18. Seidler RD, Bernard JA, Burutolu TB, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*. 2010;34:721–733.
19. Nadkarni NK, McIlroy WE, Mawji E, Black SE. Gait and subcortical hyperintensities in mild Alzheimer's disease and aging. *Dement Geriatr Cogn Disord*. 2009;28:295–301.
20. Rosano C, Brach J, Studenski S, Longstreth WT Jr, Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology*. 2007;29:193–200.
21. Rosano C, Sigurdsson S, Siggeirsdottir K, et al. Magnetization transfer imaging, white matter hyperintensities, brain atrophy and slower gait in older men and women. *Neurobiol Aging*. 2010;31:1197–1204.
22. Rosano C, Aizenstein H, Brach J, Longenberger A, Studenski S, Newman AB. Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63:1380–1388.
23. Zimmerman ME, Lipton RB, Pan JW, Hetherington HP, Verghese J. MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults. *Brain Res*. 2009;1291:73–81.
24. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol*. 2010;6:67–77.
25. Kavanagh JJ, Menz HB. Accelerometry: a technique for quantifying movement patterns during walking. *Gait Posture*. 2008;28:1–15.
26. Hirata Y, Matsuda H, Nemoto K, et al. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. *Neurosci Lett*. 2005;382:269–274.
27. Matsuda H. The role of neuroimaging in mild cognitive impairment. *Neuropathology*. 2007;27:570–577.
28. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24:709–711.
29. Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG Index of Competence. *Arch Gerontol Geriatr*. 1991;13:103–116.
30. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142–148.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
32. Doi T, Yamaguchi R, Asai T, *et al*. The effects of shoe fit on gait in community-dwelling older adults. *Gait Posture*. 2010;32:274–278.
33. Zijlstra W. Assessment of spatio-temporal parameters during unconstrained walking. *Eur J Appl Physiol*. 2004;92:39–44.
34. Yack HJ, Berger RC. Dynamic stability in the elderly: identifying a possible measure. *J Gerontol*. 1993;48:M225–M230.
35. Cromwell R, Schurter J, Shelton S, Vora S. Head stabilization strategies in the sagittal plane during locomotor tasks. *Physiother Res Int*. 2004;9:33–42.
36. Kavanagh J, Barrett R, Morrison S. The role of the neck and trunk in facilitating head stability during walking. *Exp Brain Res*. 2006;172:454–463.
37. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. 2006;61:1166–1170.
38. Kido T, Tabara Y, Igase M, et al. Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIPP study. *Dement Geriatr Cogn Disord*. 2010;29:379–387.

運動による現場での効果：とくに認知症予防の視点から

しまだ ひろゆき
島田裕之
国立長寿医療研究センター　老年学・社会科学研究センター
自立支援開発研究部自立支援システム開発室室長

【略歴】1971年生まれ。2003年：北里大学大学院卒業、2003年：東京都老人総合研究所介護予防緊急対策室、2006年：日本学術振興会特別研究員、2008年：東京都老人総合研究所自立促進と介護予防研究チーム、2010年より現職
【専門分野】老年学、リハビリテーション医学。医学博士

つつみもとこうた
堤本広大
国立長寿医療研究センター　老年学・社会科学研究センター
自立支援開発研究部自立支援システム開発室

【略歴】1986年生まれ。2010年：神戸大学保健学科卒業、2010年：神戸大学大学院博士前期課程入学、2012年：神戸大学大学院博士前期課程修了、2012年：神戸大学大学院博士後期課程入学、2011年より現職
【専門分野】老年学、リハビリテーション医学。保健学修士

はじめに

認知症は加齢とともに増加し、高齢者数の増大とともに有症者数が急激に増え、社会保障費を圧迫する原因となっている。実際に、わが国における認知症関連費用は約3兆5,000億円に達し、全世界においては米国に次ぐ世界第2位の費用となっている[1]。また、国民生活基礎調査による介護が必要となった主な原因を見ると、平成13年には認知症が原因で要介護となった者は10.7%（第4位）であったのが、平成22年には15.3%（第2位）となり、団塊世代が今後10～20年の間に認知症の好発年齢を迎える2025年頃には認知症高齢者の急増が見込まれ、その予防が急務の課題となっている。認知症の主な原因疾患であるアルツハイマー病および脳血管疾患に対する根治療法や予防薬の開発が確立されていない現在において、認知症の予防もしくは発症遅延のための非薬物療法の可能性を検討することも重要である。

本稿では、介護予防の新たな方向性として、認知症予防を目的とした認知機能の低下予防に有効な非薬物による介入の効果について概説する。

認知症予防の焦点

わが国における65歳以上の認知症有病率は約10%程度と推察されており、その有病者数は今後さらに増大することが懸念されている。中でも、認知症ではないが正常とも言い難い軽度の認知機能低下を有する状態は、軽度認知障害（mild cognitive impairment: MCI）と呼ばれ、認知症を発症する危険が高い[2]。地域に在住する高齢者を対象とした大規模疫学研究では、MCI有症率は概ね11～23%であり、このMCIは認知症に移行する危険性が高い反面、正常の認知機能に回復する場合もあり[3][4]、認知症予防を積極的に推進すべき状態と考えられる。

たとえば、健忘型MCI高齢者の半数、および非健忘型MCI高齢者の3分の2が、3年間の追跡期間中にアルツハイマー病へ移行することが示されている[5]。また、Petersenらの報告によると、正常な認知機能を有する高齢者におけるアルツハイマー病の発症率は年間1～2%であったのに対して、MCI高齢者におけるアルツハイマー病の発症率は年間10～15%であり、MCIはアルツハイマー病の前駆状態として考えられている。

一方、38.5%のMCI高齢者は5年後に正常な認知機能へと回復するとした報告もあり[7]、MCIの状態から可逆的変化を促すことが認知症を予防もしくは発症を遅延させることにつながるものと考えられる。そのため、認知症予防を目的とした介護予防においては、とくにMCI高齢者に焦点

を当てた取り組みが重要であり[6),8)]、その効果が期待される。

運動による認知症予防とそのメカニズム

薬物を使用しない療法による認知症予防としては、習慣的な運動の促進[9)]、抗酸化物質や抗炎症成分を多く含む食物の摂取[10)]、社会参加、知的活動、生産活動への参加[11)]、社会的ネットワーク[12)]が、認知症発症に対して保護的に働く因子として認められている。

中でも、有酸素運動の実施とアルツハイマー病発症予防との関連は多くの知見が得られており、MCI高齢者に対しても運動の効果を検証したランダム化比較試験の結果が報告され、限定的ではあるが認知機能に対する効果を認めている[13),14)]。運動介入プログラムはコストの面や実施しやすい点から、介護予防事業の中核を果たしている。

しかし、わが国において、運動が認知機能保持や認知症予防にどのような効果を持つかを検証した臨床試験は、未だほとんど実施されておらず、今後さらなる科学的根拠の構築が求められているところである。

運動が認知機能に対して良好な影響を及ぼすメカニズムとして、動物実験からの知見を中心に、神経炎症の減少、血管の新生、神経内分泌反応などが示唆されている。また、アルツハイマー病予防の観点からは、発症の原因と考えられているアミロイドβの蓄積を抑制する効果があるとされているネプリライシン[15)]の脳内活性が、身体活動と密接な関係を有しており、アルツハイマー病の予防に身体活動の向上が寄与する可能性が示唆されている[16)]。

近年では、運動を行うことにより活性化される脳由来神経栄養因子（brain derived neurotrophic factor: BDNF）が着目されており、認知機能の向上に寄与するとされている。とくにBDNFの効果は、記憶に重要な脳の海馬領域において観察され、可塑的変化をもたらすことが報告されている[17),18)]。また、運動の実施と脳容量増加、およびBDNFとの関係や、1年間の有酸素運動の実施による海馬容量の増加が報告されている[19)]。

BDNF以外にも運動による血管新生や、運動に伴うコリン作動性活性化による海馬の神経幹細胞活性などが明らかにされており、運動による認知機能向上のメカニズムが明白になりつつある。医療、保健、福祉の実践においても、運動によって対象者の認知的反応の向上を経験する機会があるが、それはこのような生理学的変化に基づいた帰結であると考えられる。

大府MCI介入研究

われわれはMCI高齢者を対象として認知症予防に対する運動の効果を検証するための研究事業を実施しており（主任研究者：鈴木隆雄国立長寿医療研究センター研究所長）、その研究結果の一部をここで紹介する。

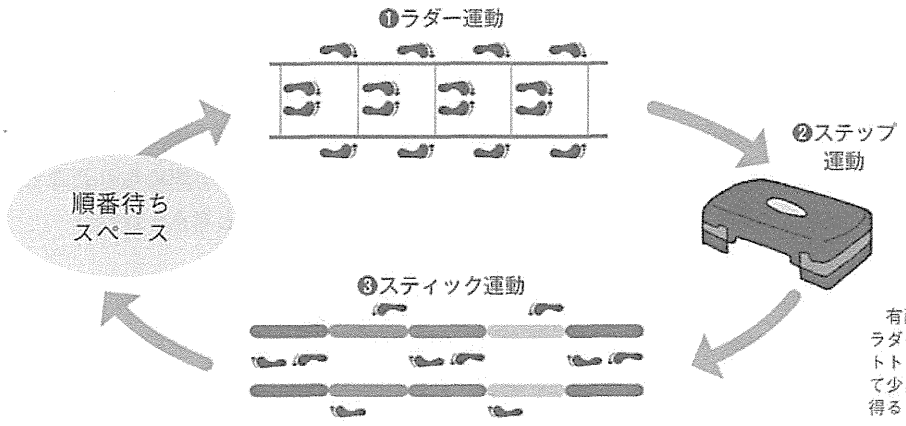
【対象者】

本研究の対象者は、愛知県大府市在住の65歳以上の高齢者。対象者の選定は、1次調査（質問紙調査n＝1,543）、2次調査（認知機能検査n＝135）、3次調査（MRI撮影n＝126）により実施した。基準に該当し研究への参加に同意した135名に対して認知機能検査を実施し、125名がMRI

図1　運動介入の方法

運動指導は理学療法士が担当し、補助員4名の体制で介入を実施した。プログラムの内容は、1）基礎体力作り（ホームプログラムとしても実施）、2）有酸素運動（ステップトレーニング、屋外歩行）、3）記憶力を必要とする運動（多重課題への適応、創造的思考などを伴う運動）、4）行動変容を促すプログラム（グループディスカッション、セルフモニタリング）により構成された。

図2　サーキットトレーニングの一例



有酸素運動であるステップ運動、脳賦活課題であるラダー運動・スティック運動を次々に行う「サーキットトレーニング」を介入後期に実施した。これによって少ない時間でさまざまな運動を実施でき高い効果を得ることが期待できる。

撮影を受けた。2次および3次調査で35名が除外基準あるいは参加を拒否し、100名のMCI高齢者が介入対象者として選択された。これらの対象者を健忘型MCIで層化して無作為に健康講座群（対照群）と運動教室群（介入群）とに割り付けた。

