特集　認知症 update

認知症の薬物療法の実際とその効果

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認知症の薬物療法の実際とその効果

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キーワード◎アルツハイマー病，治療薬，コリンエステラーゼ阻害薬，NMDA 受容体拮抗薬

■はじめに

認知症診療は，今やすべての医家にとって避けては通れない状況になっている．現在アルツハイマー病治療薬は4種類存在し，重症度やBPSD（behavioral and psychological symptoms of dementia），患者背景に合わせて，薬剤を適切に選択する時代となった．ドネペジル塩酸塩（以下ドネペジル．アリセプト®）やガランタミン臭化水素酸塩（以下ガランタミン．レミニール®），リバスチグミン（リバスタッチ®，イクセロン®），メマンチン塩酸塩（以下メマンチン．メマリー®）は認知機能障害の進行遅延のほか，ADLにかかわる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延による医療費・介護費用の削減などの効果が報告されている．さらに，認知症に対する良質なケアや脳リハビリテーションが加われば治療効果も向上し，その結果として，認知症の人や家族へのQOLの向上において重要な意義がある．そのためにも認知症診療においては家族の指導，支援が重要となる．

現在の治療薬では病気は完治しないが，病状を修飾することができ，病気の進行を遅延させることができる．すなわちこれらの薬剤の利点と欠点を知り，病期，症状に合わせて選択することが重要である．

■1 アルツハイマー病治療における選択肢

アルツハイマー病の4種類の薬が使用可能となり，診断の重要性と共に，ステージ診断やBPSDの評価が重要であり，薬剤を適切に選択する必要性がある（表1）．2010年には『認知症疾患治療ガイドライン2010』も発表されており[1]，これに従って診断，治療を行うことが望ましい．すなわち治療に当たり，知識と経験が必要とされる．

薬剤の種類としては，コリンエステラーゼ阻害薬が3種類とNMDA受容体拮抗薬が1種類ある．日本においてはまず，ドネペジルを軽度，中等度，高度で投与することが承認された．これをいわゆる「フルステージ診療」と呼ぶが，実際は予防から終末期医療までを含めてフルステージ診療と呼ぶほうが適切であろう．これはかかりつけ医が1人の患者を長く終末期まで連続してフォローする意味で，シームレスケアとも呼ばれている（推奨グレードA）．

臨床家にとってドネペジルは長く使用経験があり，安心して用いることができる薬剤である．しかしながら実際には，認知症は早期発見し，早期治療を開始することでより効果が高まることが知られており，さらに薬剤療法にとどまらず，なじみの環境を整えることや，良いケアの提供，さらには効果的な回想療法などの脳

The effects of drugs for Alzheimer's disease
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表1　アルツハイマー病の治療薬

一般名 (製品名)	ドネペジル (アリセプト®)	ガランタミン (レミニール®)	リバスチグミン (イクセロン®, リバスタッチ®)	メマンチン (メマリー®)
作用機序	アセチルコリン エステラーゼ阻害	アセチルコリン エステラーゼ阻害 および ニコチン性アセチルコリン 受容体へのAPL作用	アセチルコリン エステラーゼ および ブチリルコリン エステラーゼ阻害	NMDA受容体 チャネル阻害
剤型	錠，細粒，口腔内 崩壊錠，内服ゼリー	錠，口腔内崩壊錠， 内用液	パッチ剤	錠
投与回数	1日1回	1日2回	1日1回	1日1回

(各薬剤の添付文書より作成)

リハビリテーションを併用することで効果が高まることは言うまでもない．

ドネペジルは国内においてすでに30種類を超える後発品が出てきているが，品質の悪い製剤もあるため慎重に選択すべきである．たとえ後発品であっても，院外薬局サイドが決めるのではなく，医師が自ら後発品の種類を選定すべきである．

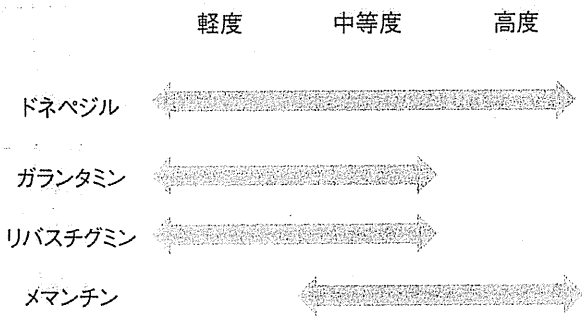


図1　認知症治療薬と適応時期

II 治療戦略について

アルツハイマー病治療薬にはそれぞれ適応の時期がある（図1）．承認された重症度に応じて薬剤を選択する必要があり，副作用や作用を適切に評価して，無効であれば他の薬剤に変更したり，併用を検討する．また，薬剤は認知症になってから始めるか，認知症の早期に治療を開始するのか，さらにMCIレベルから開始するのかについてはまだ十分なエビデンスはない．しかしながら薬剤の基礎的データからみれば，なるべく早期に治療を開始することが望ましいといえる．

III 治療薬の実際

アルツハイマー病になると，脳内の神経伝達物質のアセチルコリンが減少し，記憶障害などの認知機能障害が現れる．コリンエステラーゼ阻害薬は，脳内のアセチルコリンを分解するコリンエステラーゼを選択的に阻害することで脳内のアセチルコリンを増加させる効果作用がある．その点でドネペジル，ガランタミン，リバスチグミンはガイドラインでは推奨グレードAとされている．

1．ガランタミン

ガランタミンは軽度および中等度のアルツハイマー病における認知症症状の進行抑制に適応が認められた新しい薬剤である．1日8mgの少量から開始し，4週間の経過観察後に順次16mg，24mgへと増量する．朝夕2回に分けて服用する．

本剤はコリンエステラーゼ阻害作用だけでなく，APL(allosteric potentiating ligand)作用や神経細胞保護など他の薬剤にはない神経代謝改善作用があるため，中長期に使用した場合に他の薬剤より高い効果が得られる[2,3]．Dual action

