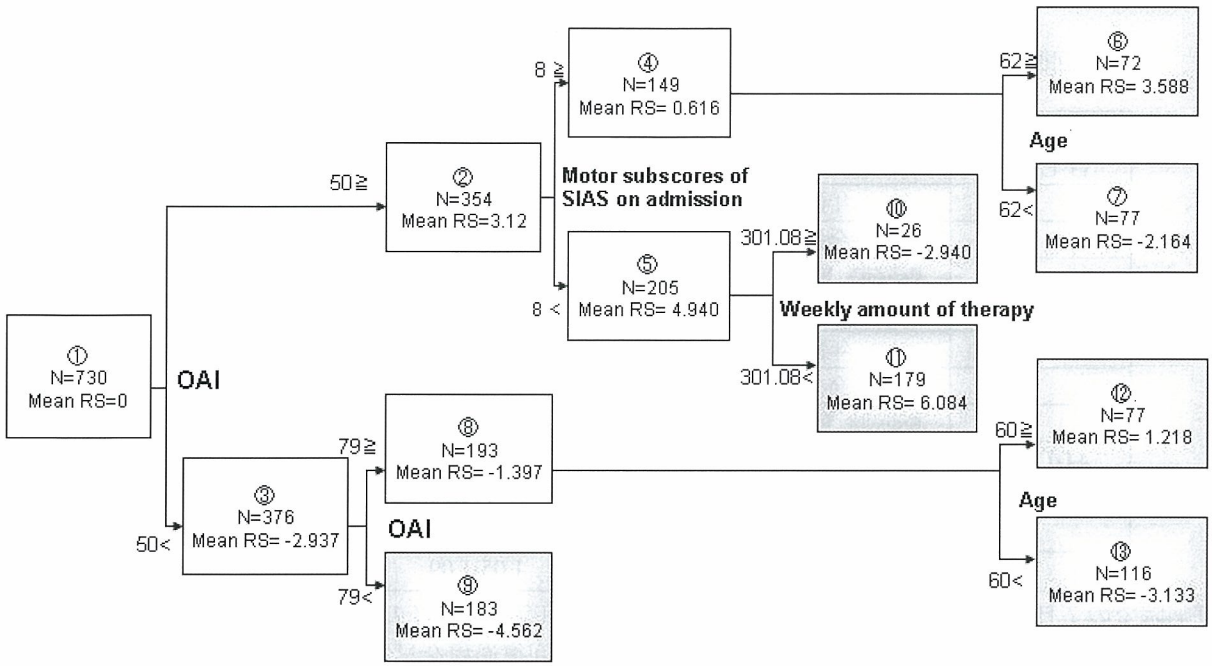
I-3. 脳卒中リハにおける訓練量増加の運動機能改善効果

図　回帰樹木法による解析



訓練量依存性の改善が見られたのは 50 日以内に回復期リハを開始し、かつ入院時の Stroke Impairment Assessment set (SIAS)の運動評価が 8 点以上(満点 25)の群のみであった。したがって回復期リハにおける訓練量依存性の機能改善効果は発症後早期かつ機能障害が重篤でない群において最も期待されることが示唆された。

