHODS

Participants

A total of 270 aMCI patients were recruited and followed prospectively with annual examinations at the Memory Clinic in Motol University Hospital in Prague, Czech Republic between 2005 and 2020 in the Czech Brain Aging Study (CBAS) [28].

All individuals were referred to the clinic by general practitioners, neurologists, psychiatrists, or geriatricians based on memory complaints reported by themselves or their close informants. They underwent standard clinical and laboratory evaluations, brain MRI, and comprehensive neuropsychological examination at baseline and were followed prospectively with yearly clinical and neuropsychological evaluations, and interviews with informants in order to detect conversion to dementia. MRI was repeated every two years. Additional clinical visits were performed in case of unusual clinical worsening reported by the patient or his/her informant. The diagnosis was determined at the joint meetings of neuropsychologists with neurologists and was based on mutual agreement. When establishing the diagnosis, the clinicians used all available information including the results of previous tests and all other clinical information. In case of conversion, the patients underwent a new brain MRI used to confirm the final diagnosis. At baseline, all participants fulfilled Petersen's criteria for aMCI including memory complaints, evidence of memory dysfunction on neuropsychological testing, generally intact activities of daily living, and absence of dementia [8]. The group included both single domain (isolated memory impairment) and multiple domain (memory impairment plus impairment of at least one other cognitive domain) aMCI participants. Memory impairment was established when the patient scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any memory test

Individuals with a history of neurological or psychiatric disease potentially interfering with cognitive function (i.e., stroke, multiple sclerosis, Parkinson's disease, major depressive symptomatology defined as >8 points on the 15-item Geriatric Depression Scale, psychosis, etc.), psychiatric medication usage excluding SSRI, or abnormal neurological examination including gait or movement difficulties were not included. In addition, we did not include patients with primary progressive aphasia. All participants in this study had signed written informed consent that was approved by a local ethics committee. The procedures were in accordance with the Helsinki Declaration of 1975 and later revision in 2000. The basic characteristics and results of neuropsychological assessment are summarized in Table 1.

The conversion to dementia and its etiology was established during the regular consensual meetings of neurologists and neuropsychologists. The diagnosis was based on clinical history reported by the patient and the caregiver, neurological examination, neuropsychological assessment, and MRI. The main criterion to diagnose dementia was based on the impairment of activities of daily living reported by the patient's informant [7]. Neuropsychological test results were used to assess the cognitive profile, which helped to specify the dementia's etiology.

The diagnosis of different types of dementia was based on current criteria for probable AD [7], probable vascular dementia [30], probable dementia with Lewy bodies [31], or probable behavioral variant of frontotemporal dementia [32]. Patients labeled

Table 1
Demographic characteristics and cognitive performance

	Baseline	Follow-Up	
	Amnestic Mild Cognitive Impairment ($n = 270$)	Non-Converters ($n = 126$)	Dementia Converters ($n = 144$)
Demographics	Mean ± SD	Mean ± SD	Mean ± SD
Days of Follow-Up (y)	2.80 ± 2.02	3.20 ± 2.32	2.44 ± 1.65*
Gender (male/female)	124/146	66/60	58/86
Age	71.71 ± 8.45	69.15 ± 8.36	73.97 ± 7.89*
Education	14.53 ± 3.39	15.12 ± 3.60	14.01 ± 3.12*
GDS-15	4.12 ± 3.25	4.52 ± 3.34	3.76 ± 3.13
∧*APOE4* carriers (≥1 allele)	45% (95)	35% (33)	53% (62)*
∧*APOE4/E4* carriers (2 alleles)	6% (13)	4% (4)	8% (9)
Dementia Classification			% (*n*)
AD	–	–	72% (104)
BV-FTD	–	–	4% (6)
LBD	–	–	5% (7)
Mixed Dementia	–	–	17% (25)
VaD (without AD)	–	–	1% (2)
Cognitive Performance (Baseline)	Mean ± SD	Mean ± SD	Mean ± SD
MMSE	26.30 ± 2.68	27.49 ± 1.94	25.24 ± 2.80*
AVLT 1	3.88 ± 1.48	4.37 ± 1.44	3.42 ± 1.36*
AVLT 5	7.88 ± 2.44	8.91 ± 2.30	6.87 ± 2.14*
AVLT 1-5	31.34 ± 8.46	35.22 ± 7.61	27.55 ± 7.49*
AVLT 30	3.43 ± 3.03	4.92 ± 2.81	1.95 ± 2.48*
ECR-FR	4.58 ± 3.00	6.13 ± 2.79	3.54 ± 2.68*
ECR-TR	13.23 ± 3.24	14.50 ± 2.09	12.38 ± 3.58*
ROCF-R	7.82 ± 6.16	10.58 ± 6.09	5.27 ± 5.06*
ROCF-C	27.07 ± 6.33	27.92 ± 5.42	26.29 ± 6.99*
LOG-I	9.36 ± 4.25	11.27 ± 4.04	7.35 ± 3.49*
LOG-D	5.74 ± 5.08	8.27 ± 4.93	3.08 ± 3.69*
TMT A	59.94 ± 27.83	57.56 ± 27.93	62.30 ± 27.67
TMT B	173.97 ± 80.76	145.91 ± 71.02	202.28 ± 80.38*
F-DigitSpan-NM	5.68 ± 1.23	5.85 ± 1.34	5.54 ± 1.11*
F-Digit Span-SC	8.44 ± 2.13	8.59 ± 2.38	8.32 ± 1.89
B-DigitSpan-NM	4.06 ± 1.20	4.23 ± 1.30	3.91 ± 1.09*
B-DigitSpan-SC	5.30 ± 1.94	5.60 ± 2.08	5.03 ± 1.76*
Digit Symbol	30.29 ± 10.42	33.62 ± 11.23	26.98 ± 8.38*
BNT	53.31 ± 6.49	53.98 ± 5.52	52.72 ± 7.21
P-VF	33.82 ± 11.73	34.36 ± 11.88	33.35 ± 11.63
S-VF-A	16.83 ± 5.47	19.00 ± 5.37	14.37 ± 4.47*
S-VF-V	8.91 ± 2.84	9.61 ± 2.98	8.12 ± 2.47*