と呼ばれ，APL作用を加えることでガランタミンの長期使用時の有用性の高さの根拠となる仮説である．つまりガランタミンは，他のコリンエステラーゼ阻害薬よりも長期に効果を示すことが報告されている．さらにアミロイドの蓄積に対する毒性を緩和する作用も報告されている．

主な有害事象は嘔気等の消化器症状である．ガランタミンの投与に当たっては，低用量から導入し，患者の状態を観察しながらゆっくりと増量することで忍容性を高め，治療を継続することが可能である．

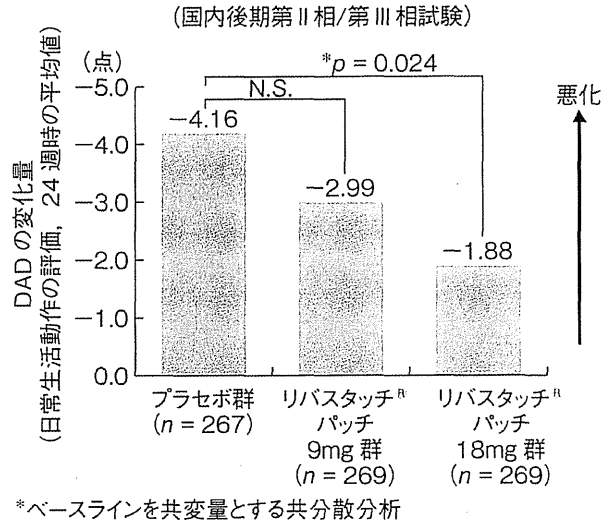
2. リバスチグミン

リバスチグミンはコリンエステラーゼ阻害薬として，長期に投与した場合の有効性の報告もあり，またDAD（disability assessment for dementia）尺度によるIADLスコアの改善効果もみられる（図2）ため，認知症の早期または軽症に使用するとよい可能性がある．

またパッチ剤の有用性として，1日1回貼付の簡便な投与方法で効果を示す．さらに食事の有無および食事時間に配慮する必要がなく，他の併用薬剤の服薬時間によって投与タイミングを制約する必要がない．介護者等が視覚的に容易に貼付状況（貼付の有無，投与量等）を確認できるため，薬剤アドヒアランスの向上が期待できる．

3. メマンチン

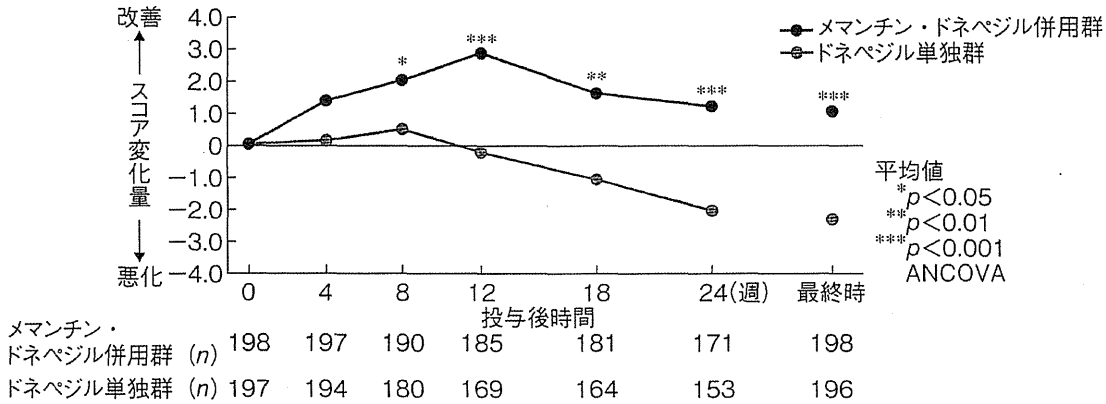
メマンチンはコリンエステラーゼ阻害薬と全く違った作用機序で認知機能障害の進行を抑制することが確かめられている．アルツハイマー病にはグルタミン酸神経系の機能異常が関与しており，グルタミン酸受容体のサブタイプであるNMDA受容体チャネルの過剰な活性化が原因の1つと考えられている．アルツハイマー病



*ベースラインを共変量とする共分散分析

図2　IADLの改善

（小野薬品工業：承認時申請資料より引用）



対象：80歳以上の中等度から高度のアルツハイマー病患者403例
- NINCDS-ADRDAのアルツハイマー病の診断基準を満たす
- MMSE（mini-mental state examination；簡易知能検査スケール）スコア5点以上14点以下
- ドネペジルの治療を6か月以上受けている

方法：ドネペジル（5～10mg）の治療を継続し，二重盲検下でメマンチンまたはプラセボを1日2回24週間，朝食後・昼食後に経口投与．メマンチンは5mg/日より開始し，1週間に5mgずつ増量していき，20mg/日を維持用量とした．