II-1. 上肢近位筋麻痺の臨床的特徴

図　上肢近位筋優位麻痺例(P)と遠位筋優位麻痺例(D)の病巣分布

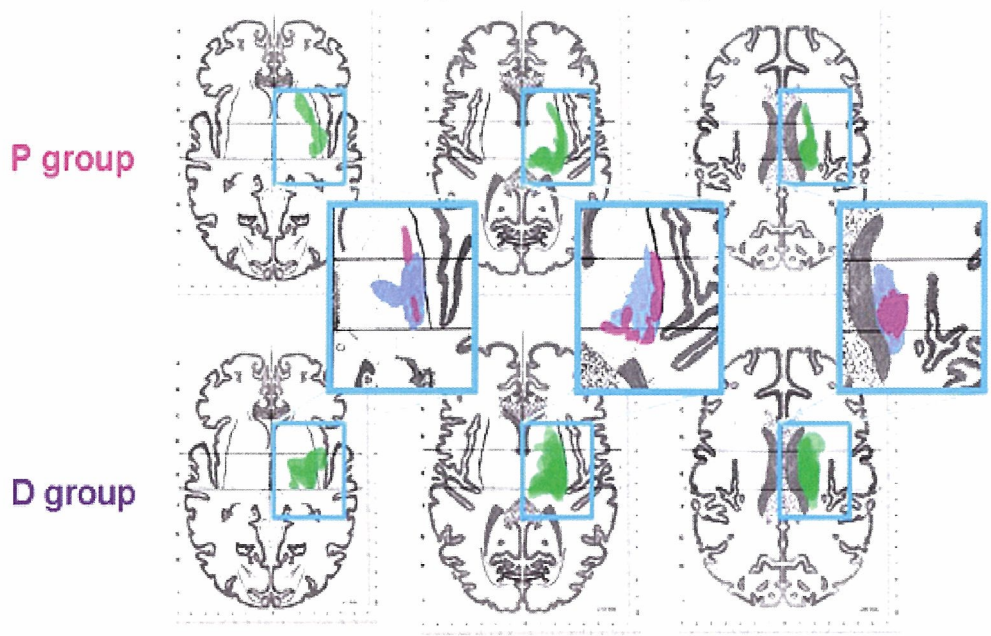


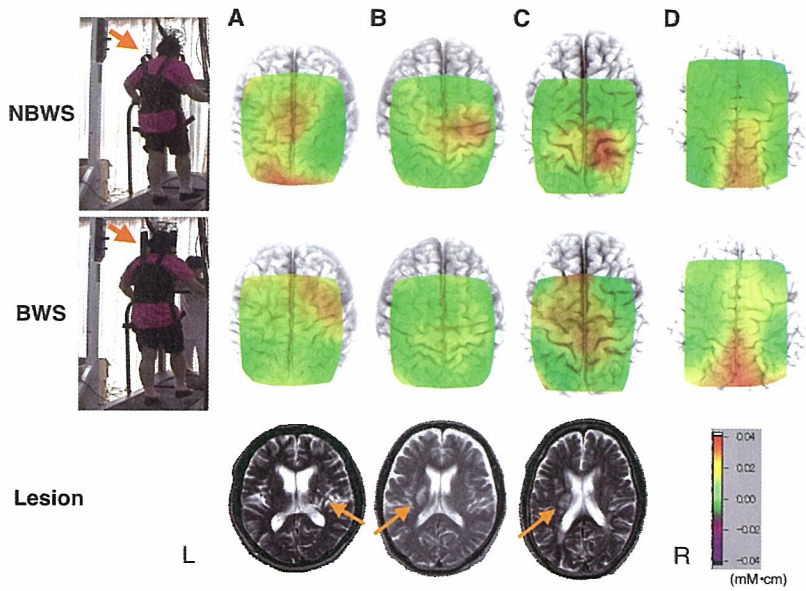
表　上肢実用使用を規定する因子

Factor	Odd ratio	95% CI	P value
Sex	11.53	0.266-500.035	0.20
Group (P vs. D)	0.03	0.001-0.973	0.048
Size of lesion	0.62	0.243-1.578	0.32
Fugl-Meyer (UE)	1.08	1.001-1.170	0.048
MEP (MAR of APB muscle)	9.86	0.116-841.127	0.31

遠位麻痺例(22 例)では被殻や内包病変が主であるが、近位麻痺例(14 例)では放線冠中部に限局していた。の出現分布は麻痺の分布と一致し,潜時は麻痺の重症度と関連,上肢遠位筋の振幅は病巣サイズと逆相関した。3 ヶ月のリハ後の実用上肢機能は経頭蓋磁気刺激による運動誘発電位(MEP)の有無、病巣容積ではなく、麻痺分布と重症度に規定された。