【介入プログラム】

運動教室群の介入は、6か月間、週2回、1回につき90分間、計40回実施した。教室は1日に3クラス設定し、1クラスの対象者を約17名として、理学療法士1～2名、運動補助員4名で介入を実施した。介入の内容は、ストレッチ、筋力トレーニング、有酸素運動、認知課題を含めた脳活性化運動（記憶や二重課題など）、行動変容技法による運動を習慣化とした（図1）。介入が後半に差しかかったあたりで、「サーキットトレーニング」を取り入れて、有酸素運動と脳賦活運動を組み合わせて、少ない時間でより効率的な介入になるよう工夫した（図2）。また、運動教室群の対象者には、歩数計の装着を促し、目標歩数への到達とストレッチ、筋力トレーニングの実施を毎日行うよう推奨した。

健康講座群には、介護や疾病予防に関する健康講座（60～90分間）を6か月間に2回実施した。

【結　果】

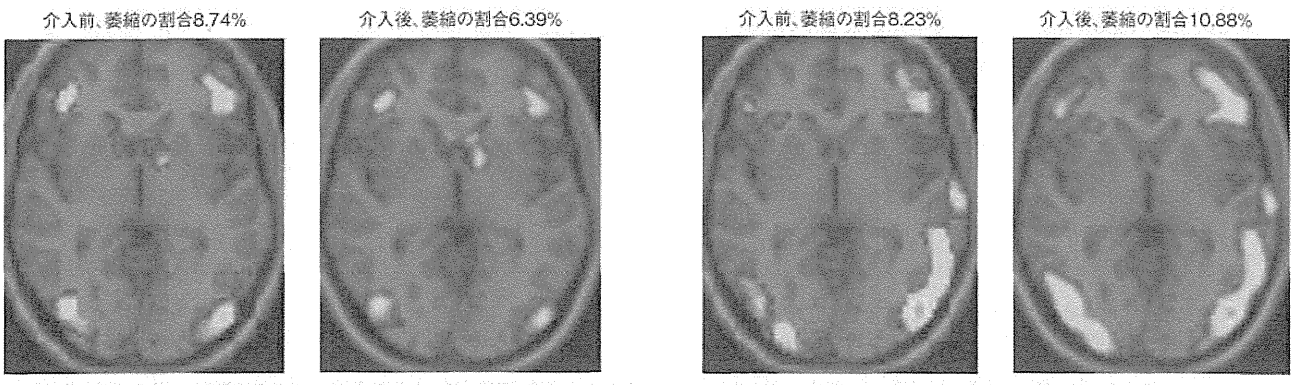
a. 運動教室の実施状況

運動教室群のうち38名（78%）が、40回の介入で80%以上出席した。また5名（10%）の対象者が30%以下の出席であった。運動教室実施中の有害事象はなかった。

b. 介入前の健康講座群と介入群の認知機能

ベースライン時における健康講座群と運動教室群間での比較において、年齢、運動機能、活動状態、教育歴、認知機能、脳容量のすべての項目で、全例および健忘型MCI

図3　MRI指標による脳萎縮の変化



典型的な変化を示した両群の対象者の例を図示した。運動教室に参加した高齢者（81歳、男性）は、介入期間中に脳萎縮の大きな変化は認められなかったが（左図）、健康講座に参加した高齢者（78歳、男性）では脳萎縮の割合が上昇した（右図）。

群ともに有意差は認められなかった。

c. 介入前後の認知機能の変化 ―全対象者―

言語機能であるWord Fluency Test（カテゴリー課題）および遂行機能（digit symbol coding）において、運動介入群と健康講座群間に有意な交互作用が認められた。

d. 介入前後の認知機能の変化 ―健忘型MCI高齢者―

健忘型MCI高齢者における群間差を比較した結果、Mini-Mental State Examination（全般的な認知機能）、ウェクスラー記憶検査、Word Fluency Test（言語機能）において、有意な交互作用が認められた。

e. 脳容量測定

介入前後の比較において、全対象者および健忘型MCI高齢者の両方の分析にて、健康講座群の脳萎縮領域の割合が有意に上昇した。群間比較では健忘型MCI高齢者の分析において、運動教室群と健康講座群間に交互作用が認められ、運動による脳萎縮の抑制効果が観察された（図3）。

まとめ

多面的な運動の実施は、MCI高齢者の認知機能の向上に有効であった。とくに、アルツハイマー病へ移行する危険性が高い健忘型MCI高齢者[20) 21)]の全般的な認知機能の保持や記憶機能の向上が運動によって認められたことは、認知症予防の可能性を示唆するものと考えられた。

おわりに

自ら実践可能な運動によって認知症予防の可能性が見えてきたことは、高齢者本人や社会にとって大きな希望となるだろう。ただし、運動の効果は一朝一夕になし得るものではなく、継続した取り組みが重要である。活動的に老いることが健康を保持するための鍵となり、これを支援するためのシステムの構築が急がれる。

【参考文献】
1) Wimo A, Winblad B, Jonsson L. The worldwide societal costs of dementia: Estimates for 2009. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2010;6 (2) :98-103.
2) Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58 (12) :1985-92.
3) Larrieu S, Letenneur L, Orgogozo JM, Fabrigoule C, Amieva H, Le Carret N, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology. 2002;59 (10) :1594-9.
4) Matthews FE, Stephan BC, McKeith IG, Bond J, Brayne C. Two-year progression from mild cognitive impairment to dementia: to what extent do different definitions agree? J Am Geriatr Soc. 2008;56 (8) :1424-33.
5) Palmer K, Backman L, Winblad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. Am J Geriatr Psychiatry. 2008;16 (7) :603-11.
6) Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56 (3) :303-8.
7) Ishikawa T, Ikeda M, Matsumoto N, Shigenobu K, Brayne C, Tanabe H. A longitudinal study regarding conversion from mild memory impairment to dementia in a Japanese community. Int J Geriatr Psychiatry. 2006;21 (2) :134-9.
8) Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol. 2005;62 (7) :1160-3; discussion 7.
9) Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003;348 (25) :2508-16.
10) Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA. 2002;287 (24) :3230-7.
11) Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA. 2002;287 (6) :742-8.
12) Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet. 2000;355 (9212) :1315-9.
13) van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med. 2008;42 (5) :344-51.
14) Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010;67 (1) :71-9.
15) Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, et al. Metabolic regulation of brain Abeta by neprilysin. Science. 2001;292 (5521) :1550-2.
16) Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, et al. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. Cell. 2005;120 (5) :701-13.
17) Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Experimental physiology. 2009;94 (10) :1062-9.
18) Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2001;21 (17) :6706-17.
19) Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108 (7) :3017-22.
20) Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006;367 (9518) :1262-70.
21) Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256 (3) :240-6.

Gait & Posture xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females

Hiroyuki Shimada [a,*], Kenji Ishii [b], Kiichi Ishiwata [b], Keiichi Oda [b], Megumi Suzukawa [c], Hyuma Makizako [a], Takehiko Doi [a], Takao Suzuki [d]

[a] Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Japan
[b] Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Japan
[c] Faculty of Health Science, Department of Rehabilitation, Course of Physical Therapy, University of Human Arts and Science, Japan
[d] Research Center, National Center for Geriatrics and Gerontology, Japan

ARTICLE INFO

Article history:
Received 8 February 2012
Received in revised form 19 July 2012
Accepted 10 November 2012

Keywords:
Treadmill walking
FDG–PET
Primary sensorimotor area
Prefrontal area
Hippocampus

ABSTRACT

This study evaluated brain activity during unaccustomed treadmill walking using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose. Twenty-four healthy elderly females (75–82 years) participated in this study. Two PET scans were performed after 25 min of rest and after walking for 25 min at 2.0 km/h on a treadmill. Participants were divided into low and high step-length variability groups according to the median coefficient of variation in step length during treadmill walking. We compared the regional changes in brain glucose metabolism between the two groups. The most prominent relative activations during treadmill walking compared to rest in both groups were found in the primary sensorimotor areas, occipital lobe, and anterior and posterior lobe of the cerebellum. The high step-length variability group showed significant relative deactivations in the frontal lobe and the inferior temporal gyrus during treadmill walking. There was a significant relative activation of the primary sensorimotor area in the low step-length variability group compared to the high step-length variability group ($P = 0.022$). Compared to the low step-length variability group, the high step-length variability group exhibited a greater relative deactivation in the white matter of the middle and superior temporal gyrus ($P = 0.032$) and hippocampus ($P = 0.034$) during treadmill walking compared to resting. These results suggest that activation of the primary sensorimotor area, prefrontal area, and temporal lobe, especially the hippocampus, is associated with gait adaptability during unaccustomed treadmill walking.

1. Introduction

Increased gait instability and inconsistency from one step to the next are common in many elderly adults [1,2]. Gait variability, such as the coefficient of variation (CV) in step length [1,2], is a quantifiable feature of walking that is altered in clinical situations, such as falling, frailty, and gait disorders in neurodegenerative diseases [3–5]. The increase in gait instability observed in elderly adults without apparent neurological disease is multifactorial. Age-associated changes may contribute to gait instability, including reduced range of motion, decreased aerobic capacity and muscle function, and impaired balance [6,7]. However, the relationship between gait instability and brain function has not been studied in detail.

Gait is a complex sensorimotor action that is based on automated and reflexive spinal programs that are under the control of several distinct supraspinal centers located in the brainstem, basal ganglia, cerebellum, and cerebral cortex. Several imaging techniques have been developed to identify activation patterns during walking. These include the measurement of glucose metabolism during actual walking using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) [8–10] and single-photon emission tomography (SPECT) with technetium-99m hexamethylpropylene amine oxime or ^{99m}Tc-ethyl cysteinate dimer to measure fixed regional cerebral blood flow [11–13].

Previous PET and SPECT studies revealed that gait disturbance in Parkinson's disease may be associated with underactivity in the medial motor area and cerebellar hemispheres and overactivity in the cerebellar vermis [8,10–12] Recently, it was reported that elderly adults with gait disturbance, secondary to age-related white matter changes, exhibited underactivation

* Corresponding author at: Section for Health Promotion, Department of Health and Medical Care, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan. Tel.: +81 562 44 5651x5254; fax: +81 562 46 8294.
E-mail address: shimada@ncgg.go.jp (H. Shimada).

0966-6362/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

of the supplementary motor area, thalamus, and basal ganglia compared to elderly adults without gait disturbance [13].

Treadmills are commonly used for gait analysis in clinical and research settings [14]. Treadmill walking, in theory, is mechanically equivalent to overground walking [15,16]. In reality, however, walking on a treadmill can initially be an unfamiliar experience [16,17]. Unimpaired younger adults required 4–6 min to familiarize themselves with the treadmill [14,17]. However, complete familiarization with treadmill in a 15-min single session was not attained in elderly adults [18]. Therefore, a treadmill walking task may be used to investigate the process of adaptation to an unfamiliar environment during walking.