*indicates statistical significance between non-converters and converters. Patients who did not convert with less than 360 days of follow-up were excluded ($n = 12$). ^Sample size for apolipoprotein (*APOE*) was 213. AD, Alzheimer's disease; BV-FTD, behavioral-variant frontotemporal dementia; LBD, Lewy body dementia; VaD, vascular dementia; MMSE, total score; AVLT 1, trial 1 recall; AVLT 5, trial 5 recall; AVLT 1-5, sum of trials 1 to 5; AVLT 30, recall after 30 min; ECR-FR, free recall; ECR-TR, total recall after cueing; ROCF-R, visual reproduction after 3 min; ROCF-C, copy score [44]; LOG-I, Logical Memory Immediate Recall from the Uniform Data Set; LOG-D, Logical Memory Delayed Recall from the Uniform Data Set; TMT A, given in seconds; TMT B, given in seconds; F-DigitSpan-NM, forward Digit Span – numbers; F-Digit Span-SC, forward Digit Span – score; B-DigitSpan-NM, backward Digit Span – numbers; B-DigitSpan-SC, backward Digit Span – score; Digit Symbol, Digit Symbol Score from the WAIS-R; BNT, Boston Naming Test; P-VF, Phonemic Verbal Fluency; S-VF-A, Semantic Verbal Fluency – Animals; S-VF-V, Semantic Verbal Fluency – Vegetables.

as mixed (AD+vascular) dementia were considered to have predominance of AD pathology accompanied by evidence of extensive vascular changes or vascular changes in areas important for cognition (hippocampus, thalamus). In the clinical phenotype, the patients manifested episodic memory impairment and impaired attention/working memory, executive function, and slow processing speed [33].

Neuropsychological assessment

All individuals were interviewed using the following questionnaires: Clinical Dementia Rating [34], Functional Activities Questionnaire to assess activities of daily living [35], Hachinski Ischemic Scale, and 15-item Geriatric Depression Scale (GDS-15) [36]. The neuropsychological battery included the Mini-Mental State Examination (MMSE), Digit Span forward and backward tests, Digit Symbol, Trail Making Tests (TMT) A and B, Boston Naming Test (30 odd-items version), Semantic Verbal Fluency (Animals, Vegetables), Phonemic Verbal Fluency (Czech version, letters N, K, P) [37, 38] and visuospatial tests (The Rey–Osterrieth complex figure test (ROCFT) – copy condition) [39].