II-2. 体重免荷(BWS)の歩行時の脳活動に及ぼす影響

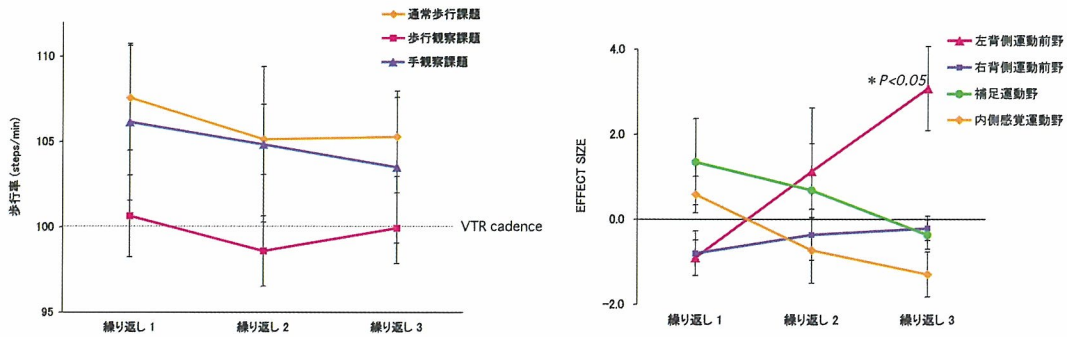
図２　片麻痺歩行時の脳賦活（oxyHb増加）マッピングのBWSによる変化



歩行訓練として注目される BWS によるトレッドミル訓練の脳内機構を検討した。脳卒中患者では BWS で歩行がより対称的になり、内側一次感覚運動野の酸素化ヘモグロビン増加を指標とした脳活動が有意に低下した。その変化は BWS による歩行率(cadence)の変化と相関した。BWS による感覚運動野活動の非対称性改善は歩行の非対称性改善と相関した。階層的な歩行制御系の下位へのシフトや自動的な歩行と関連が示唆された。BWS は健常人の歩行や脳活動に一定の変化をもたらさなかった(上段が BWS なしの歩行、下段が BWS ありの歩行)。

II-3. 歩行観察が歩行時の脳活動に及ぼす影響

図　各課題の繰り返しと歩行率の変化　　課題の繰り返しと各脳領域のeffect size（平均±SE）

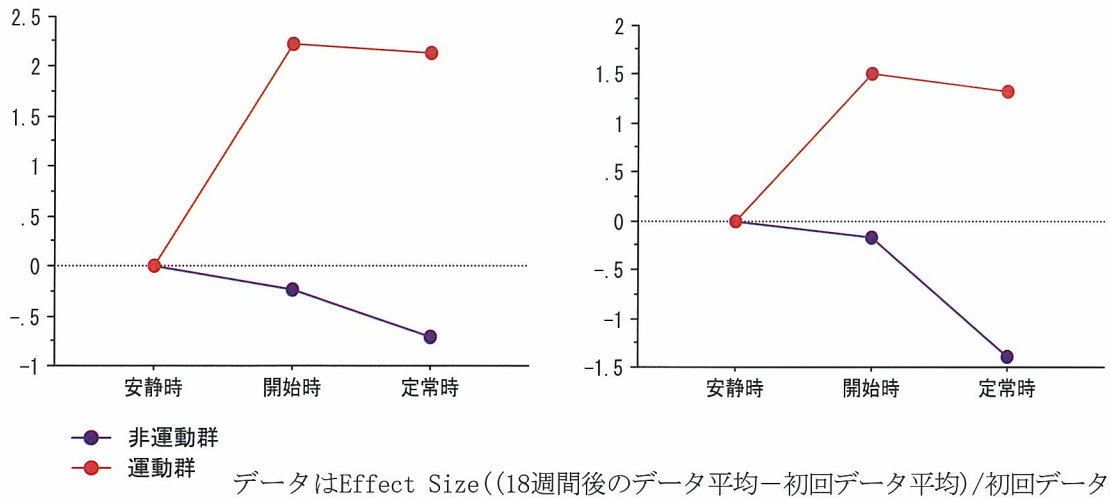


最近、運動の観察が脳活動に影響を与えることが明らかになった(mirror neuron)。リハの方法論への応用の基礎データとして、健常人の歩行と脳活動への動作観察の影響を健常人８名で光イメージング装置を用いて検討した。VTR 上の歩行を観察しながら歩行する課題では、課題の繰り返しとともに左背側運動前野賦活が上昇し、cadence（歩行率も VTR に近づいた。左背側運動前野が観察している歩行と自己の歩行を一致させることに関与することが示唆された。