図3　メマンチン・ドネペジル併用によるSIB（severe impairment battery）スコア変化量の推移

（Tariot PN, *et al*：*JAMA* 2004：291：317-324より引用）

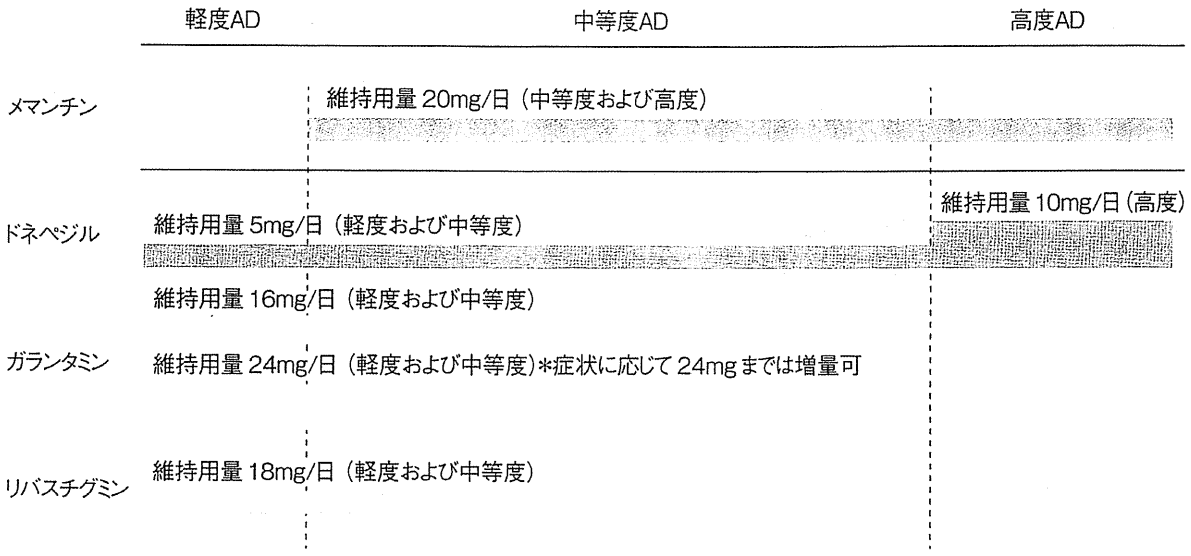


図4　日本におけるアルツハイマー病（AD）治療薬の治療アルゴリズム

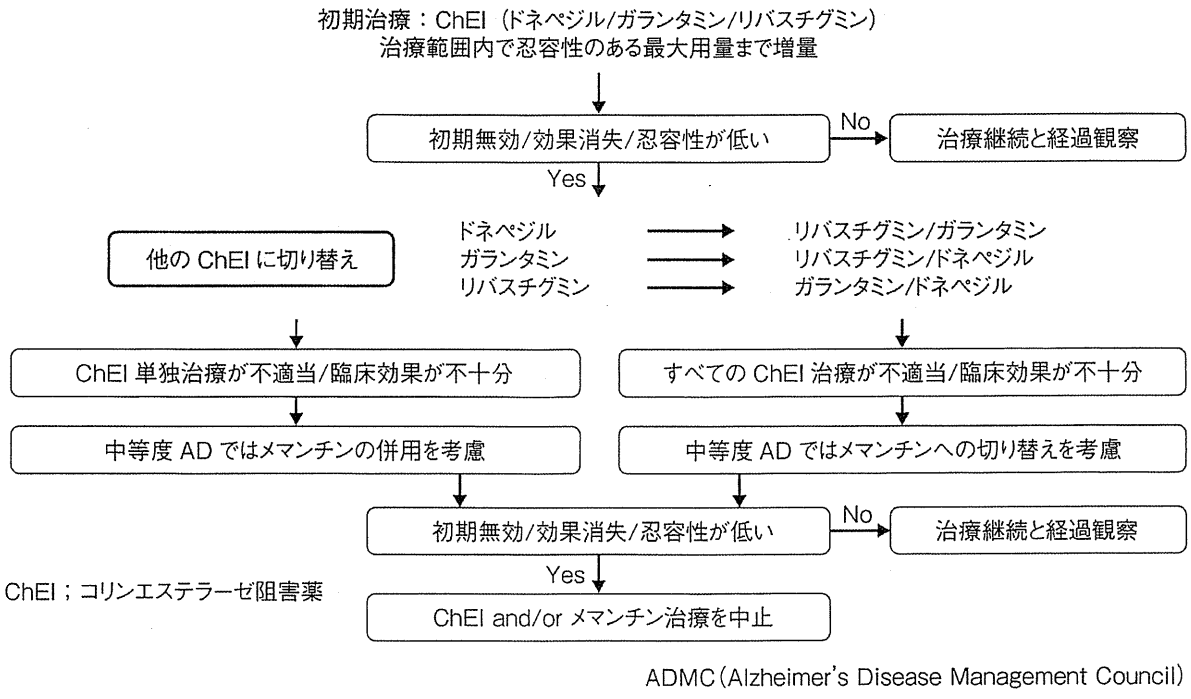


図5　軽度～中等度アルツハイマー病（AD）に対する治療アルゴリズム
（Farlow MR, *et al*：*Am J Med* 2007；120：388-397 より引用，一部改変）

の病態時は，シナプス間隙のグルタミン酸濃度の持続的な上昇によってNMDA受容が活性化され，細胞内へのCaイオンの流入，シナプティックノイズの発生などによって認知機能障害が引き起こされると考えられている．メマンチンは，NMDA受容体拮抗作用により，神経細胞内への過剰なCaイオンの流入抑制による神経細胞保護作用と，シナプティックノイズの抑制による記憶・学習機能障害抑制作用を有するとされている．

さらにメマンチンは，コリンエステラーゼ阻害薬と併用すると，より認知機能障害の進行を遅延させることが知られている（図3）．効果は単独の場合より遅延し，3か月後に効果のピー

クがあり，その後比較的長期に持続する可能性がある．またメマンチンを長期投与した場合には，対照群に比べ脳萎縮の程度が抑制されたとの報告もある．

4. 薬剤の投与変更のポイント

ドネペジルは軽度，中等度のアルツハイマー病であれば5mgの投与を行うが，高度であれば10mgに増量する．メマンチンを併用する場合は，中等度になったら併用し，その後高度になったらドネペジルを10mgに増量する．また，ドネペジル投与中に消化器症状や易興奮などの副作用があれば，10mgを5mgへ，5mgであれば3mgへ減量する．

ガランタミンは朝夕2回の服用が特徴であるが，16mgで経過をみて，重症化するようであれば24mgへの増量を考慮する．リバスチグミンは接触性皮膚炎などの副作用がみられることがあるが，18mgまで増量し，メマンチンとの併用を検討する．一般的な治療のアルゴリズムを図4に示した．