The purpose of the study was, first, to compare the relative brain activation and/or deactivation during treadmill walking compared to resting condition and, second, to determine whether gait adaptability measured as gait variability could be explained through differences of brain activation and/or deactivation in response to an unaccustomed treadmill walk in the elderly adults.

2. Materials and methods

Two hundred and seventy-four females were selected from our database of elderly volunteers ($n = 1289$). Inclusion criteria were: age $\geq$ 75 years, no history of neurological or psychiatric disorders, cardiovascular disease, hypertension, heart failure, diabetes mellitus, head trauma, drug or alcohol abuse, or severe pain. Of the initial 274 females, 106 completed cognitive and physical performance tests including preferred walking speed. Sixty-nine females were excluded because of low cognitive function (Mini Mental State Examination score < 27 points), multiple medications, drug allergy, and gait disturbance (gait freezing, wide-based gait, or remarkable body sway during gait). Magnetic resonance imaging (MRI) with T1-weighted contrast was performed in 37 females using a 1.5-T Sigma Horizon scanner (GE, Milwaukee, WI, USA). Thirteen females were excluded based on MRI exclusion criteria (cerebrovascular lesions or high cortical atrophy). The remaining 24 females participated in the study (mean age, 78.0 ± 2.3 years; range, 75–82 years).

Participants were fully informed of the purpose and potential risks of the experiments, including radiation dose, and provided written, informed consent. The Ethics Committee of the Tokyo Metropolitan Institute of Gerontology approved the study protocol.

Brain glucose uptake in the rest and treadmill walking conditions was assessed on separate days (within two weeks, at least two days apart). Each condition consisted of three phases: preparation, rest or treadmill walking, and a PET scan. Total time of the FDG–PET measurement was about 85 min in each condition. The preparation period was 40 min in duration, after which the participants either rested for 35 min or walked for 25 min on a treadmill. A 6 min FDG–PET scan was performed subsequently.

During the preparation period, a catheter for injection of FDG was inserted into a vein of the left forearm. FDG (180 MBq) was injected intravenously at the onset of rest and treadmill walking. For the resting condition, participants lay supine with their eyes closed for 35 min. For the treadmill walking condition, participants walked on a treadmill (PW-21; Hitachi, Tokyo, Japan) for 25 min at 2.0 km/h while holding the handrails, to avoid falling during walking and to provide a uniform visual environment. The participants then rested on a bed with their eyes closed for 10 min.

A step counter with an infrared ray device (m-Stride ST-1100; S & ME, Tokyo, Japan) recorded walking speed, cadence, and step length during the treadmill walking period to evaluate temporal changes in gait characteristics. The step counter was placed on side-rail of a treadmill to measure belt speed (cm/s) of the treadmill and step time (s) during treadmill walking using infrared ray. The step length (cm) and cadence (steps/min) were calculated as follows.

$$\text{Step length} = \text{Belt speed} \times \text{Step time}, \quad (1)$$

$$\text{Cadence} = 60/\text{Step time}, \quad (2)$$

Step length was measured for 1 min at 0, 5, 10, 15, 20, and the 24th–25th min. We used 200 steps for the analysis of step length and cadence, 50 steps from each 1 min period starting at the 10th–11th min, 15th–16th min, 20th–21st min, 24th–25th min of treadmill walking. Five minutes following the rest or walking periods, PET scans were performed using a Headtome-V (SET 2400W, Shimadzu, Kyoto, Japan) in the three-dimensional (3D) mode. This 6 min emission scan therefore occurred 40 min after the intravenous injection of FDG. The scan produced images that had the following parameters: matrix size, 96 × 96 × 50; and voxel size, 2 mm × 2 mm × 3.125 mm. The attenuation was corrected via a transmission scan using a $^{68}Ga/^{68}Ge$ source.

The images were reconstructed using a filtered back projection algorithm with a second-order low-pass filter with a cutoff frequency of 1.25 cycles/cm. Corrections were applied for dead time and detector non-uniformity. Image processing and data analysis were performed using statistical parametric mapping (SPM8 software, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK) implemented on MATLAB (MathWorks, Natick, MA, USA). The tasks performed using SPM8 were MRI/PET coregistration, spatial normalization, spatial smoothing, MRI segmentation, normalization, and SPM analysis. Anatomical brain MR images were spatially normalized into the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) standard template using an affine transformation (12 parameters for rigid transformations) [19]. The parameters were applied to the coregistered FDG–PET images. Therefore, all stereotactic coordinates given in this paper refer to the MNI coordinate system. Subsequently, the spatially normalized images were blurred with a Gaussian filter (FWHM 12 mm) to increase signal-to-noise ratio. All scans were analyzed after normalization to the white matter. The normalization prior to voxel-based statistics was performed using an anatomical mask in MNI space. This normalization was used for all participants to remove the effects of differences in the overall counts. The pixel values were normalized by scaling the activity in each pixel in proportion to the global activity. This ensured that the variance related to the substantially different global activity between high- and low-dose images was stabilized. In this process, the mean global activity of each scan was adjusted to 50. Planned comparisons between the rest and exercise conditions were performed using t statistics for each voxel. These analyses generated statistical parametric maps of the t statistic (SPM {t}), which were subsequently converted to unit normal distribution (SPM {Z}). The estimated final spatial resolution was 19 mm × 21 mm × 18 mm.

The standard deviation for the CV, the ratio of the standard deviation to the mean, in step length during the treadmill walk was large in our sample (mean 7.2 ± 6.0%). However, there was a bimodal distribution around the median value for the CV for step length and it was therefore appropriate to use the median step length for CV as the cut-point dividing the females into low step-length variability (LSV) and high step-length variability (HSV) groups. Student's t test was used to compare age and gait variables between the LSV and HSV groups during treadmill walking. The significance threshold was set at $P < 0.05$. SPSS version 19 (Chicago, IL, USA) was used for statistical analyses.

The locations of relatively activated and deactivated brain areas were identified and listed according to stereotaxic coordinates and visual inspection of the structural MRI provided by SPM8. Significant relative increase (walk > rest) and decrease (rest > walk) in cerebral glucose uptake during the gait condition compared with the rest condition were explored for each group separately. Both relative increases and decreases in glucose metabolism were calculated and considered significant at $P < 0.05$, and were corrected for multiple comparisons using a familywise error (FWE) method [20].

A region of interest (ROI) analysis was used to assess activated and deactivated brain areas during treadmill walking between the HSV and LSV groups, which were interpreted as the relative difference in gait-induced glucose uptake changes between groups. The ROIs were determined on visually apparent regions of relative activation (walk > rest) and deactivation (rest > walk) images for all participants. Glucose metabolism in the ROIs was measured based on the standardized uptake value (SUV), which was defined as follows.

$$\text{SUV} = C/D/w, \quad (3)$$

where C represents the radioactive concentration in the tissue (Bq/mL), D represents the injected dose (Bq), and w represents body mass (g) [21]. FDG dose was adjusted to body weight. Student's t test was used to compare the SUV between the LSV and HSV groups. The significance threshold was set at $P < 0.05$ during between-group comparisons in specific regions. The ROI analysis was performed using the Dr. View software (AJS, Tokyo, Japan). The anatomical designations used to the Talairach Client and MRI atlas of human white matter [22].

3. Results

There was no difference in age between the LSV and the HSV groups (77.4 ± 2.3 versus 78.7 ± 2.2 years; $P = 0.19$) or the following treadmill variables: walking speed (34.7 ± 0.4 versus 34.4 ± 0.5 m/min; $P = 0.26$), cadence (101.4 ± 15.1 versus 96.0 ± 15.7 steps/min; $P = 0.39$), and step length (34.9 ± 5.2 versus 37.4 ± 6.4 cm; $P = 0.31$). The HSV group had a higher step length CV compared to the LSV group (2.7 ± 0.8 versus 11.8 ± 5.5; $P < 0.001$).

The most prominent relative activations during treadmill walking in the LSV group were found in the primary sensorimotor areas (Broadman area (BA) 3 and 4), occipital lobe (BA 17, 18, and 19), and anterior and posterior lobe of the cerebellum compared with the resting condition (Table 1, Fig. 1A). The LSV group did not

Please cite this article in press as: Shimada H, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture (2012), http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