Four memory tests were used:

1) *Memory test with controlled encoding and free and cued recall* – A modified version of the FCSRT called Enhanced Cued Recall (ECR test in Czech validated version) [40, 41]. The test uses category cues at both acquisition and retrieval to ensure semantic encoding and to enhance recall. The subject is asked to search through a card containing line drawings of four objects and to identify the one that belongs to a category named by the examiner, such as fruit. Each of the 16 items to be learned appears on one of four cards that are used. After each item is correctly identified on the first card, the card is removed and immediate recall of the four items is tested by cueing with the category prompt. Errors are corrected. The other 12 items are presented four at a time in the same manner. A learning phase and subsequent interfering task (Clock Drawing Test) were followed by one free recall and subsequent cued recall for items not freely recalled. Free recall (ECR-FR) and total recall (ECR-TR = free + cued recall) were evaluated.
2) *Verbal memory test with uncontrolled encoding and delayed recall – Auditory verbal learning test (AVLT)* [42, 43]. The examiner reads a list of 15 words from List A at the rate of one word per 1.5 s after instructing the participant to listen and remember them. The examiner writes down the words recalled, then rereads the test for trials II to V with immediate recall recorded after every trial. After the fifth trial, the words from List B are read and recalled. Following the List B trial, the examiner asks the patient to recall as many words from List A as possible (trial VI). A 30-min delayed recall trial is administered to measure retention. In our study, word span under overload conditions (trial I: AVLT 1), final acquisition (trial V: AVLT 5), total acquisition (Σ I-V: AVLT 1–5), and delayed recall after 30 min (trial VII- AVLT 30) were analyzed.
3) *Story learning memory test – Logical memory test (LM) [38].* The examiner reads a story and the subject is asked to recall it immediately and after a 20-min delay. The number of correctly recalled items was analyzed.
4) *Visuospatial memory test – Rey-Osterrieth Complex Figure Test (ROCFT) [44].* Participants were asked to copy and, after a 3-min delay, recall a line drawing of a figure. The subject had not been previously instructed to memorize the figure. The copy and the reproduction of the drawing were scored by an experienced rater (neuropsychologist) using the 36-points Meyers system. Both the copy and reproduction were used in the final analysis.

To allow the direct comparison of the memory tests, several verbal tests were used in the neuropsychological battery, potentially leading to the memory interference effect. To minimize this effect, we ensured that the administration of memory tests did not overlap in the battery (i.e., the learning phase of the new test started after the delayed recall of the previous one).

Results of the neuropsychological battery including memory tests are summarized in Table 1.

Statistical analysis

Initially, demographic characteristics and baseline cognitive scores were compared for individuals who did versus did not convert using *t*-tests for differences in means and chi-square tests for differences in frequencies. Subsequently, cognitive test scores were converted to z-scores for ease of comparison across individual cognitive tests. To allow further direct comparison, the z-scores for TMT A and B were reversed. In the main analyses, conversion to dementia as a function of cognitive performance was examined using Cox proportional hazard models in R3.6.1 [45], which yields hazard ratios (HRs). HRs greater than 1.00 indicate increased risk, those lower than 1.00 indicate decreased risk. 95% confidence intervals are also reported. When the entire confidence interval for one cognitive test falls outside the

confidence interval for another test, we can infer that the difference in the magnitude of the effect is statistically significant for the two tests.

First, age, sex, and education were included as covariates in the models and the corresponding HRs and confidence intervals were extracted. Next, global cognition as measured by the MMSE was added as a covariate to all models. We opted to control for MMSE to better understand whether certain neuropsychological tests are less predictive of progression from aMCI to dementia than a simple measure of global functioning MMSE, and conversely to highlight tests that are robust even after controlling for global cognition. In a third step, we included the GDS-15 and *APOE* ε4 variant as covariates. If a HR from a non-memory test was statistically significant in the first step (controlling for age, sex, education), it was further analyzed after controlling for delayed LM, which was identified as the best predictor of conversion in our analyses with respect to effect magnitude. Multiple logistic regression was conducted to extract the Area Under the Curve (AUC) with DeLong 95% confidence intervals from the first set of models (controlling for age, sex, and education). Values of 0.80 suggest excellent discriminatory ability for a given neuropsychological test after adjustment for age, sex, and education. In order to visualize the time to conversion, a Kaplan-Meier curve with 95% confidence intervals was provided with the cumulative number of incident dementia cases per year.

RESULTS

A total of 270 patients with aMCI who reached out to the memory clinic were recruited at baseline. During the follow-up, 144 (53%) individuals converted to dementia. The majority of converters developed AD dementia or mixed (AD+vascular) dementia (72% and 17%, respectively). The mean and median follow-up times were 2.80 (SD = 2.02 years, range 0.23–13.85) and 2.19 respectively for the full sample. The mean time to conversion was 2.44 years (SD = 1.65 years, range 0.23–10.41) and the median time was 2.12 years. The mean follow-up time of non-converters was 3.20 years (SD = 2.32, range 0.99–13.85) and the median follow-up time was 2.45 years. The Kaplan-Meier curve analyzing time to conversion is provided in Fig. 1.