さらに薬剤の切り替えを検討する場合には以下のアルゴリズムを参考にするとよい（図5）．すなわち，初期にはまずコリンエステラーゼ阻害薬から1剤を選択し，2〜3か月ごとに効果を観察し，6か月程度みても効果が得られない場合には他の薬剤に変更する．その際には薬剤の特徴と共に，メマンチンの併用も選択肢として考慮する．興奮や攻撃性などのBPSDがある場合にはメマンチンを初期から投与することも考慮する．

薬剤の中止時期については，嚥下障害などで食事が摂れなくなったとき，介護施設に入所したとき，病状が悪化したときなど，また重度化して薬剤の効果が期待できないと判断された場合である．

Ⅳ BPSDの治療とケア

BPSDに関しては保険適用がとれていない薬剤が多い．以前は抗精神病薬が用いられてきたが，最近ではリスペリドンやオランザピン，アリピプラゾールなどの非定型抗精神病薬が用いられるようになってきた．しかし米国ではこの種類の薬剤は脳卒中の発生率が高いとして，アルツハイマー病には禁忌となっている．日本では保険適用外であるが，有用性があるため，慎重に適応を判断したうえで使用されている．これらの薬剤では副作用の頻度が比較的高いため，副作用を軽減するためにも少量から投与することがポイントである．

また，漢方薬の抑肝散がよく用いられており，特にレビー小体型認知症のBPSDには有効性が高いとされている．副作用としては低カリウム血症に注意する．

メマンチンは興奮や攻撃性などのBPSDに有効であることが知られており，頻度は低いが傾眠傾向が報告されている．

BPSDをコントロールすることは，医師にとって，家族や本人の苦痛をとる意味においても重要である．

おわりに

アルツハイマー病を早期に発見し，早期に治療するに当たり，これら4剤のさらなる有用性に期待している．長期使用時の効果についても一定のエビデンスが存在しており，その有用性は確かであろう[4]．しかし日本での効果の検証は，今後一定の時間を経て判断する必要がある．

新薬に対する認知症患者や家族の期待は大きいが，効果に対する過剰な期待は問題である．

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words
Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract
Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. ***Methods:*** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backword (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. ***Results:*** In all subjects, MTA-ERC atrophy showed significant relationships with age (r = 0.43), education (r = –0.25), WMS-R, LM I (r = –0.21), DSC (r = –0.32), and SCWT-IL (r = 0.32). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age (r = 0.34), DSC (r = –0.28), and SCWT-IL (r = 0.25). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min (r = –0.70) and RCF-30 min (r = –0.74). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age (β = 0.374) and SCWT-IL (β = 0.247) in all subjects. Age (β = 0.301), and RCF-30 min (β = –0.521) and age (β = 0.460) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. ***Conclusion:*** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between in vivo measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to interregional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnestic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men n = 48, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean ± SD)

Age, years	75.3 ± 6.8
Male, %	50
Education, years	10.6 ± 2.5
Body mass index	23.0 ± 3.1
Cognitive functions	
MMSE, points	26.5 ± 2.5
WMS-R, LM I, points	14.4 ± 7.1
WMS-R, LM II, points	10.0 ± 7.4
RCF-3 min, points	15.5 ± 6.3
RCF-30 min, points	14.9 ± 6.7
DSB, points	5.2 ± 1.6
DSC, points	46.1 ± 15.9
SCWT-IL, s	21.1 ± 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number ± SD	2.3 ± 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T_1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time 1,700 ms, echo time 4.0 ms, flip angle 15°, acquisition matrix 256 × 256, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T_1 MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) – (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