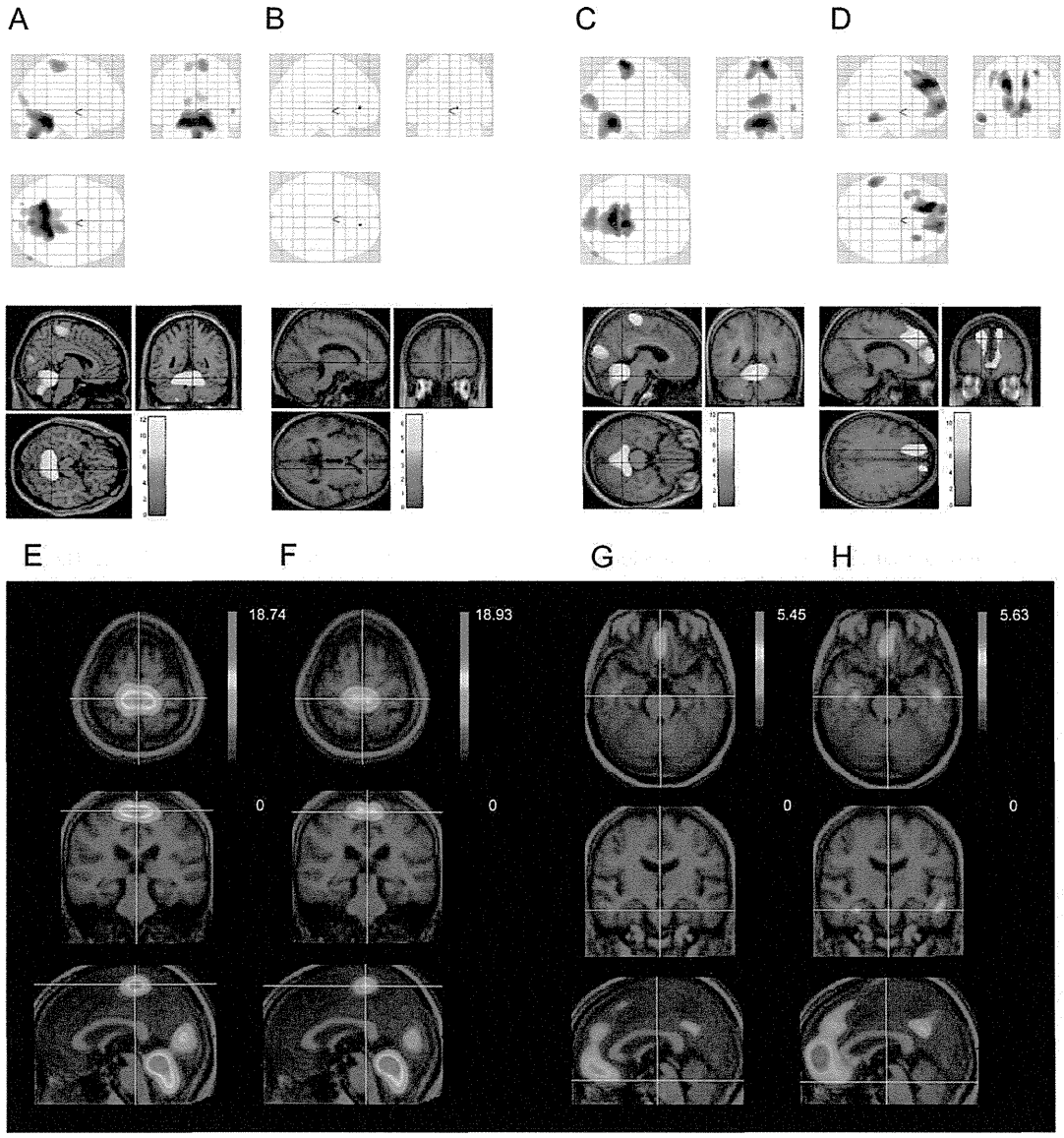


Fig. 1. FDG–PET activations and deactivations during treadmill walking in the LSV and HSV groups. During treadmill walking in the LSV group, activations (A) were prominent in the primary motor areas, visual cortical areas and anterior and posterior lobe of cerebellar. Slight deactivation (B) was found in the right sub-gyral. In the HSV group, activations (C) were prominent in the primary motor areas, visual cortical areas and anterior and posterior lobe of cerebellar. Deactivations (D) were found in the supplementary motor areas (superior and medial frontal cortex, dorsolateral prefrontal cortex). The primary sensorimotor cortex was activated more during treadmill walking versus the resting condition, in the LSV group (E) compared to the HSV group (F). Hippocampus and temporal lobe were deactivated more for treadmill walking versus the resting condition, in the HSV (H) group compared to the LSV group (G).

exhibit prominent relative deactivation during treadmill walking compared with the resting condition (Table 1, Fig. 1B)

The HSV group exhibited marked relative activation in the primary sensorimotor areas (BA 3 and 4), occipital lobe (BA 17, 18, and 19), and anterior and posterior lobe of the cerebellum during treadmill walking compared with the resting condition (Table 2, Fig. 1C). However, the HSV group showed relative deactivation in some regions during treadmill walking. The most prominent relative deactivations during treadmill walking were found in the frontal lobe, including the dorsolateral prefrontal cortex (BA 9 and 46), supplementary motor area (BA 6 and 8), and inferior temporal gyrus (Table 2, Fig. 1D).

Lower panels of Fig. 1 show FDG images of relative activations and deactivations during treadmill walking compared with the resting condition in the participants of the LSV and HSV groups. The SUV uptakes of the relatively activated and deactivated regions are shown in Table 3. The primary sensorimotor areas (BA 3 and 4), occipital lobe (BA 17, 18, and 19), and cerebellum (especially the vermis) were activated during treadmill walking. Relative deactivation of FDG was observed in the orbitofrontal cortex (BA 11), superior frontal gyrus (BA 10), dorsolateral prefrontal cortex (BA 9 and 46), supplementary motor area (BA 6 and 8), middle and superior temporal gyrus white matter, posterior cingulate cortex (BA 31), pons, and hippocampus in all participants. A detailed comparison of the relative activations and deactivations using ROI analysis revealed a more prominent activation of the primary sensorimotor area in the LSV group (Table 3, Fig. 1E) compared with the HSV group (Table 3, Fig. 1F) ($P = 0.02$). The HSV group

Please cite this article in press as: Shimada H, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture (2012), http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

Table 1
FDG activations and deactivations during treadmill walking in the low step-length variability group.

(a) FDG activation during treadmill walking in the low step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Left cerebellum, anterior lobe, culmen		5196	6.57	12.26	<0.001	−20	−52	−16
Right cerebellum, anterior lobe, culmen			6.46	11.75	<0.001	12	−46	−16
Right cerebellum, posterior lobe, inferior semi-lunar lobule			5.83	9.4	<0.001	4	−68	−38
Right cerebrum, frontal lobe, precentral gyrus		936	5.44	8.22	0.001	10	−30	66
Left cerebrum, parietal lobe, postcentral gyrus	3		4.84	6.69	0.014	−10	−32	66
Right cerebrum, occipital lobe, inferior occipital gyrus	19	39	5.17	7.48	0.004	56	−72	−2
Right cerebellum, posterior lobe		57	4.89	6.8	0.011	20	−50	−58
Left cerebrum, occipital lobe, superior occipital gyrus, cuneus	17	130	4.82	6.63	0.015	−14	−78	12
Right cerebrum, occipital lobe, cuneus	18	147	4.68	6.31	0.027	8	−84	16
Left cerebellum, posterior lobe		4	4.64	6.24	0.03	−24	−84	−46
Left cerebellum, posterior lobe		23	4.63	6.21	0.032	−20	−52	−56
Right cerebrum, occipital lobe, middle or lateral occipital gyrus	19	1	4.54	6.02	0.045	28	−86	38

(b) FDG deactivation during treadmill walking in the low step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Right cerebrum, frontal lobe, genu of the corpus callosum		5	4.82	6.64	0.015	12	40	0

(Table 3, Fig. 1H) showed relative deactivation in the middle and superior temporal gyrus white matter ($P = 0.03$) and hippocampus ($P = 0.03$) during treadmill walking compared with resting than did the LSV group (Table 3, Fig. 1G). There were no significant differences in occipital lobe, cerebellum, frontal lobe, posterior cingulate cortex, and pons between groups.

4. Discussion

This study examined changes in whole brain glucose metabolism using FDG-PET during rest and unaccustomed treadmill walking in healthy elderly females, classified as either low or high step-length variability walkers. The main findings of the study were that females with high step-length variability showed relative deactivations in the supplementary motor areas and dorsolateral prefrontal cortex compared to rest and that females with low step-length variability exhibited greater relative activations in the primary motor area during treadmill walking compared to the HSV group. The HSV group showed greater relative deactivations in the temporal lobe, especially in the hippocampus, during treadmill walking compared with the LSV group.

Hanakawa [23] proposed a hypothesis regarding the neural mechanisms that control human bipedal gait. This author postulated that multiple channels from the basal ganglia–thalamocortical system and basal ganglia–brainstem system are involved in the regulation of the central pattern generator (CPG) in the spinal cord (Fig. 2). In the present study, the most prominent relative activations during treadmill walking were found in the primary sensorimotor areas, occipital lobe, and cerebellar areas for both groups. The primary motor area projects to the spinal cord through the corticospinal tract, and it is believed that the primary motor area is involved in the precise control of limb movement during walking. The coordination of limb and trunk movements to adjust for a shift in the center of gravity associated with locomotion may be one of the primary functions of the cerebellum in gait control. Previous neuroimaging experiments have shown that the cerebellar vermis and the anteromedial part of the cerebellar hemispheres are bilaterally activated during walking in healthy individuals [9,11,12]. The cerebellum is able to make immediate alterations in ongoing movement patterns [24]. It functions as a real-time sensory processing device and modulates motor responses in a reactive or feedback manner based on sensory perturbations [25].

Our findings also suggest that the cerebellum plays an important role in gait adaptation to unfamiliar environments, such as walking on a treadmill. The occipital lobe, including the

Table 2
FDG activations and deactivations during treadmill walking in the high step-length variability group.

(a) FDG activation during treadmill walking in the high step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Right cerebellum, anterior lobe, culmen		3715	6.54	12.12	<0.001	0	−50	−18
Right cerebrum, parietal lobe, postcentral gyrus	6	1878	6.37	11.38	<0.001	8	−32	72
Left cerebrum, parietal lobe, postcentral gyrus	3		5.75	9.16	<0.001	−10	−34	72
Left cerebrum, parietal lobe, postcentral gyrus white matter			5.4	8.09	0.001	−14	−28	54
Right cerebrum, occipital lobe, cuneus		1402	5.52	8.46	0.001	2	−84	18
Left cerebrum, occipital lobe, cuneus			5.47	8.29	0.001	−6	−82	14
Right cerebrum, occipital lobe, middle or lateral occipital gyrus		60	5.06	7.2	0.005	52	−78	4
Left cerebellum, posterior lobe		40	4.74	6.45	0.017	−22	−46	−52
Right cerebellum, posterior lobe		7	4.67	6.3	0.022	36	−84	−40
Right cerebrum, occipital lobe, middle or lateral occipital gyrus	17	3	4.52	5.99	0.039	26	−100	−12

(b) FDG deactivation during treadmill walking in the high step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Left cerebrum, frontal lobe, superior frontal gyrus		5131	6.31	11.14	<0.001	−18	46	40
Right cerebrum, frontal lobe, superior frontal gyrus white matter			5.74	9.13	<0.001	10	60	6
Right cerebrum, frontal lobe, superior frontal gyrus	8		5.7	8.98	<0.001	12	54	40
Left cerebrum, temporal lobe, inferior temporal gyrus		397	5.62	8.74	<0.001	−52	−44	−14
Right cerebrum, frontal lobe, middle frontal gyrus	6	113	5.38	8.04	0.001	30	22	58

Please cite this article in press as: Shimada H, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture (2012), http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

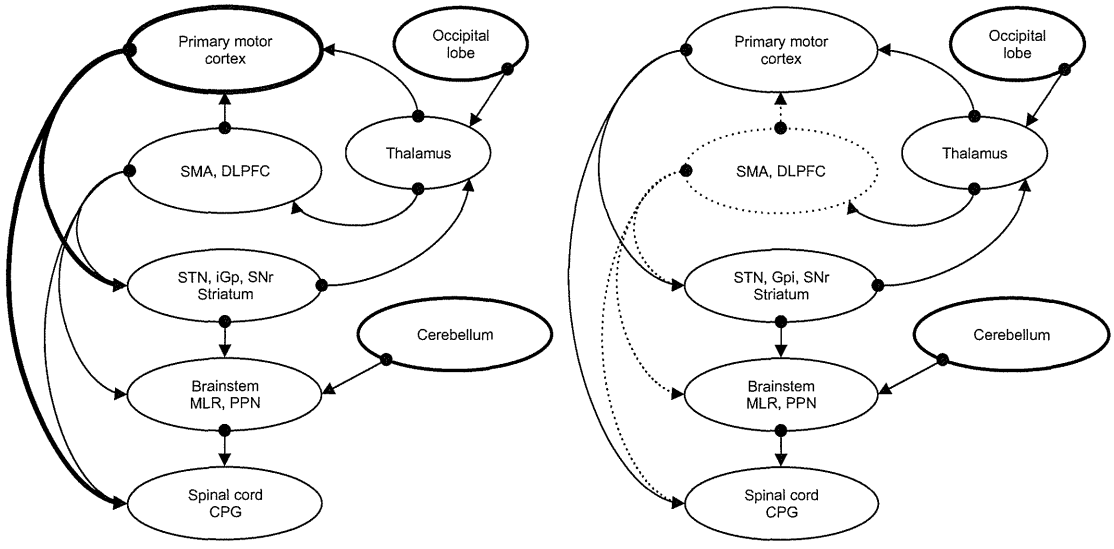


Fig. 2. Differences in neural mechanisms controlling treadmill walking in LSV compared to HSV individuals. Multiple channels from the 'basal ganglia–thalamo-cortical system' and 'basal ganglia–brainstem system' are both involved in regulating the central pattern generator (CPG) in the spinal cord. The primary motor cortex and non-primary motor areas such as supplementary motor areas constitute multiple parallel circuits with the basal ganglia counterparts. (a) Left panel displays our hypothesized neural network for the LSV group. The projections from M1 increased during walking to adapt to the unaccustomed environment (treadmill walking). (b) Right panel displays our hypothesized neural network for the HSV group. The HSV group deactivated FDG uptakes in SMA during treadmill walking and the deactivations may lead to dysfunction of 'basal ganglia–thalamo-cortical system' and 'basal ganglia–brainstem system'. *Abbreviations*: STN, subthalamic nucleus; iGP, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; MLR, midbrain locomotor region; PPN, pedunculopontine nucleus.

cuneus (BA 17) and precuneus (BA 7/31), is believed to play a role in visuomotor coordination. The areas which showed relative activation were compatible with those reported in a previous activation study using FDG–PET [10]. In addition, online visual feedback was the requisite for locomotor adaptation [26] and was thought to override internal model predictions of control during locomotion [27]. Our study further supports the hypothesis that locomotor adaptation requires neuronal activation in the region related to visuomotor coordination.