Basic demographic characteristics of the group and comparison of converters versus non-converters are in the Table 1. The HRs linked to different neuropsychological scores are listed in Table 2.

Cognitive tests predicting conversion to dementia

At baseline, the converters were significantly older and less educated, and they differed in the majority of neuropsychological tests, but not in the number of depressive symptoms on the GDS-15. In Cox proportional hazard models adjusted for age, sex, and education, the risk of conversion was best predicted by the delayed recall in three memory tests (Delayed LM, AVLT 30, and ROCFT – reproduction), followed by MMSE, immediate recall scores and tests of other cognitive domains. Among the memory tests, the HR for delayed (HR = 2.43) and AVLT delayed recall after 30 min (HR = 2.25) reflected the relatively greatest effect, followed closely by the ROCFT reproduction (HR = 2.10), all conferring more than two times greater risk of conversion per one standard deviation decrease in the scores. The immediate recalls in other memory tests (AVLT 1-5, LM) and ECR-free recall score had HRs between 1.68–1.78 which was similar to semantic verbal fluency animals and vegetables (HR = 1.68 and 1.78 respectively) and TMT B (HR = 1.70). All digit span tests and the TMT-A did not reach statistical significance. The results are summarized in Table 2.

Six neuropsychological tests reported excellent discriminatory ability as determined by the AUC (≥0.80). These tests were: delayed LM (AUC = 0.839), AVLT 30 (AUC = 0.826), immediate LM (AUC = 0.819), semantic verbal fluency – animals (AUC = 0.811), AVLT 1-5 (AUC = 0.803), and ROCFT – reproduction (AUC = 0.801). In addition, the MMSE (AUC = 0.798), ECR-free recall (AUC = 0.794), and the AVLT 5 (AUC = 0.793) also reported near-excellent discriminatory ability.

Controlling for global cognition and memory performance

After controlling for MMSE, ROCFT–Copy, Boston Naming Test, and phonemic verbal fluency were no longer statistically significant predictors of conversion to dementia (Table 2). Controlling for MMSE modestly reduced the HRs of all memory tests, though Delayed LM, AVLT 30, and ROCFT–reproduction remained most strongly associated with conversion. Among the non-memory tests that were statistically significant after controlling for MMSE (TMT B, Digit Symbol Test, and semantic flu-