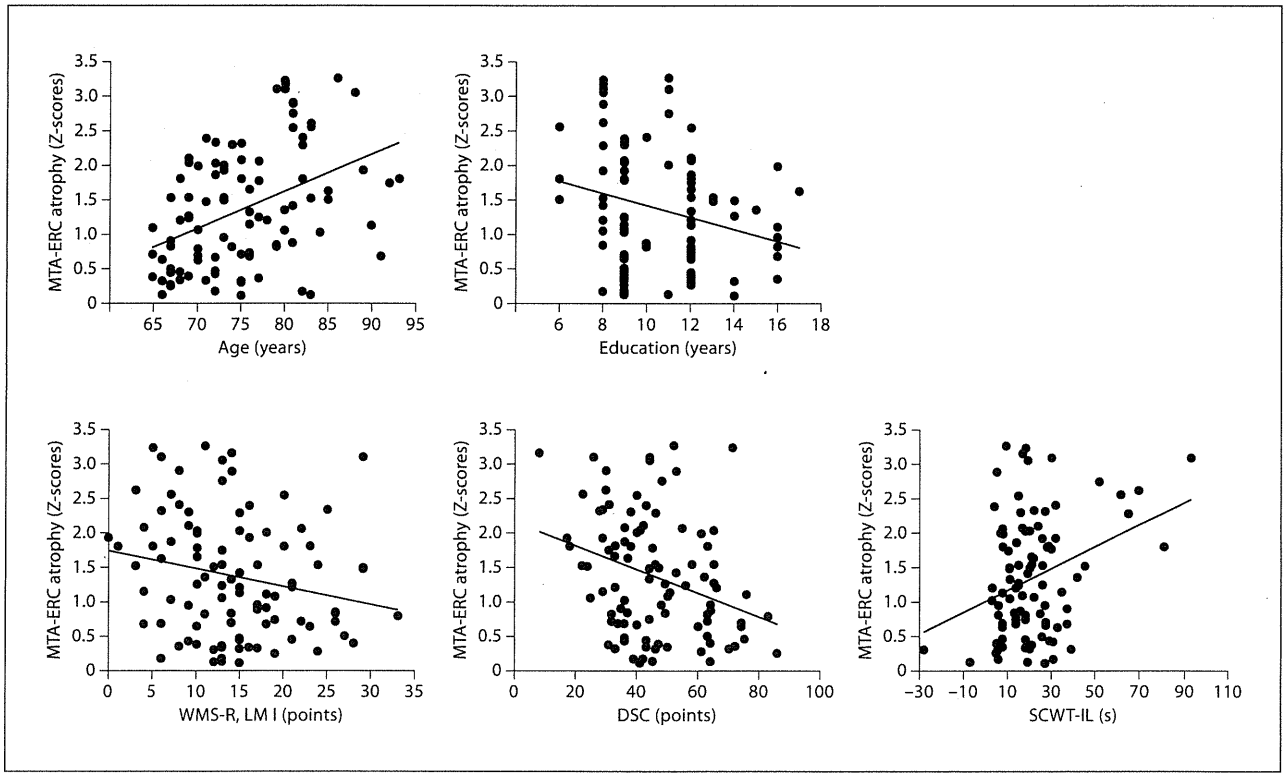

Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	**<0.001**	0.34	**0.003**	0.71	**<0.001**
Education	−0.25	**0.012**	0.01	0.921	−0.26	0.224
WMS-R, LM I	−0.21	**0.040**	−0.17	0.155	−0.06	0.774
WMS-R, LM II	−0.09	0.370	0.03	0.812	−0.22	0.308
RCF-3 min	−0.16	0.119	−0.10	0.396	−0.70	**<0.001**
RCF-30 min	−0.13	0.201	−0.11	0.386	−0.74	**<0.001**
DSB	−0.15	0.134	−0.12	0.298	−0.14	0.511
DSC	−0.32	**0.002**	−0.28	**0.016**	−0.05	0.825
SCWT-IL	0.32	**0.002**	0.25	**0.031**	0.18	0.404

For abbreviations, see table 1.

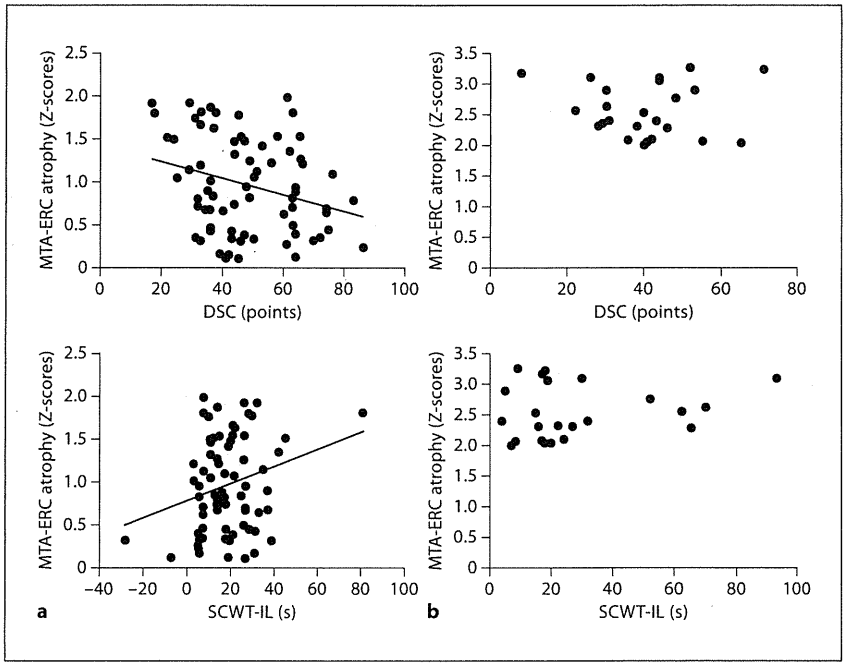

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	−0.521	−3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta = 0.374$, $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-

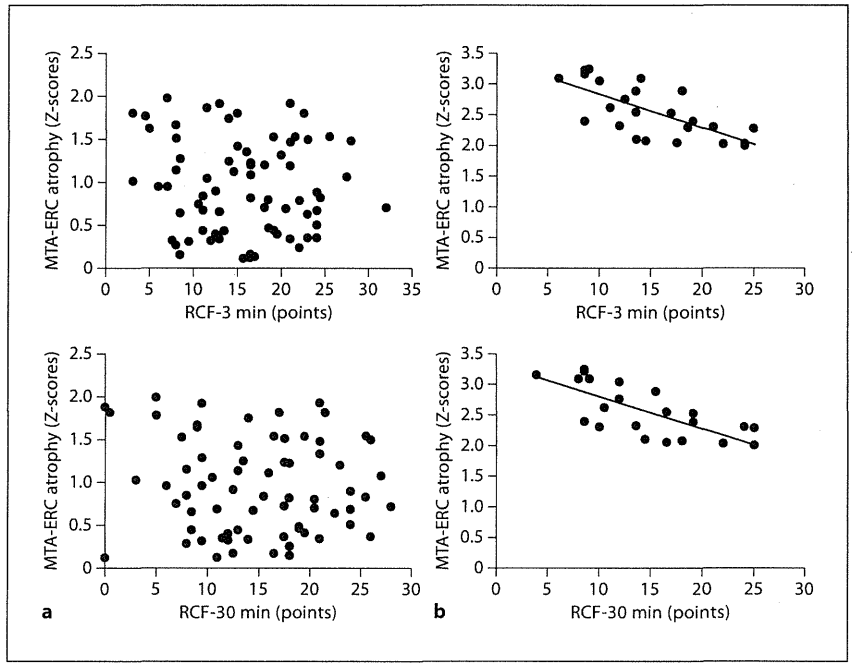

Fig. 3. Relationship between the Z-score of MTA-ERC and Rey complex figure retention test in mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and RCF-3 min and the lower panel shows scatter plots between MTA-ERC atrophy and RCF-30 min. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group.

dence that these brain regions are substantially affected by disease in the early stages of AD [34, 35], in accord with the finding that memory impairment is the earliest symptom of disease in most AD patients. The ERC is part of a critical pathway in the neural system underlying memory. Zola-Morgan et al. [36] reported that this area receives afferents from widespread association and limbic areas, projects to the dentate gyrus of the hippocampal formation, receives afferents from the hippocampus, and sends afferents back to association neocortex. An epidemiological study reported that ERC atrophy was greater than hippocampal atrophy in patients suffering from MCI [35]. However, the two measures were found not to differ in AD, suggesting that the ERC atrophies before the hippocampus in incipient AD [37]. An autopsy study of early AD patients reported neurofibrillary tangles in the ERC before evidence of hippocampal involvement [35]. Thus, volumetric MRI analysis of the MTA included ERC may be a sensitive predictor to identify AD conversion and decline of neuropsychological performances in MCI elderly adults.