In the HSV group, relative deactivations in FDG uptake were observed over a broad area of the prefrontal cortex, including the supplementary motor area and the dorsolateral prefrontal cortex. Cortical locomotor commands originating from the premotor and supplementary motor cortices are conveyed to the brainstem locomotor centers via the basal ganglia. The structure of the dorsolateral prefrontal cortex is important for selecting and planning voluntary movements [28] or simulating motor actions [29]. The relative deactivation of the supplementary motor area and dorsolateral prefrontal cortex may be associated with the finding that the participants in the HSV group might have found it difficult to adapt to an unfamiliar environment, i.e., treadmill walking.

Detailed group comparison revealed that the LSV group had a more prominent relative activation in the primary sensorimotor area compared to the HSV group and that the HSV group exhibited relative deactivation in the hippocampus compared to the LSV group during treadmill walking. The relative activation of the primary motor area may improve projection to the basal ganglia and to the CPG in the spinal cord, thus facilitating the strengthening of the basal ganglia–thalamocortical system during walking (Fig. 2). Regarding relative deactivation in the hippocampus, Zimmerman et al. (2009) found that increased variability in step length was associated with poorer hippocampal metabolism in elderly individuals. The authors suggested

Table 3
A region of interest analysis based on the standardized uptake value as the relative difference in gait-induced glucose uptake changes between groups.

	LSV group Mean (SD)	HSV group Mean (SD)	*p* value
Walk>Rest			
Primary sensorimotor area (BA 3, 4)	13.56 (3.01)	10.93 (2.16)	0.02
Occipital lobe (BA 17, 18, 19)	11.42 (4.29)	9.25 (3.55)	0.19
Cerebellum (vermis, anterior and posterior lobe)	17.18 (4.85)	17.36 (4.07)	0.92
Rest>Walk			
Orbitofrontal cortex (BA 11)	3.85 (3.18)	3.67 (2.94)	0.89
Superior frontal gyrus (BA 10)	4.16 (2.54)	4.76 (2.83)	0.59
Dorsolateral prefrontal cortex (BA 9, 46)	3.16 (2.09)	4.45 (2.25)	0.16
Supplementary motor area (BA 6, 8)	3.79 (1.74)	4.12 (1.83)	0.65
Middle and superior temporal gyrus white matter	1.85 (1.45)	3.07 (1.15)	0.03
Posterior cingulate cortex (BA 31)	3.01 (2.16)	3.67 (3.58)	0.59
Pons	2.40 (1.89)	1.84 (0.94)	0.37
Hippocampus	1.24 (1.31)	2.44 (1.29)	0.03

LSV: high step-length variability; HSV: low step-length variability.

Please cite this article in press as: Shimada H, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture (2012), http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

that the hippocampus plays an important role in the timing or rhythmicity of locomotion, which may be compromised in elderly adults [30]. Additionally, PET study showed that imagined walking with obstacles was associated with increased prefrontal and parahippocampal activation, suggesting that higher brain centers become progressively engaged when the locomotor task demands increased cognitive and sensory information processing [31]. Beauchet et al. (2003) reported that stride-to-stride variability increased significantly in older subjects with the interfering task of counting, although there was no significant change in young subjects. The authors suggested the involvement of higher cortical regions for the motor control of gait under a dual-task in older adults [32]. Our findings therefore support and extend previous research via the identification of an association between FDG–PET activation/deactivation and gait *variability* in an unfamiliar environment in elderly adults. Walking task used a treadmill, as a stimulator to increase cognitive demand may be beneficial tool for identifying the involvement of cortical regulation in gait of the older adults.

Limitations of our study were that the sample was drawn from a larger study of community-dwelling adults over the age of 75 years, and we were not able to examine the relationships between brain activity and cognitive functions across the entire adult lifespan.

In conclusion, FDG PET revealed that the most prominent relative activations during treadmill walking were the primary sensorimotor areas, occipital lobe, and cerebellar areas. The high step-length variability group exhibited a lesser relative activation in the primary sensorimotor area and a greater relative deactivation in the white matter of the middle and superior temporal gyrus and hippocampus during treadmill walking than the low step-length variability group. These results suggested the involvement of cortical regulation in gait adaptation of the older adults. Additional studies are necessary to examine the longitudinal sequence and relationships of gait, cognitive status, and presynaptic functional changes that emerge across the spectrum from normal aging to advanced functional decline.

Acknowledgements

We thank Masahiro Mishina for technical support. This study was supported in part by a grant from the Grant-in-Aid for Scientific Research from the Ministry of Education and Culture of Japan.

Conflict of interest statement

The authors have no conflicts of interest to disclose. This study was supported in part by a grant from the Grant-in-Aid for Scientific Research from the Ministry of Education and Culture of Japan. No support was received from industry. All authors declare that they have no competing interests and have nothing to declare. The researchers were all independent from the funder.

The sponsors had no role in the design or conduct of the study, the collection, management, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript.

References

[1] Hausdorff JM, Edelberg HK, Mitchell SL, Goldberger AL, Wei JY. Increased gait unsteadiness in community-dwelling elderly fallers. Archives of Physical Medicine and Rehabilitation 1997;78:278–83.
[2] Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. Journal of the American Geriatrics Society 1997;45:313–20.
[3] Hausdorff JM, Nelson ME, Kaliton D, Layne JE, Bernstein MJ, Nuernberger A, et al. Etiology and modification of gait instability in older adults: a randomized controlled trial of exercise. Journal of Applied Physiology 2001;90:2117–29.
[4] Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. Journal of the Neurological Sciences 2003;212: 47–53.
[5] Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. Journal of the American Geriatrics Society 2003;51: 1633–7.
[6] Alexander NB. Postural control in older adults. Journal of the American Geriatrics Society 1994;42:93–108.
[7] Schultz AB. Mobility impairment in the elderly: challenges for biomechanics research. Journal of Biomechanics 1992;25:519–28.
[8] Ishii K, Senda M, Toyama H, Oda K, Ishii S, Ishiwata K, et al. Brain function associated with bipedal gait: a PET study. Journal of Cerebral Blood Flow and Metabolism Official Journal of the International Society of Cerebral Blood Flow and Metabolism 1993;13:S521.
[9] Mishina M, Senda M, Ishii K, Ohyama M, Kitamura S, Katayama Y. Cerebellar activation during ataxic gait in olivopontocerebellar atrophy: a PET study. Acta Neurologica Scandinavica 1999;100:369–76.
[10] la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M, et al. Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. Neuroimage 2010;50:1589–98.
[11] Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, et al. Brain functional activity during gait in normal subjects: a SPECT study. Neuroscience Letters 1997;228:183–6.
[12] Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, et al. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 1999;122(Pt 7):1271–82.
[13] Iseki K, Hanakawa T, Hashikawa K, Tomimoto H, Nankaku M, Yamauchi H, et al. Gait disturbance associated with white matter changes: a gait analysis and blood flow study. Neuroimage 2010;49:1659–66.
[14] Matsas A, Taylor N, McBurney H. Knee joint kinematics from familiarised treadmill walking can be generalised to overground walking in young unimpaired subjects. Gait and Posture 2000;11:46–53.
[15] Savelberg HH, Vorstenbosch MA, Kamman EH, van de Weijer JG, Schambardt HC. Intra-stride belt-speed variation affects treadmill locomotion. Gait and Posture 1998;7:26–34.
[16] van Ingen Schenau GJ. Some fundamental aspects of the biomechanics of overground versus treadmill locomotion. Medicine and Science in Sports and Exercise 1980;12:257–61.
[17] Taylor NF, Evans OM, Goldie PA. Angular movements of the lumbar spine and pelvis can be reliably measured after 4 minutes of treadmill walking. Clinical Biomechanics (Bristol Avon) 1996;11:484–6.
[18] Wass E, Taylor NF, Matsas A. Familiarisation to treadmill walking in unimpaired older people. Gait and Posture 2005;21:72–9.
[19] Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Human Brain Mapping 1995;3: 165–89.
[20] Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 2002;15: 870–8.
[21] Sadato N, Tsuchida T, Nakaumra S, Waki A, Uematsu H, Takahashi N, et al. Noninvasive estimation of the net influx constant using the standardized uptake value for quantification of FDG uptake of tumours. European Journal of Nuclear Medicine 1998;25:559–64.
[22] Oishi K, Faria A, van Zijl PC, Mori S. MRI atlas of human white matter. Burlington: Elsevier; 2011.
[23] Hanakawa T. Neuroimaging of standing and walking: special emphasis on Parkinsonian gait. Parkinsonism and Related Disorders 2006;12:S70–5.
[24] Shimansky Y, Wang JJ, Bauer RA, Bracha V, Bloedel JR. On-line compensation for perturbations of a reaching movement is cerebellar dependent: support for the task dependency hypothesis. Experimental Brain Research Experimentelle Hirnforschung Experimentation Cerebrale 2004;155:156–72.
[25] Bower JM. Control of sensory data acquisition. International Review of Neurobiology 1997;41:489–513.
[26] Marigold DS, Patla AE. Visual information from the lower visual field is important for walking across multi-surface terrain. Experimental Brain Research Experimentelle Hirnforschung Experimentation Cerebrale 2008;188:23–31.
[27] Torres-Oviedo G, Bastian AJ. Seeing is believing: effects of visual contextual cues on learning and transfer of locomotor adaptation. The Journal of Neuroscience The Official Journal of the Society for Neuroscience 2010;30:17015–22.
[28] Frith CD, Friston K, Liddle PF, Frackowiak RS. Willed action and the prefrontal cortex in man: a study with PET. Proceedings Biological Sciences/The Royal Society 1991;244:241–6.
[29] Decety J, Perani D, Jeannerod M, Bettinardi V, Tadary B, Woods R, et al. Mapping motor representations with positron emission tomography. Nature 1994;371:600–2.
[30] Zimmerman ME, Lipton RB, Pan JW, Hetherington HP, Verghese J. MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults. Brain Research 2009;1291:73–81.
[31] Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: a PET study. Human Brain Mapping 2003;19:47–62.
[32] Beauchet O, Kressig RW, Najafi B, Aminian K, Dubost V, Mourey F. Age-related decline of gait control under a dual-task condition. Journal of the American Geriatrics Society 2003;51:1187–8.