II-4. 高齢者の歩行訓練による脳賦活の変化

図　運動群、非運動群における測定前後での脳賦活の変化

A．70%強度歩行中の左側前頭前野の経時的脳賦活　B．70%強度歩行中の左側運動前野の経時的脳賦活

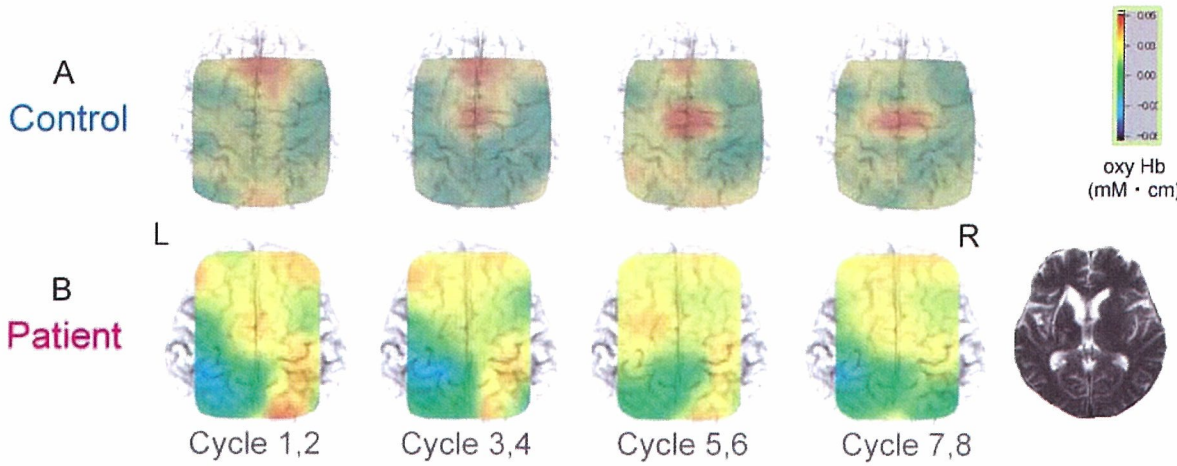


データはEffect Size((18週間後のデータ平均－初回データ平均)/初回データSD)

健常高齢者を対象に１８週間の歩行運動訓練をした運動群、非運動群の２群に分け、歩行運動量増加による歩行中の大脳賦活の変化を光イメージング装置で評価した。高齢者における歩行の開始と継続に必要な一次感覚運動野、運動前野、前頭前野などの活動は、日常生活における歩行量や歩行強度に影響されている可能性があり、高齢者の歩行遂行に関与する脳領域の活動低下を日常生活における歩行習慣の定着により予防できる可能性がある事が示唆された。

II-5. 脳卒中患者の運動学習と脳活動の関連

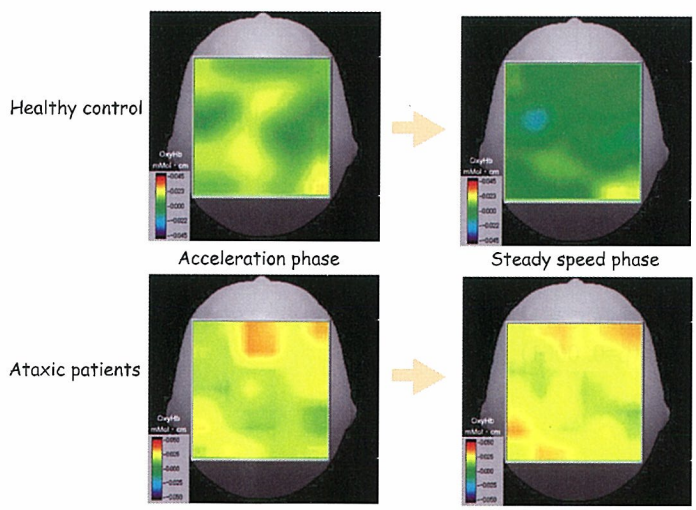
回転板課題中(30秒×8回のターゲットへの接触時間を測定)の脳活動(A. 対照、B. 脳卒中患者非麻痺手)