In the current study, 25% of elderly adults with MCI exhibited severe atrophy in the MTA-ERC. The VSRAD analysis revealed that Z-scores indicating probable AD and amnestic MCI patients averaged 1.94 ± 1.24 (ranging from 0 to 4.69) [22]. Subjects exhibiting MTA-ERC atrophy as well as probable AD were included in the present MCI study. Numerous imaging studies have reported a correlation between increasing age and decreasing brain volume [38–42]. This decline in brain volume may be due to a non-linear acceleration in rates of atrophy after 70 years of age [43]. In the current study, 72 subjects (75%) were 70 years and over. Thus, the brain volume of our sample may have been affected by advancing age. In fact, we found significant relationships between age and MTA-ERC atrophy in MCI elderly adults. Similar findings were revealed in the relationship between MTA-ERC atrophy and educational level. Educational level was also a potential confounding factor of the prevalence and risk of dementia [44–46]. Educational level is thought to construct cognitive reserve, which modifies the relationship between brain atrophy and cognitive decline [47].

In the cognitive tests, WMS-R, LM I, DSC, and SCWT-IL showed significant correlations with MTA-ERC atrophy in univariate regression analysis. However, a multivariate regression model that included age and educational level revealed that MTA-ERC atrophy, i.e. high Z-score of VSRAD, was related only to SCWT-IL score in all subjects. Functional neuroimaging studies during executive tasks suggest that dorsolateral prefrontal cortex is responsible for maintenance of task demands and preparatory deployment of attention, and anterior cingulate

cortex is responsible for monitoring performance in order to detect cognitive and behavioral conditions with potential negative outcomes, and triggering dorsolateral prefrontal cortex to increase attention or change behavior [48–52]. A volumetric MRI study showed that there was an association between left hemisphere dorsolateral prefrontal cortex and anterior cingulate cortex atrophy and poorer attentional control accuracy. In the right hemisphere, atrophy of the temporal-parietal junction and ventrolateral and dorsolateral prefrontal cortices were associated with slower response times during attentional control on accurate trials [53]. This evidence from neuroimaging studies suggests that an executive deficit was caused by brain disorders in widespread regions that included prefrontal cortex, parietal lobe, and cingulate cortex. Neuropathological studies have shown that axonal pathology is strongly associated with cognitive impairment [54], and MCI patients may have increased white matter diffusivity in frontal and temporal regions [55]. The disruption of neural networks between the anterior and posterior cerebral areas, known as disconnection syndrome, during the initial stage of AD and MCI causes executive dysfunction, including changes in inhibition control [56–58]. Atrophy of the MTA is correlated with the degree of dementia and also with the extent of temporoparietal hypometabolism; both results are assumed to reflect changes in cerebral connectivity, especially between the MTA and the neocortex [59–61]. AD patients, as well as older adults with MCI, have shown selective disruption of default network intrinsic connectivity, most prominently in connectivity between the precuneus/posterior cingulate and medial temporal lobe regions [58, 61–64]. In diffusion tensor imaging study, the cingulum fibers, which connect the posterior cingulate gyrus and the hippocampus, may be compromised in the early stage of AD [65]. In recent years, Grambaite et al. [66] reported that frontal and temporal white matter diffusivity changes in the posterior cingulate region as well as the anterior cingulate region in MCI patients who had attention and executive dysfunctions. Reciprocal connections between the dorsolateral frontal cortex and anterior cingulate cortex [67–70] are part of a frontolimbic network [71, 72]. In the present study, MCI subjects showed a relationship between Z-score of the VSRAD and cognitive tests, especially tests of executive function. This relationship may be affected by not only MTA-ERC atrophy but also disconnectivity among MTA, temporoparietal, anterior cingulate, and prefrontal regions.

In a sub-analysis dividing subjects into two groups, the mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and DSC and SCWT-IL. The multivariate analysis on the mild to moderate atrophy group did not sustain the statement that DSC and SCWT-IL performances may be a reliable indicator of MTA-ERC atrophy in MCI patients. Increasing age is related closely with decreasing brain volume [38–42]. In fact, age remains the only significant variable indicating that its relative weight is too high and deletes the association between Z-scores and DSC and SCWT-IL observed in univariate models. In contrast, MTA-ERC atrophy was related closely to RCF-3 min and RCF-30 min in the severe atrophy group. In the multivariate regression model, MTA-ERC was associated independently with visual memory adjusted for age, educational level, and other cognitive functions. For the right temporal lobe there is some evidence that damage specifically in temporomesial structures may be the cause of impairments in nonverbal memory functions. Patients with hippocampal damage showed preoperatively [73] and postoperatively [74] impaired visual memory performance, whereas patients without hippocampal damage exhibited no deficiencies in visual memory. In line with previous operative studies, our results from MCI elderly adults with severe atrophy suggest a special involvement of MTA in visual memory performance. However, the VSRAD system was developed to measure the total atrophy in the bilateral parahippocampal gyrus and ERC. Thus, the association between visual memory and right hippocampal volume reduction should be investigated in the future.