Please cite this article in press as: Shimada H, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture (2012), http://dx.doi.org/10.1016/j.gaitpost.2012.11.008

Geriatrics Gerontology INTERNATIONAL 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2012

ORIGINAL ARTICLE

Relationship between dual-task performance and neurocognitive measures in older adults with mild cognitive impairment

Hyuma Makizako,[1,4] Takehiko Doi,[1] Hiroyuki Shimada,[1] Daisuke Yoshida,[1] Yuko Takayama[3] and Takao Suzuki[2]

[1]Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, [2]National Institute of Longevity Science, National Center for Geriatrics and Gerontology, [3]Department of Speech Therapy, Ukai Rehabilitation Hospital, Aichi, and [4]Japan Society for the Promotion of Science, Tokyo, Japan

Aim: The aim of this study was to examine the relationship between dual-task performance and neurocognitive measures in community-dwelling older people with mild cognitive impairment (MCI).

Methods: A total of 98 subjects (mean age 74.8 years, 52.0% female) participated in the study. We compared 36 participants with amnestic MCI (aMCI) with 62 participants with non-amnestic MCI (non-aMCI) on dual-task performance as measured by reaction time responses. The relationships between dual-task performance and multiple domains of neurocognitive functions, including general cognitive function, visual memory, working memory, executive function and processing speed, were examined.

Results: Although there were no statistically significant group differences in simple reaction times ($P = 0.734$), the aMCI group showed significantly slower dual-task reaction times than the non-aMCI group ($P = 0.012$). Using multiple regression analysis, we found that there was a significant relationship between executive function and dual-task reaction times ($\beta = 0.298$, $P = 0.006$).

Conclusion: These results showed that aMCI subjects showed a specific deficit in dual-task performance compared with non-aMCI subjects, and poor dual-task performance was associated with declines in executive function in older people with MCI. Future longitudinal and interventional studies should investigate the use of dual-task testing with varying levels of cognitive demand in older adults at risk of dementia. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: dual-task, executive functioning, mild cognitive impairment, reaction time.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, and mild cognitive impairment (MCI) is associated with an elevated risk of developing AD.[1] Along with amnesia, a decline of attentional control of executive function is one of the earliest symptoms of dementia.[2]

Dual-task performance can be measured while a person carried out two concurrent tasks, and reflects divided attention, considered an important executive function.[3,4] Several studies have reported an association between AD and impairments in dual task performance, indicating a specific deficit of dual-task functioning in the disease.[5–8] Additionally, MCI patients might also show specific deficits in dual-task performance, as impaired executive function in MCI plays a crucial role in the conversion to AD.[9,10] In contrast, a previous study reported that dual-task performance has been found to have lower sensitivity in discriminating between controls, MCI patients and AD patients, whereas dual-task performance during walking in MCI patients resembled that of AD patients but not control subjects.[11] Thus, it is currently unclear whether poor dual-task performance is related to decline in neurocognitive functions among older adults with MCI.

Sheridan *et al.* suggested that dual-task-related performance changes were correlated with executive and neuropsychological function in patients with AD.[12] In MCI patients, neuropsychological functioning of working memory was associated with impaired dual-task performance.[13] However, few studies of dual-task performance and multiple domains of neurocognitive

Accepted for publication 6 May 2012.

Correspondence: Dr Hyuma Makizako PhD, Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan. Email: makizako@ncgg.go.jp

functioning have focused on older adults at risk of developing dementia, especially those with MCI.[14] If dual-task performance is closely related to specific domains of neurocognitive function, it might provide an objective measure of the effectiveness of new intervention strategies in older adults with cognitive decline.

In the present study, the dual-task reaction time (RT) paradigm[15–17] was used to assess attentional demands, because we considered that measurements of RT were simple and easy to understand in older adults (including MCI patients), even in a clinical setting. It is currently unclear whether neuropsychological measures in MCI patients are correlated with dual-task performance. The current study sought to assess attention-related performance using RT in a dual-task, and to examine the relationships between dual-task performance and multiple domains of neurocognitive functions, including general cognitive function, visual memory, working memory, executive function and processing speed in community-dwelling older adults with MCI. Furthermore, we compared amnestic MCI (aMCI) and non-amnestic MCI (non-aMCI) participants, because aMCI is likely to progress to AD.[18,19]

Methods

Participants

Participants were recruited from two volunteer databases ($n = 1543$), which included elderly individuals aged 65 years and older, selected either by random sampling or when they attended a health check in Obu, Japan. For inclusion, all participants were required to meet the definition of MCI using the Petersen criteria.[20] A total of 126 older adults that had a clinical dementia rating (CDR) of 0.5 or a memory complaint were assessed for 2 days by neuropsychological tests, physical performance tests and face-to-face interviews. Other criteria for inclusion into the present study required that the participant was aged 65 years or older, living independently in the community (i.e. no impairment of activities of daily living) and Japanese speaking, with sufficient hearing and visual acuity to participate in the examinations, and general cognitive functioning (Mini-Mental State Examination [MMSE][21] scores between 24 and 30). Exclusion criteria included a history of major psychiatric illness, other serious neurological or musculoskeletal diagnoses, and clinical depression. Finally, 98 participants with MCI (mean age 74.8 years, male/female 47/51, mean education 10.7 years) satisfied the inclusion criteria, and their data were analyzed in the present study. Participants were classified into aMCI and non-aMCI groups. Of the 98 participants, 36 were included in the aMCI group, because they showed memory impairments that were objectively established through education-adjusted scores on the Wechsler memory Scale – Revised (WMS-R) Logical Memory II.[22,23] The non-aMCI participants ($n = 62$) did not show objective memory impairment as measured by education-adjusted scores on the WMS-R Logical Memory II scale. However, they had a CDR of 0.5 or a memory complaint, and they met the threshold for an MCI diagnosis using the Petersen criteria (not normal for age, not demented, cognitive decline and essentially normal functional activities).[20] The present study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants provided written informed consent.

Dual-task performance measures

We measured RT under two conditions of cognitive demand of attentional resources: a low demand (simple-task) condition and a high demand (dual-task) condition. Simple RT was measured by pushing a handheld button as quickly as possible in response to a visual stimulus (a bright red light). In addition, each participant's RT were measured in the dual-task condition while carrying out a concurrent cognitive task. This was defined as dual-task performance. First, participants' simple RT were measured in a quiet standing position. RT were defined as the temporal interval between the presentation of a visual stimulus and the onset of a pushing response. During simple RT measurement, participants were asked to push a handheld button as quickly as possible after the presentation of a red light stimulus composed of seven small lights (each with a diameter of 5 mm). The experimenter confirmed that participants stood quietly, then issued the verbal command, "ready", as a verbal starting signal before RT measurement. The visual starting signal and verbal command preceded each trial. RT responses were measured by a time counter (PTS-010; DKH, Itabashi, Japan) and displayed in milliseconds (ms). In the dual-task condition, participants were asked to count backward to 1, starting from 100, 90, 80, 70, 60, 50, 40, 30 and 20 (selected randomly). They were asked to carry out RT responses during the dual-task with cognitive demands. RT were measured three times for each participant in both conditions. In both task conditions, participants practiced once before data collection commenced. In each task condition, the average RT over three trials was submitted to statistical analysis.

Neurocognitive assessments

Participants underwent comprehensive neurocognitive evaluation, including measures of general cognitive function, visual memory, working memory and executive function. The neurocognitive assessment had a standardized format and was administered by licensed and well-trained clinical speech therapists.

General cognitive function was examined using the Japanese version of MMSE.[24] The Rey-Osterrieth Complex Figure Test (ROCF)[25] and the verbal digit span test[26] were used to assess visual and working memory, respectively. The ROCF is a widely-used instrument for assessing visual memory. The participant was requested to copy the ROCF figure and reproduce it after a 30-min delay. We assessed working memory using the verbal digit span test.[26] The digit span test includes both forwards and backwards conditions, in which a participant is given a number sequence and is asked either to repeat it as it was given or to repeat it in the reverse order. The test includes two sequences of each length and testing ceases when the participant fails to recollect any two with the same length. The score recorded, ranging from 0 to 14, is the number of successful sequences. The difference between the verbal digits forward test score and the verbal digits backward test score was used as an index of the central executive component of working memory. Smaller difference scores indicate better working memory.

We used the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III (WAIS-III)[26] and Trail Making Test (TMT)[27] to assess processing speed and executive function. In the Digit Symbol-Coding test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score is the number of correct symbols drawn within 120 s, and a maximum score of 133. Higher scores indicate better processing speed. The TMT consists of two parts, A and B. Part A requires the participant to draw a line as rapidly as possible joining consecutive numbers (1–25). In Part B, the participant must draw a line alternately between consecutive numbers and letters (1-A-2-B-12-L). In the Japanese version of the TMT-B, letters from the Roman alphabet are exchanged for Kana characters. We recorded the amount of time (in seconds) it took to complete each task. We calculated the difference between Part B and Part A completion time (delta TMT). Smaller difference scores indicate better executive function.

Statistical analyses

Student's *t*-tests or χ^2-tests were used to compare the demographic, reaction time responses, and neurocognitive functions between the aMCI and non-aMCI groups. Pearson's correlation coefficients were used to quantify the bivariate associations between RT during single-task and dual-task conditions, and neurocognitive measures. While controlling for the possible confounding influences of age-related changes and length of education in reaction times during simple-task and dual-task conditions, standardized β-values were calculated using linear regression analysis to assess the relationships between the variables. Multiple linear regression models were constructed to determine the independent association of neurocognitive measures using simple RT and dual-task RT. We calculated the R^2- and standardized β-values for each regression model. The statistical analyses were carried out using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). The level of statistical significance was set at 0.05 for all analyses.

Results

Table 1 summarizes the characteristics of the participants in the aMCI and non-aMCI groups. There were no statistically significant between-group differences in age, sex, hypertension, diabetes mellitus, medication and clinical depression status. The participants in the aMCI group had significantly lower ROCF scores compared with the non-aMCI group ($P = 0.008$). There were no statistically significant between-group differences in other neurocognitive measurements. Although there were no statistically significant group differences in simple RT ($P = 0.734$), the participants in the aMCI group had significantly longer dual-task RT than the participants in the non-aMCI group ($P = 0.012$).