健常対照は成績の向上にともない、酸素化ヘモグロビン増加を指標とした脳活動中心は、前補足運動野から補足運動野付近へシフトした。脳卒中患者の成績は向上するものの対照にくらべ低く,プラトー化は遅延した。しかし脳活動のシフトは対照に比べ不明確であった。脳卒中患者の運動学習はある程度保たれているものの、健常者に比べ,視運動連関に依存する学習初期の状態が遷延することが示唆された。すなわち運動学習能力に関しては、脳卒中患者でも到達度は健常人に比べて低く、時間がかかるもののある程度保たれていること、その原因としていわゆる「身体でおぼえる」(implicit motor learning)のに時間がかかることが示唆された。

II-6. 小脳失調患者における歩行中の脳活動変化

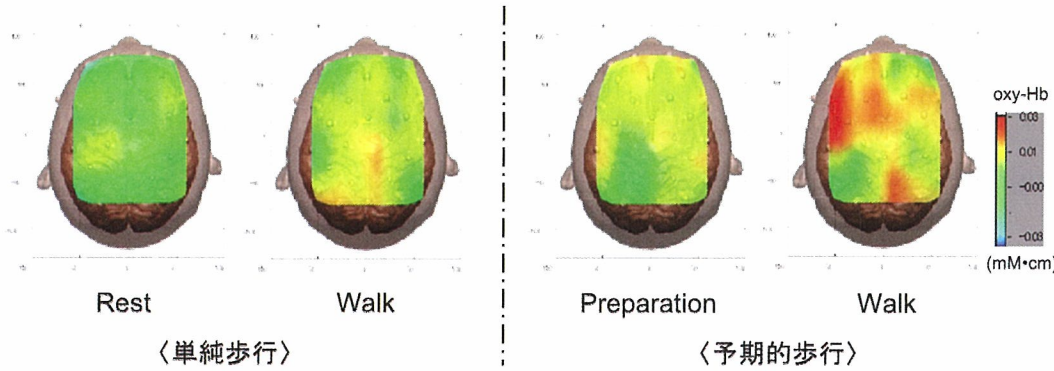
図　健常者（上段）、失調患者（下段）の加速歩行時（左）と定常歩行時の脳活動の変化



健常人では、トレッドミル速度が定常状態になった後に、歩行を続けると補足運動野や前頭前野における脳活動が低下してくるが小脳失調を呈する脳卒中患者では同部の活動は維持されたままであった。健常人では自動的な定常歩行の維持期には、皮質下への制御の移行が示唆されているが、患者では意識的な歩行の調整が継続して必要であると考えられた。