It should be noted that this study may have been limited by a restricted sample. In addition, we did not include an analysis of genetic factors. Because genetic and physical factors such as apolipoprotein E genotype [75] and head size [76] may impact on neurodegenerative disorders and brain volume, analyzing genetic factors may extend the current results. Fitness level may have also acted as a confounding factor. Many studies have reported that physical activity can reduce the likelihood of the development of cognitive decline over time [77, 78]. Higher levels of fitness related to increased physical activity have been associated with enhanced neuronal survival in response to brain insult [79, 80], increased vascularization [81], and elevation of growth factors in areas important for memory [82]. More detailed analysis adjusting for these confounding variables will be required to further elucidate the relationship between MTA-ERC atrophy and memory function.

Overall, the present findings revealed that MTA-ERC atrophy was associated with age, educational level, and executive function, whereas no significant relationship

was found between MTA-ERC atrophy and memory tests in elderly subjects with MCI. This included the adults who had mild to moderate atrophy in MTA-ERC. In contrast, there was a significant relationship between MTA-ERC atrophy and visual memory test scores in elderly adults with severe MTA-ERC atrophy. These results suggest that executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy. A decline of visual memory function suggested severe MTA-ERC atrophy in elderly adults with MCI. Future research needs to determine the relationships between cognitive functions and brain atrophy except MTA-ERC in elderly adults with MCI.

Take Home Message

(1) MTA-ERC atrophy was significantly related to age, educational level, and executive function in elderly subjects with MCI.
(2) The subjects with severe MTA-ERC atrophy showed significant relationships between MTA-ERC atrophy and a decline in visual memory score.
(3) Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and decline in the RCF test suggests severe MTA-ERC atrophy in elderly adults with MCI.

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原著論文

認知機能障害を伴う要介護高齢者の日常生活動作と行動・心理症状を測定する新評価票

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[原著論文]

認知機能障害を伴う要介護高齢者の日常生活動作と行動・心理症状を測定する新評価票

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抄録

認知機能障害がある高齢者の日常生活動作の程度を測定する「認知機能障害に伴う日常生活動作評価票（以下，ADL-Cog）」と行動と心理状態を測定する「認知機能障害に伴う行動・心理症状評価票（以下，BPS-Cog）」を考案し，要介護度認定調査員ならびに日本老年精神医学会員医師に依頼し，その信頼性と妥当性の検証を行った．方法は，認知機能障害を伴う高齢者に2つの新しい評価票を用いてADLと行動・心理症状を測定した．信頼性の検証では，DVD画像を用いて認定調査員42人，医師39人の評価者間一致率を，また認定調査員のみ評価者内一致率を検証した．妥当性の検証では，565人の認知機能障害を伴う高齢者にADL-CogならびにBPS-CogとFAST，Behave-AD，「認知症高齢者の日常生活自立度」を同時に実施し，相互の相関関係を求めた．結果では，評価者間一致率が2つの評価票ともに69%以上と高く，また認定調査員による評価者内一致率もADL-Cog，BPS-Cogともに87%以上の一致率がみられ，さらに級内相関係数（ICC）は認定調査員間で相関係数が0.77以上，医師と調査員間では0.71以上であった．既存測度のFASTとADL-Cogの相関は相関係数が0.715，またBehave-ADとBPS-Cogは相関係数0.611の相関が認められた．以上から，ADL-CogならびにBPS-Cogの信頼性と妥当性は，検証された．

Key words：認知症，ADL-Cog，BPS-Cog，認知機能，評価測度

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はじめに

平成20年6月に厚生労働省は「認知症の医療と生活の質を高める緊急プロジェクト」を発表し，今後の認知症対策の基本方針として，①実態の把握，②研究開発の促進，③早期診断の推進と適切な医療の提供，④適切なケアの普及および本人・家族支援，⑤若年性認知症対策を掲げた．そのなかで認知症の研究開発の促進では，現在介護保険認定調査等で用いられている「認知症高齢者の日常生活自立度」（以下，日常生活自立度）の信頼性と妥当性の検証が求められた[8]．

本研究では，これまでの介護保険要介護認定調査時の認定調査ならびに主治医意見書で評価される日常生活自立度に代わる主治医や認定調査員などが簡便に，かつ一致した評価ができる新しい測度の開発を目的とした．この新測度は，認知機能の障害を伴った高齢者の日常生活動作（activities of daily living；ADL）と行動・心理症状を評価し，彼らの生活状態を判定する測度と位置づけた．それゆえ，認知機能障害の原因疾患が認知症のみならず高次脳機能障害，精神障害あるいは発達障害等の高齢者で，認知機能の障害を疑う者のADLと行動・心理状態が適切に評価できる測度の開発

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を試みた.

この新測度の開発により，要介護認定に伴う被保険者の日常生活動作（ADL）と行動・心理症状の程度を客観的に判定でき，要介護度認定の精度を高めることに寄与することが期待できる.

Ⅰ．研究方法

1．新評価票の信頼性・妥当性の検証

1）新評価票の作成

全国の要介護認定調査員（以下，認定調査員）ならびに介護支援専門員によるグループディスカッションを実施した．方法は①認知症高齢者の介護の大変さ，②認定調査時の評価で困ること，の2点をブレーンストーミング法より明らかにし，そこでの結果をもとに認知機能の障害を伴った高齢者の日常生活状況を評価する測度案を作成した.

2）新評価票の信頼性検証

認知機能障害を伴う高齢者の日常生活状態を判定する評価測度の信頼性を検証するために，認定調査員ならびに医師の評価者間一致度と，認定調査員の評価者内一致度の検証を以下の手順で行った.

a）DVD の作成

新評価票の信頼性検証のために，実際の認定調査員ならびに医師が担当する3組の患者・家族の面接場面を再現したDVDを作成した．認知症者ならびに家族のプライバシー保護の理由から，実際の面接場面を撮影，録音したものから台本を起こし，それに沿って認知症者とその家族を役者が演じてDVDを作成した.

b）評価者の選定

DVDを用いた信頼性検証の調査では，評価者を認定調査員と診療所勤務医師とした．前者は，A市の協力により過去に介護保険認定調査を実施した認定調査員のなかから，本研究の参加に同意が得られた協力者42人である．後者は，日本老年精神学会会員2,197人（2009年4月現在の会員医師）のうち，郵送で信頼性検証の研究協力依頼に同意した39人である.

c）DVD 評価方法

認定調査員によるDVD評価では，評価者間一致率と評価者内一致率を求めるために2回にわたり評価を実施した．1回目は，3事例の認定調査員と医師の面接場面を計6本視聴した．1回目の評価日から1週間後に同じ評価者が集合して，2回目の評価を1回目と同じ方法で実施した.