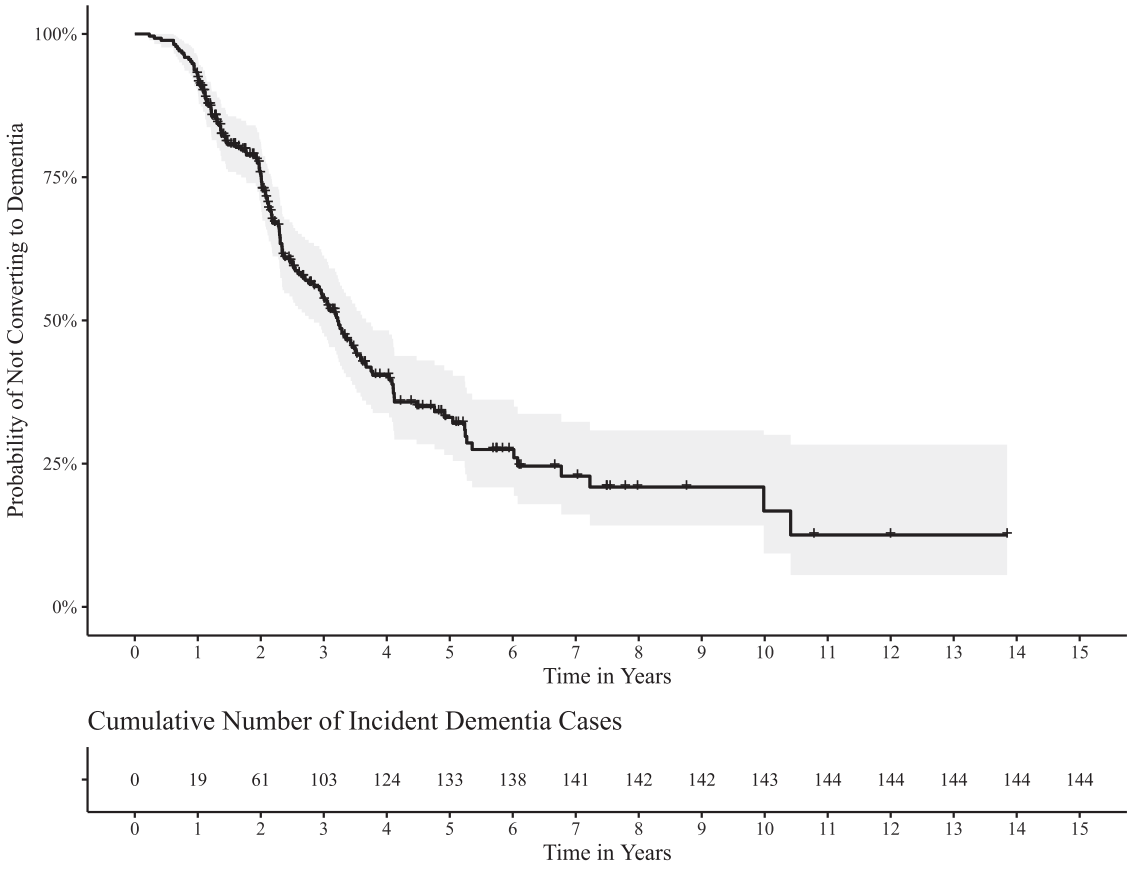

Fig. 1.

ency animals and vegetables), only semantic fluency vegetables (HR = 1.49) and the Digit Symbol Test (HR = 1.38) remained significant predictors of conversion when controlling for delayed LM (Table 3).

DISCUSSION

Analyzing a neuropsychological battery which comprised one non-verbal and three widely used verbal memory tests, we found three of them to be better predictors of conversion to dementia than the tests representing other cognitive domains. Comparing the memory tests, we found the delayed recall in LM, AVLT, and ROCFT to be the best predictors of conversion to dementia in aMCI. Thus, our results do not support the superiority of the ECR a memory test with 16 items using controlled encoding and cued recall, to the memory tests without this paradigm (AVLT, LM) or a nonverbal memory test ROCFT. The predictive power of the immediate recall memory scores was similar to semantic verbal fluency. In addition, semantic verbal fluency vegetables was predictive of conversion to dementia beyond delayed memory performance, global cognition, and relevant demographics.

The predictive power of neuropsychological tests in non-demented older adults has been a topic of several longitudinal studies. Previous research has consistently shown the superiority of memory tests over the tests of other cognitive domains in predicting future dementia in non-demented older adults [15, 16, 46]. These results are in general agreement with our study demonstrating better predictive power of three of four memory tests (AVLT, LM, and ROCFT reproduction) over the tests of executive functions (TMT B), attention and working memory (digit span forward and backward), language (Boston Naming Test), and visuoconstruction (ROCFT copy condition), as well as general cognition measured by MMSE.

The superiority of delayed recall over other memory scores is not surprising as delayed memory represents the most sensitive measure of the mem-

Table 2
Cox proportional hazard models with neuropsychological tests predicting conversion from amnestic mild cognitive impairment to all-cause dementia