Table 2 shows the correlation coefficients of the relationships between RT during the single-task and dual-task conditions and neurocognitive measures, and shows the standardized β-values derived from the linear regression analyses after controlling for age and education. Simple RT were significantly correlated with Digit Symbol-Coding test scores ($r = -0.282$, $P = 0.027$) in the participants in the non-aMCI group, but this was not statistically significant after controlling for age and education ($\beta = -0.111$, $P = 0.476$). Dual-task RT were significantly correlated with Digit Symbol-Coding scores in the participants in both groups (non-aMCI $r = -0.386$, $P < 0.001$; aMCI $r = -0.402$, $P = 0.015$). These relationships were no longer significant in the participants in the aMCI group after controlling for age and education ($\beta = -0.163$, $P = 0.374$), but remained significant in the participants in the non-aMCI group ($\beta = -0.363$, $P = 0.021$). Additionally, dual-task RT were associated with ROCF scores ($r = -0.317$, $P = 0.012$) and delta TMT (times of TMT-B minus TMT-A; $r = -0.429$, $P = 0.001$) in the participants in the non-aMCI group, and these relationships were still significant after controlling for age and education (ROCF $\beta = -0.275$, $P = 0.035$, delta TMT $\beta = 0.380$, $P = 0.003$).

Table 3 shows the results of the multiple regression models that were used to independently determine the associations between neurocognitive functions and simple RT and dual-task RT. The group (aMCI), age, education, MMSE, ROCF, delta TMT, scores of the Digit Span Forward–Backward and Digit Symbol-Coding score parameters accounted for 13.0% of the variance in simple RT. Using multiple regression

Table 1 Characteristics, reaction times, and neurocognitive functions in the participants in the non-amnestic mild cognitive impairment and amnestic mild cognitive impairment groups

Characteristics	non-aMCI ($n = 62$)	aMCI ($n = 36$)	P-value
Age (years)	74.0 (6.1)	76.2 (7.2)	0.119
Sex, n (%)			
Male	26 (41.6)	21 (58.3)	0.117
Female	36 (58.1)	15 (41.7)	
Diagnosis, n (%)			
Hypertension†	31 (50.8)	13 (36.1)	0.160
Diabetes mellitus	6 (9.7)	5 (13.9)	0.524
Medication† (three or more)	22 (36.1)	17 (50.0)	0.186
GDS (score)	3.0 (2.3)	2.9 (2.4)	0.857
Reaction time/dual-task performance			
Simple reaction time (ms)	257.6 (45.9)	260.8 (41.7)	0.734
Dual-task reaction time (ms)	398.5 (117.2)	473.5 (171.2)	0.012
General cognitive function			
MMSE (score)	27.0 (2.0)	27.1 (1.8)	0.858
Visual memory			
ROCF‡ (score)	16.4 (5.7)	12.8 (6.5)	0.008
Working memory			
Digit Span Forward–Backward (score)	2.5 (2.3)	2.8 (1.9)	0.458
Executive function			
Trail Making Test Part B–Part A‡ (s)	52.8 (86.4)	73.6 (75.5)	0.245
Processing speed			
Digit Symbol-Coding (score)	47.6 (15.7)	47.3 (15.2)	0.934

The data are expressed as the mean (SD) score unless otherwise indicated. Significance was arbitrated at $P < 0.05$ using the unpaired Student's t-test or χ^2-test (for sex and diagnosis). †One participant in the non-amnestic mild cognitive impairment (aMCI) group did not report whether he or she had hypertension. One participant in the non-aMCI group and two participants in the aMCI group could not describe their current medication. ‡One participant in the aMCI group did not complete the Rey-Osterrieth Complex Figure Test (ROCF). Two participants in the aMCI group and two participants in the non-aMCI group did not complete the Trail Making Tests. GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

analysis to examine dual-task RT, we found a R^2-value of 30.5% and a standardized β-value of 0.298 for executive function assessed by the delta TMT ($P = 0.006$).

Discussion

The present results examined the relationships between neurocognitive measures and dual-task performance (measured by RT to visual stimuli) in older adults with MCI. The aMCI participants showed specific deficits in dual-task performance compared with the non-aMCI participants, and low dual-task performance was associated with declines in executive function in older adults with MCI.

A large number of previous studies reported a relationship between dual-task performance and cognitive function, particularly attentional capacity[28] and executive function.[29–32] Executive function plays an important role in older adults' ability to effectively adapt to complex environments and to adequately allocate the attentional resources necessary for successfully completing a given task.[28,29,33,34] Additionally, executive function is an important mediator of memory function in older adults suffering from age-related functional decline,[35] and MCI.[36] In the present study, we found that increased attentional costs under dual-task conditions were related to reduced executive function in older people with MCI. These findings are in accord with the results of previous studies showing a relationship between dual-task costs and neurocognitive functions. However, the relationship between the Digit Symbol-Coding scores, the delta TMT and dual-task RT in the aMCI group did not remain after controlling for age and education. Our data could not provide a definite association between dual-task performance and neurocognitive functions in the aMCI participants.

Dual-task performance reflects divided attention and is considered an important executive function.[3,4] Therefore, it would be expected that participants with non-aMCI showed lower dual-task performance based on

Table 2 Bivariate correlations between reaction times and neurocognitive functions

Outcome measure	Non-aMCI (n = 62)				aMCI (n = 36)			
	Simple-task RT		Dual-task RT		Simple-task RT		Dual-task RT	
	Simple-Correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)
MMSE	−0.089	0.006	−0.102	−0.035	−0.221	−0.177	−0.231	−0.083
ROCF	−0.084	0.004	−0.317*	−0.275*	−0.081	−0.038	−0.180	0.027
Digit Span Forward–Backward	−0.175	−0.215	−1.000	−0.130	−0.218	−0.191	−0.066	0.105
Trail Making Test Part B–Part A	0.251	0.171	0.429**	0.380**	0.025	0.043	0.370*	0.229
Digit Symbol-Coding	−0.282*	−0.111	−0.386**	−0.363*	−0.135	−0.042	−0.402*	−0.163

*P < 0.05, **P < 0.01. aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth Complex Figure Test; RT, reaction time.

criteria for classification of groups. Contrary to expectations, the aMCI group showed significantly lower dual-task performance than the non-aMCI group in the present study. The aMCI group included not only participants with amnestic single domain MCI subtype (showing a memory deficit), but also those with amnestic multiple domain MCI subtype (showing deficits of memory in addition to other domains). The results of the present study showed that there were no statistically significant between-group differences in other domains, such as executive function and processing speed. The present findings might suggest that older adults showing deficits of multiple domains including memory deficits exhibit decline of dual-task performance compared with those without memory deficits. Unfortunately, it was difficult to analyze using detailed subtype categories of MCI, because the sample size was small. Clarifying these problems by future research with a large sample size would be required.

The present findings indirectly corroborate a number of other studies, showing that patients with MCI experienced high dual-task costs.[11,37,38] Previous studies reported that dual-task-related changes in performance were greater in patients with MCI compared with cognitively normal age-matched controls,[37,38] and that dual-task performance during walking was significantly impaired in MCI patients.[11] However, the current findings conflict with the results of some previous studies. One study reported that there were no differences in dual-task performance between aMCI patients and controls.[14] Additionally, in a study using the Talking While Walking assessment as a dual-task test, no differences in dual-task performance were reported between MCI and healthy participants, although participants with AD showed greater performance changes between single task and dual-task conditions compared with healthy participants.[39] Previous results regarding the relationships between cognitive status and dual-task decrements among older adults at risk of dementia have not been consistent, particularly for MCI patients.[6,7,40] Studies investigating the relationship between dual-task performance and cognitive status have tended to focus on patients with AD, who generally show impaired dual-task performance. AD patients also show difficulties in dual-task performance requiring the completion of a cognitive task while walking.[7,40] These results suggest that the ability to divide attention, in combination with a cognitive task, is reduced among patients with AD. Thus, decreased dual-task performance might be considered an early symptom of AD. Although the present study included only MCI patients, our findings provide indirect evidence that poor dual-task performance with cognitive demand might be related to impaired executive functioning in older adults with MCI.

Executive functions are higher order cognitive processes that control, integrate, organize and maintain

Table 3 Multiple linear regression model summary for simple reaction time and dual-task reaction time experiments

Independent Variable	Simple reaction time (ms)			Dual-task reaction time (ms)		
	R^2	Standardized β	*P*-value	R^2	Standardized β	*P*-value
Model	0.130			0.305		
Group (aMCI)		0.028	0.797		0.184	0.061
Age		0.153	0.233		0.211	0.067
Education		−0.155	0.175		−0.073	0.470
MMSE		−0.059	0.213		0.052	0.622
ROCF		0.051	0.661		−0.107	0.302
Digit Span Forward–Backward		−0.216	0.038		−0.071	0.433
Trail Making Test Part B–Part A		0.137	0.246		0.298	0.006
Digit Symbol-Coding		0.030	0.829		−0.063	0.616

Dependent variable: simple reaction time (ms) and dual-task reaction time (ms). aMCI, amnestic mild cognitive impairment; MMSE, Mini Mental State Examination; ROCF, Rey-Osterrieth Complex Figure Test.

other cognitive abilities.[41] Associations between physical performance and executive function were shown in community-dwelling older adults.[42] Similarly, these associations were confirmed in older adults with MCI.[43] The beneficial effects of physical exercise have been shown in older adults with MCI.[44,45] It might be clinically important to improve executive function among older adults with MCI, because deficits in executive function strongly predict conversion to AD.[46] The results of the present study support the hypothesis that interventions that include the dual-task paradigm might be effective for increasing executive function among older adults with MCI.

Several limitations of the current study should be considered. First, we used cross-sectional data, meaning causal relationships could not be assessed. For lack of longitudinal cognitive changes, the results of the present study fail to indicate that measurements of dual-task performance might be useful as a prognostic measure of cognitive decline. Second, the absence of a large sample size limits the conclusions that can be drawn. The sample size of aMCI participants was markedly smaller than the non-aMCI participants, limiting the interpretation of the results. Third, we could not assess whether the participants correctly and rapidly participated in the concurrent task (counting backwards) that relied on increasing demands of the dual-task. In the present study, it was important for the participants to divide their attention during the dual-task conditions. Although participants in both groups showed significantly longer RT under the dual-task conditions compared with the simple-task conditions, some participants would divide the minimum attention required to complete the concurrent tasks. Finally, our study cohort did not contain healthy subjects or AD patients, meaning that we could not examine the association between dual-task performance and the risk of cognitive decline in AD-related processes. In addition, analysis of neuroimaging data was not included in the present study. MCI represents a complex heterogenous condition, including degenerative and vascular brain pathologies. Brain conditions potentially affect cognitive decline including dual-task performance.[47]

In conclusion, we found that aMCI patients showed deficits in dual-task performance compared with non-aMCI participants, and poor dual-task performance was associated with declines in executive function in older people with MCI. Future longitudinal and interventional studies should investigate the use of dual-task testing with varying levels of cognitive demand in subjects at risk of dementia, and analyses of imaging data, because these studies might elucidate the factors that lead to the conversion to AD from MCI.