医師によるDVD評価は，医師が同一の場所に集合することが不可能なので，認定調査員とは異なる方法で評価者間一致率の検証を行った．協力者39人の医師に郵送で3事例の医師面接場面のDVDのみを郵送し，自宅でそれを視聴し新測度の評価を実施した．結果は1か月以内に郵送してもらった.

調査期間は，2009年12月1日～12月31日である.

3）新評価票の妥当性検証

評価者として研究同意が得られた認定調査員ならびに医師が，新評価票を用いて実際の臨床で評価を行った．その際には，同時に既存測度であるFAST（Functional Assessment Staging of Alzheimer's disease）[10]，Behave-AD（Behavioral Pathology in Alzheimer's Disease）[11]，「認知症高齢者の日常生活自立度」[5]を測定した.

a）調査実施者

認定調査員の選定は，日本介護支援専門員協会とA市，B市の協力を得た．関係機関の長に本研究の主旨と研究方法ならびに倫理的配慮について文書で説明し，研究協力者を募った．各機関所属の認定調査員に依頼し，本調査に協力可能と回答を得た認定調査員を対象とした．また医師は，信頼性検証調査の協力者依頼時に妥当性調査協力についても同時に依頼し，返信用の書面で研究参加の同意が確認できた医師を評価者とした.

b）調査対象者

認定調査員ならびに医師による妥当性調査の対象者は以下の条件を満たす者とした.

①介護保険要支援・要介護の認定者

②認知症をはじめ認知機能障害をきたす疾患の診断がなされていて，明らかに認知機能の障

害がある者
③在宅で家族と同居し，主たる介護者から対象者の日常生活の情報が得られる者
④本研究の目的と方法を調査者から文書ならびに口頭で説明し，調査実施の同意が対象者ならびにその家族から得られる者

認定調査員による調査では認定調査終了後に，また医師による調査は外来通院時に本調査を実施した．

c）調査期間

2009年12月1日～2010年2月15日である．

2．研究倫理

本研究は，研究開始前に研究目的，方法，調査者の選定方法と倫理的配慮，調査対象者の説明と同意取得方法ならびに倫理的配慮に関する事項に関して，日本社会事業大学研究倫理委員会の研究倫理審査に申請し，その承認を得て実施した．

Ⅱ．結　果

1．新評価票

新評価票の開発に際して全国42人の認定調査員ならびに介護支援専門員によるグループディスカッションを実施した．ここでは，認知症高齢者の生活状態を測定するには，ADLと行動・心理状態を評価することが望ましいことが示された．これらの提案に基づき，「認知機能障害に伴う日常生活動作評価票（以下，ADL-Cog）」（表1）と行動と心理状態を測定する「認知機能障害に伴う行動・心理症状評価票（以下，BPS-Cog）」（表2）の認知機能障害を伴う高齢者の日常生活状態を判定する評価測度を作成した．なお，予備調査では，ADL-Cogの評価項目のクロンバックα係数が0.859を示しており，ADL-Cogの下位測度の内的整合性が確認された．なおBPS-Cogのクロンバックα係数は下位測度を設定していないためにα係数は算出できなかった．

2．新評価票の信頼性と妥当性

1）信頼性の検証結果

評価者である認定調査員ならびに医師の属性を表3に示す．認定調査員と医師がDVDに収録された3事例（事例1，事例2，事例3）について，新評価票であるADL-CogとBPS-Cogを用いて評価し，その一致率を算出した．ADL-Cogの測定では，事例1をカテゴリー1と評価した者が認定調査員，医師ともに80%以上で，とくに医師は全員がカテゴリー1と評価した．同様に事例2はカテゴリー2と，また事例3はカテゴリー4と評価した認定調査員ならびに医師はともに80%以上であった（表4）．BPS-Cogの測定では，事例1でカテゴリーⅠと評価した者は調査員でやや低く，とくに医師の診察場面のDVDを見ての評価は64.3%であった．事例2をカテゴリーⅠと，事例3をカテゴリーⅡと評価した者はともに80%前後であった（表4）．認定調査員の評価者内一致率は3事例とも高い一致率が示された（表4）．

また，評価者間の一致率について，信頼性係数のひとつである級内相関係数（intraclass correlation coefficient；ICC）により分析を行ったところ，認定調査員の1回目と2回目の相関係数が0.77以上，また医師のDVDを見て評価した医師と認定調査員の相関係数は0.71以上と，どの組合せも高い正の相関が認められた（表4）．

2）妥当性の検証結果

評価者として妥当性の検証の調査に参加した認定調査員は111人，医師は81人であった．それぞれの性別，年齢ならびに専門分野については表3に示す．また，認定調査員の評価対象者は307人，医師は258人で，合計565人の対象者の性別，年齢，原因疾患名，要介護度別の人数を表5に示す．

現行の要介護度，日常生活自立度の5段階評価（Ⅰ，Ⅱ，Ⅲ，Ⅳ，M）と7段階評価（Ⅰ，Ⅱa，Ⅱb，Ⅲa，Ⅲb，Ⅳ，M），既存測度のFAST，Behave-AD，ならびにADL-Cog，BPS-Cogの計7つの変数について，565例におけるピアソンの積率相関係数による相関分析を行った（表6）．結果は，FASTと最も相関係数が高いのがADL-Cogであり，相関係数は0.715であった．また，Behave-ADとBPS-Cogとの相関係数は0.611で