	Adjusted Hazard Ratio (Age, Sex, Education)	*p*	AUC [DeLong 95% CI]	Adjusted Hazard Ratio + MMSE (Age, Sex, Education, MMSE)	*p*	Adjusted Hazard Ratio + GDS-15 + *APOE* ε4 (Age, Sex, Education, GDS-15, *APOE* ε4)	*p*
Neuropsychological Tests							
MMSE*	1.82 [1.54, 2.14]	<0.001	0.798 [0.745, 0.852]	–	–	1.71 [1.42, 2.06]	<0.001
AVLT 1	1.58 [1.30, 1.92]	<0.001	0.764 [0.704, 0.823]	1.42 [1.15, 1.75]	0.001	1.31 [1.04, 1.66]	0.02
AVLT 5	1.60 [1.32, 1.93]	<0.001	0.793 [0.736, 0.849]	1.36 [1.11, 1.66]	0.003	1.45 [1.15, 1.83]	0.002
AVLT 1-5	1.73 [1.43, 2.09]	<0.001	0.803 [0.749, 0.858]^	1.46 [1.19, 1.80]	<0.001	1.53 [1.22, 1.93]	<0.001
AVLT 30	2.25 [1.75, 2.90]	<0.001	0.826 [0.772, 0.879]^	1.93 [1.48, 2.52]	<0.001	1.81 [1.34, 2.45]	<0.001
ECR-FR	1.78 [1.43, 2.21]	<0.001	0.794 [0.731, 0.856]	1.46 [1.16, 1.84]	0.001	1.62 [1.26, 2.09]	<0.001
ECR-TR	1.44 [1.23, 1.69]	<0.001	0.761 [0.695, 0.828]	1.26 [1.06, 1.50]	0.009	1.31 [1.08, 1.58]	0.005
ROCF-R	2.10 [1.62, 2.72]	<0.001	0.801 [0.745, 0.858]^	1.76 [1.34, 2.32]	<0.001	1.74 [1.30, 2.33]	<0.001
ROCF-C	1.36 [1.14, 1.62]	<0.001	0.727 [0.664, 0.791]	1.13 [0.94, 1.37]	0.19	1.33 [1.09, 1.62]	0.005
Log-I*	1.68 [1.35, 2.08]	<0.001	0.819 [0.762, 0.876]^	1.35 [1.06, 1.72]	0.01	1.50 [1.17, 1.91]	0.001
Log-D*	2.43 [1.83, 3.22]	<0.001	0.839 [0.786, 0.892]^	2.05 [1.51, 2.78]	<0.001	2.52 [1.76, 3.60]	<0.001
TMT A*	1.19 [0.98, 1.44]	0.08	0.722 [0.649, 0.795]	1.08 [0.87, 1.33]	0.48	1.17 [0.94, 1.45]	0.16
TMT B*	1.70 [1.39, 2.07]	<0.001	0.744 [0.679, 0.808]	1.32 [1.04, 1.67]	0.02	1.60 [1.27, 2.01]	<0.001
F-DigitSpan-NM*	1.13 [0.95, 1.35]	0.17	0.716 [0.654, 0.778]	1.08 [0.90, 1.31]	0.40	1.15 [0.93, 1.42]	0.19
F-Digit Span-SC*	1.12 [0.93, 1.35]	0.22	0.709 [0.647, 0.772]	1.04 [0.86, 1.26]	0.69	1.13 [0.90, 1.41]	0.29
B-DigitSpan-NM*	1.15 [0.94, 1.40]	0.17	0.713 [0.651, 0.775]	0.94 [0.77, 1.15]	0.55	1.12 [0.90, 1.39]	0.32
B-DigitSpan-SC*	1.16 [0.95, 1.42]	0.15	0.713 [0.651, 0.775]	0.90 [0.73, 1.12]	0.35	1.14 [0.91, 1.43]	0.25
Digit Symbol*	1.51 [1.24, 1.84]	<0.001	0.754 [0.692, 0.817]	1.30 [1.05, 1.62]	0.02	1.97 [1.44, 2.70]	<0.001
BNT*	1.33 [1.10, 1.63]	0.004	0.728 [0.661, 0.796]	1.23 [0.99, 1.51]	0.06	1.20 [0.96, 1.49]	0.11
P-VF	1.35 [1.09, 1.67]	0.007	0.730 [0.662, 0.798]	1.21 [0.97, 1.51]	0.08	1.45 [1.14, 1.84]	0.002
S-VF-A*	1.68 [1.29, 2.20]	<0.001	0.811 [0.745, 0.877]^	1.40 [1.06, 1.85]	0.02	1.87 [1.39, 2.53]	<0.001
S-VF-V*	1.78 [1.34, 2.38]	<0.001	0.780 [0.709, 0.851]	1.49 [1.11, 2.00]	0.008	1.75 [1.29, 2.39]	<0.001

*indicates that this test is part of the Uniform Data Set (UDS). ^indicates that this test has an Area Under the Curve (AUC) above 0.80, suggesting excellent discrimination ability. AUC was extracted from multiple logistic regression with each cognitive test as the main predictor variable and age, sex, and education as covariates. For Hazard ratios 95% confidence intervals are reported in the brackets. MMSE, total score; AVLT 1, trial 1 recall; AVLT 5, trial 5 recall; AVLT 1-5, sum of trials 1 to 5; AVLT 30, recall after 30 min; ECR-FR, free recall; ECR-TR, total recall after cueing; ROCF-R, visual reproduction after 3 min; ROCF-C, copy score [44]; LOG-I, Logical Memory Immediate Recall from the Uniform Data Set; LOG-D, Logical Memory Delayed Recall from the Uniform Data Set; TMT A, given in seconds; TMT B, given in seconds; F-DigitSpan-NM, forward Digit Span – numbers; F-Digit Span-SC, forward Digit Span – score; B-DigitSpan-NM, backward Digit Span – numbers; B-DigitSpan-SC, backward Digit Span – score; Digit Symbol, Digit Symbol Score from the WAIS-III; BNT, Boston Naming Test; P-VF, Phonemic Verbal Fluency; S-VF-A, Semantic Verbal Fluency – Animals; S-VF-V, Semantic Verbal Fluency – Vegetables.