Acknowledgments

This work was supported in part by a grant from the Japanese Ministry of Health, Labour and Welfare (Project for optimizing long-term care, B-3) and a Grant-in-Aid for JSPS Fellows (23–9862) from the Japan Society for the Promotion of Science.

Disclosure statement

There are no financial and personal relationships with other people or organizations that may lead to a conflict of interest.

References

1 Petersen RC, Doody R, Kurz A *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; 58: 1985–1992.

2 Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease. A critical review. *Brain* 1999; **122** (Pt 3): 383–404.
3 Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. Attentional control in Alzheimer's disease. *Brain* 2001; **124**: 1492–1508.
4 Logie RH, Cocchini G, Delia Sala S, Baddeley AD. Is there a specific executive capacity for dual task coordination? Evidence from Alzheimer's disease. *Neuropsychology* 2004; **18**: 504–513.
5 Baddeley AD, Bressi S, Della Sala S, Logie R, Spinnler H. The decline of working memory in Alzheimer's disease. A longitudinal study. *Brain* 1991; **114** (Pt 6): 2521–2542.
6 MacPherson SE, Della Sala S, Logie RH, Wilcock GK. Specific AD impairment in concurrent performance of two memory tasks. *Cortex* 2007; **43**: 858–865.
7 Pettersson AF, Olsson E, Wahlund LO. Motor function in subjects with mild cognitive impairment and early Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005; **19**: 299–304.
8 Sala SD, Logie RH. Theoretical and practical implications of dual-task performance in Alzheimer's disease. *Brain* 2001; **124**: 1479–1481.
9 Ewers M, Walsh C, Trojanowski JQ *et al.* Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiol Aging* 2012; **33**: 1203–1214.
10 Rozzini L, Chilovi BV, Conti M *et al.* Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. *Int J Geriatr Psychiatry* 2007; **22**: 1217–1222.
11 Gillain S, Warzee E, Lekeu F *et al.* The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Ann Phys Rehabil Med* 2009; **52**: 453–474.
12 Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J Am Geriatr Soc* 2003; **51**: 1633–1637.
13 Montero-Odasso M, Bergman H, Phillips NA, Wong CH, Sourial N, Chertkow H. Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory. *BMC Geriatr* 2009; **9**: 41.
14 Lonie JA, Tierney KM, Herrmann LL *et al.* Dual task performance in early Alzheimer's disease, amnestic mild cognitive impairment and depression. *Psychol Med* 2009; **39**: 23–31.
15 Bardy BG, Laurent M. Visual cues and attention demand in locomotor positioning. *Percept Mot Skills* 1991; **72**: 915–926.
16 Lajoie Y, Teasdale N, Bard C, Fleury M. Attentional demands for static and dynamic equilibrium. *Exp Brain Res* 1993; **97**: 139–144.
17 Sparrow WA, Bradshaw EJ, Lamoureux E, Tirosh O. Ageing effects on the attention demands of walking. *Hum Mov Sci* 2002; **21**: 961–972.
18 Gauthier S, Reisberg B, Zaudig M *et al.* Mild cognitive impairment. *Lancet* 2006; **367**: 1262–1270.
19 Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on mild cognitive impairment. *J Intern Med* 2004; **256**: 240–246.
20 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; **256**: 183–194.
21 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
22 Iwatsubo T. Japanese Alzheimer's disease neuroimaging initiative: present status and future. *Alzheimers Dement* 2010; **6**: 297–299.
23 Wechsler D. *Wechsler Memory Scale-revised Manual.* San Antonio, TX: The Psychological Corporation, 1987.
24 Mori E, Mitani Y, Yamadori A. Usefulness of a Japanese version of the mini-mental state test in neurological patients. *Jpn J Neuropsychol* 1985; **1**: 2–10.
25 Meyers J, Meyers K. *Rey Complex Figure Test and Recognition Trial. Professional Manual.* Odessa, FL: Psychological Assessment Resources, 1995.
26 Wechsler D. *Wechsler Adult Intelligence Scale-revised.* New York: Psychological Corporation, 1981.
27 Lezak M. *Neuropsychological Assessment,* 4th edn. New York: Oxford University Press, 2004.
28 Allali G, Assal F, Kressig RW, Dubost V, Herrmann FR, Beauchet O. Impact of impaired executive function on gait stability. *Dement Geriatr Cogn Disord* 2008; **26**: 364–369.
29 Ble A, Volpato S, Zuliani G *et al.* Executive function correlates with walking speed in older persons: the INCHIANTI study. *J Am Geriatr Soc* 2005; **53**: 410–415.
30 Coppin AK, Shumway-Cook A, Saczynski JS *et al.* Association of executive function and performance of dual-task physical tests among older adults: analyses from the InChianti study. *Age Ageing* 2006; **35**: 619–624.
31 Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N. Dual-task decrements in gait: contributing factors among healthy older adults. *J Gerontol A Biol Sci Med Sci* 2008; **63**: 1335–1343.
32 Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord* 2006; **21**: 950–957.
33 Carlson MC, Fried LP, Xue QL, Bandeen-Roche K, Zeger SL, Brandt J. Association between executive attention and physical functional performance in community-dwelling older women. *J Gerontol B Psychol Sci Soc Sci* 1999; **54**: S262–S270.
34 Royall DR, Lauterbach EC, Cummings JL *et al.* Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* 2002; **14**: 377–405.
35 Salthouse TA. Aging and measures of processing speed. *Biol Psychol* 2000; **54**: 35–54.
36 Chang YL, Jacobson MW, Fennema-Notestine C *et al.* Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. *Cereb Cortex* 2010; **20**: 1305–1313.
37 Dannhauser TM, Walker Z, Stevens T, Lee L, Seal M, Shergill SS. The functional anatomy of divided attention in amnestic mild cognitive impairment. *Brain* 2005; **128**: 1418–1427.
38 Maquet D, Lekeu F, Warzee E *et al.* Gait analysis in elderly adult patients with mild cognitive impairment and patients with mild Alzheimer's disease: simple versus dual task: a preliminary report. *Clin Physiol Funct Imaging* 2010; **30**: 51–56.
39 Pettersson AF, Olsson E, Wahlund LO. Effect of divided attention on gait in subjects with and without cognitive impairment. *J Geriatr Psychiatry Neurol* 2007; **20**: 58–62.

40 Camicioli R, Howieson D, Lehman S, Kaye J. Talking while walking: the effect of a dual task in aging and Alzheimer's disease. *Neurology* 1997; **48**: 955–958.
41 Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. *Psychol Res* 2000; **63**: 289–298.
42 Hirota C, Watanabe M, Sun W *et al.* Association between the trail making test and physical performance in elderly Japanese. *Geriatr Gerontol Int* 2010; **10**: 40–47.
43 McGough EL, Kelly VE, Logsdon RG *et al.* Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test. *Phys Ther* 2011; **91**: 1198–1207.
44 Baker LD, Frank LL, Foster-Schubert K *et al.* Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010; **67**: 71–79.
45 Scherder EJ, Van Paasschen J, Deijen JB *et al.* Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging Ment Health* 2005; **9**: 272–280.
46 Tabert MH, Manly JJ, Liu X *et al.* Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006; **63**: 916–924.
47 Nadkarni NK, Levine B, McIlroy WE, Black SE. Impact of subcortical hyperintensities on dual-tasking in Alzheimer disease and aging. *Alzheimer Dis Assoc Disord* 2012; **26**: 28–35.

The relationship between atrophy of the medial temporal area and daily activities in older adults with mild cognitive impairment

Daisuke Yoshida[1,2], Hiroyuki Shimada[1], Hyuma Makizako[1], Takehiko Doi[1], Kengo Ito[3], Takashi Kato[3], Hiroshi Shimokata[4], Yukihiko Washimi[5], Hidetoshi Endo[6] and Takao Suzuki[7]

[1]Section for Health Promotion, Department of Health and Medical Care, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, [2]Japan Foundation for Aging and Health, [3]Department of Clinical and Experimental Neuroimaging, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, [4]Department for Development of Preventive Medicine, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, [5]Department of Cognitive Disorders, Hospital of National Center for Geriatrics and Gerontology, [6]Department of Comprehensive Geriatric Medicine, Hospital of National Center for Geriatrics and Gerontology, [7]Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan

ABSTRACT. ***Background and aims:*** *Many studies have suggested that social network, leisure activity, and physical activity can have protective effects against dementia and Alzheimer's disease. However, previous studies have not examined the relationship between daily activities and brain atrophy in older adults. This study aimed to explore what kind of daily activities were associated with atrophy of the medial temporal area including the entorhinal cortex (MTA-ERC) in older adults.* ***Methods:*** *In total, 122 older adults (aged 65 and over) with subjective memory complaints or a Clinical Dementia Rating of 0.5 underwent magnetic resonance imaging, and MTA-ERC atrophy was assessed by the voxel-based morphometry method. Based on magnetic resonance imaging data, the subjects were divided into atrophy and non-atrophy groups. Daily activities were assessed using a 20-item questionnaire (e.g., instrumental activities of daily living, social activities), and we compared activity participation between the groups.* ***Results:*** *The atrophy group (n=37) showed significantly lower participation in 4 out of 20 activity items (cleaning, intellectual activity, culture lessons, and using a personal computer) than the non-atrophy group (n=85). Summed scores of these 4 items (range from 0 to 4) were significantly associated with MTA-ERC atrophy even after adjustment for age, sex, education status, and Mini-Mental State Examination score.* ***Conclusions:*** *In conclusion, MTA-ERC atrophy was associated with cognitive activities or household-related activities requiring planning.*

(Aging Clin Exp Res 2012; 24: ###-###)

INTRODUCTION

Memory impairment is the earliest symptom of Alzheimer's disease (AD) in most patients (1), and brain atrophy of the medial temporal region is observed in those patients (2). The medial temporal lobe has long been known to play a critical role in memory (3). In a recent review, the most reliable and well-documented finding was an association between impaired verbal memory and medial temporal lobe atrophy that is particularly robust for the hippocampal and entorhinal regions (3). Moreover, hippocampal and entorhinal cortex atrophy have been shown to predict conversion to AD (1, 4, 5). It is important to assess atrophy of the medial temporal areas (MTA), especially the hippocampus and entorhinal cortex for understanding AD pathology.

Many studies have suggested that social network, leisure activity, and physical activity have protective effects against dementia and AD (6-13). For example, a popu-

Key words: Alzheimer's disease, magnetic resonance imaging, brain atrophy, activities of daily living.

Correspondence: Daisuke Yoshida, Section for Health Promotion, Department of Health and Medical Care, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi, 474-8511, Japan. E-mail: yoshida@ncgg.go.jp

Received April 13, 2011; accepted in revised form February 24, 2012.

First published ahead of print March 6, 2012 as DOI: 10.3275/8297