Table 3
Effect of non-memory tests on conversion after controlling for memory performance

	Adjusted Hazard Ratio + MMSE + Memory Performance (Age, Sex, Education, MMSE, Log-D)	*p*
Neuropsychological Tests		
TMT B*	1.23 [0.90, 1.68]	0.19
Digit Symbol*	1.38 [1.05, 1.81]	0.02
S-VF-A*	1.36 [1.00, 1.86]	0.05
S-VF-V*	1.49 [1.10, 2.02]	0.01

For Hazard ratios 95% confidence intervals are reported in the brackets. *indicates that this test is part of the Uniform Data Set (UDS). TMT B, given in seconds; Digit Symbol, Digit Symbol Score from the WAIS-III; S-VF-A, Semantic Verbal Fluency – Animals, S-VF-V, Semantic Verbal Fluency – Vegetables.

ory deficit and its decline precedes the decline in immediate scores by several years [47, 48].

In our study we found that future dementia was better predicted by free rather than total recall in ECR, although the latter score has been considered specific for hippocampal dysfunction. This paradox can be explained by the ceiling effect. In a recently published longitudinal study, the total recall in the FCSRT began to decline no sooner than 2 years before dementia onset and its impairment remained rather mild until the onset of dementia, contrasting with free recall which began to decline 7 years before dementia onset [49]

To the best of our knowledge, only one longitudinal study used several memory tests simultaneously with different encoding and recall paradigms, and compared a memory test with controlled encoding and cued recall to a memory test without this paradigm [20]. The authors tested 40 MCI patients with a neuropsychological battery comprising two memory tests: MIS (Memory Impairment Screen) plus – a memory tests with 6 words using controlled encoding and cued recall, and a 10-item version of AVLT. They found cued recall in the MIS plus to be a better predictor of conversion at 18 months than delayed free recall in a 10-item version of AVLT. The authors indicated that a score of 0 or 1 out of 6 on the MIS plus may be a good indicator of future (within 18 months) conversion to AD dementia among MCI patients. The low initial performance among future converters suggested a rather substantial memory impairment at baseline; however, even the non-converters in this study performed relatively poorly, and it is possible that the advantage of the MIS over the short version of AVLT was caused by the presence of floor effect in the AVLT test in both clinical groups compared to the considerably less difficult MIS test. As the authors stated, the other weakness of their study was a very short period of follow-up raising questions about the conversion in following years in the rest of the group. Thus, the application of these results to non-demented older adults in general seems problematic.

One more longitudinal study compared a memory test using free and cued recall with other verbal memory test [21]. However, according to its description published elsewhere [50], it seems that the version of Free and Cued Recall Test (FCRT) used in that study did not include controlled encoding procedures, and the paradigm of this test was much closer to the California verbal learning test than to the original FCSRT.

In our study, we found delayed recall in LM and AVLT to be the best predictors of conversion to dementia in patients with aMCI. For several decades, delayed free recall has been considered to be the episodic memory measure with the greatest sensitivity for early detection of AD [51]. Still, its specificity was judged to be problematic because other cognitive deficits beyond pure memory impairment (attentional difficulties and strategy problems) may interfere with poor performance. This was one of the reasons why the tests with controlled encoding and cued recall were developed. Although the effectiveness of memory tests based on CECR paradigm in predicting dementia was demonstrated [15, 16], there is no longitudinal evidence showing their superiority over tests without this paradigm.

According to our results, it is possible that memory tests with the CECR paradigm predict dementia with less accuracy compared to standard memory tests challenging also attention and strategy to encode the to-be-learned material. The reason may be the ceiling effect, caused by easier learning and recall in less impaired patients in the predementia stage—the CECR paradigm probably increases specificity for

hippocampal impairment, but on the other hand, it can diminish sensitivity [27].

Previously, several attempts were made to overcome this issue, including the 48-item version of FCSRT which was developed but has not been used probably because of its extensive time requirement and difficulty for even mildly impaired patients. Another solution which combines the CECR paradigm with a novel memory binding paradigm has been proposed in early AD diagnostics, and newly developed tests were introduced [52], such as the Face-Name Associative Memory Exam or Memory Binding Test (MBT). There is growing evidence showing performance in these tests to be associated with biomarkers indicative of AD very early during the disease trajectory. In one longitudinal study, the MBT was shown to outperform conventional memory and non-memory tests, including the FCSRT, in prediction of incident dementia [53]; however, further studies are needed to support its clinical usefulness.

Among non-memory tests, the deficit in semantic verbal fluency conferred the same risk of conversion to dementia as the immediate scores in memory tests and, contrary to phonemic verbal fluency, predicted the conversion even when the analysis was controlled for MMSE score and delayed LM. This is analogous to the previous results showing semantic fluency to predict incident dementia even when controlling for memory test scores [53] and brings other arguments that deficits in semantic fluency may constitute a dysnomic aMCI phenotype that progresses to dementia more quickly than memory impairment alone [26]. It has been previously shown that semantic fluency is greatly reduced in early stages of AD [24, 25, 54–56], qualitatively impaired already in patients with subjective cognitive decline [57], and the predictive power to predict future conversion to dementia in MCI patients was only slightly inferior to memory tests [58]. At the functional level, the impairment of semantic fluency in AD is probably caused mainly by the degradation of semantic knowledge and impairment of associations between concepts in semantic knowledge manifesting as reduced cluster size [59]. We believe that analysis of advanced verbal fluency measures such as clustering and switching strategies could reveal an even greater potential of semantic fluency test in predicting dementia. Moreover, semantic fluency impairment in AD is more pronounced compared to phonemic fluency [60]. The reason for this differential impairment could be the dependence of semantic verbal fluency on temporal lobes demonstrated previously on fMRIs [61, 62]. As the majority of convertors in our study progressed to AD dementia, which affects temporal lobes early in the disease course, our results are in line with previous evidence.

The major strength of our study is the use of an extensive neuropsychological battery, including the UDS and complemented by several widely used memory tests. To the best of our knowledge, we are the first study comparing head-to-head four widely used memory tests in a longitudinal design in order to compare their power to predict future dementia. In addition, using longitudinal data from 270 aMCI patients, this is the largest longitudinal study analyzing the predictive power of several memory tests in this clinical population (compared to 30 patients in [20], 105 patients in [19], 38 patients in [46], and 251 patients in [15]).

Our study also has several limitations. We used two memory tests with almost the same number of words (15 in AVLT $\times$ 16 in ECR), the tests differed in the encoding paradigm (controlled encoding in ECR to strengthen acquisition versus uncontrolled encoding but five consecutive trials in AVLT to strengthen acquisition) and recall conditions (free and cued recall in ECR $\times$ free recall in AVLT), and differed in other characteristics: number of learning trials (5 trials in AVLT $\times$ 1 trial in ECR) and time between learning and recall (10 min in ECR $\times$ 30 min in AVLT), making the interpretation of the results complex and the generalization difficult.

We used Peterson's criteria as they are most widely used in clinical praxis and our paper was intended mainly for clinical use. We are aware that compared to other criteria [63], this approach can cause overdiagnosing of MCI, leading to more patients classified as MCI at baseline remaining stable or reverting back to normal during the follow-ups. In terms of our study, this could underestimate the predictive power of the examined neuropsychological tests. As the date of death was not recorded in the Czech Brain Aging Study dataset, we were unable to conduct Fine-Gray competing risks models to control for the competing risk of death.

Another source of bias may be our long inclusion timeline (i.e., including participants from 2005–2020). However, this methodology is a necessary byproduct of recruitment in prospective cohort studies. It should be noted that the conversion rate in our sample was higher than expected in the typical community-dwelling population, which is common in memory clinic samples. Some HR confidence intervals overlapped, suggesting that tests may not

truly be statistically different from each other when predicting conversion to dementia. This may be caused by the real absence of difference but can also indicate that although we assume to be the largest study comparing memory tests as predictors of the conversion to dementia in MCI, still our sample size and follow-up time did not allow to draw clear differences among tests. Future work with larger sample sizes and longer follow-up periods may reduce this problem and therefore provide more definitive conclusions on test superiority or ranking. However, we also acknowledge that very large sample sizes may reveal clinically irrelevant results. To this end, we hope that future work will focus on effect sizes and the width of confidence intervals rather than conventional *p*-values.

In conclusion, we found that delayed scores in three memory tests (AVLT, LM, and ROCFT) had the highest power to predict conversion to dementia in aMCI patients. Thus, superiority of the ECR, a test employing the CECR paradigm previously proposed to be specific for a true memory impairment, to AVLT and LM, tests previously shown to be more susceptible to non-memory interference effects, was not supported by the results of this study. This could be at least partially due to a ceiling effect of the ECR in the mildly impaired cohort of aMCI patients. Further studies comparing the potential of uncontrolled learning and free recall and CECR paradigm to better predict conversion to dementia are needed to unravel the issue. Novel challenging tests combining the memory binding process with the CECR paradigm might be a promising direction. Memory tests were not the only predictors of incident dementia. The predictive power of semantic verbal fluency was comparable to the power of immediate recall memory scores. Semantic verbal fluency continues to relate significantly to conversion after adjustment for delayed memory, which supports its clinical usefulness for the cognitive deficit progression monitoring.

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