II-7. 歩行運動の準備に関連した皮質活動

図　単純歩行と予期的歩行における歩行開始前と歩行中の皮質活動

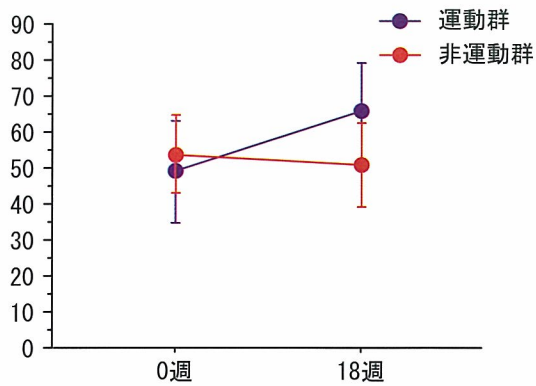


歩行開始前の準備期に言語指示を与えて、歩行運動や前頭野領域の皮質活動がどのような変化が起きるかを調べた。予期的歩行では単純歩行に比し、ケーディンス（歩数/分）が有意に少なく歩幅は有意に長かった。皮質活動では歩行開始前および歩行中に、内側の感覚運動野・補足運動野・運動前野・前頭連合野領域の酸素化ヘモグロビン増加が予期的歩行の方が単純歩行に比して有意に大きかった。言語指示による課題に対する準備（構え）が前頭連合野と運動関連領域の皮質活動を歩行開始前から賦活させ、その後の歩行運動に対する皮質制御にも影響を与える可能性が示唆された。

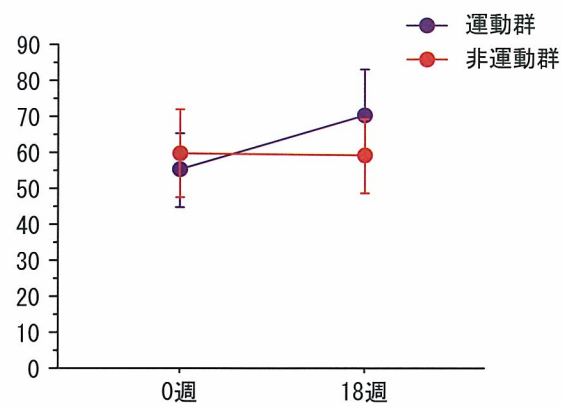
II-8. 高齢者の歩行訓練による前頭葉機能の変化

図　訓練前後（0週、18週間）におけるブランチング課題の変化

A. ブランチング課題の成績



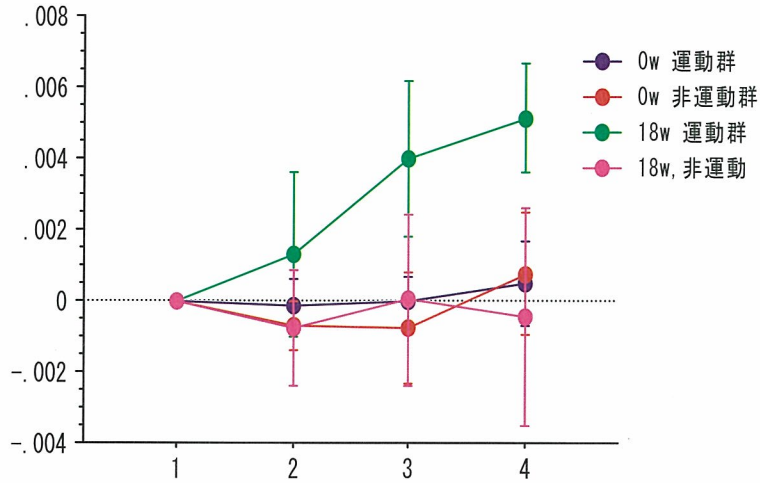
Bブランチング課題におけるゴーノーゴー課題の成績



ブランチング課題の成績は運動群で有意に増加し(p=0.0044)、この課題におけるゴーノーゴー課題の成績が運動群で有意な増加を示した(p=0.0061)。

図　運動群、非運動群における測定前後での脳賦活の変化

ブランチング課題遂行中の運動前野(左)の酸素化ヘモグロビンの変化



歩行訓練後に、左側運動前野において、ブランチング課題遂行時の賦活が運動群で有意な増加を示した($p<0.01$)。１はベースライン、２は記銘期、3は遅延期、4は想起期を示す。

高齢者の歩行運動訓練による前頭葉機能の変化および前頭葉課題遂行中の大脳賦活の変化を検討した。日常生活の活動記録を一軸加速度計をもとに、運動群と非運動群の２群に分けた。前頭葉機能の測定には、空間性遅延反応課題、ゴーノーゴー課題、およびこれら両方を組み合わせたブランチング課題を用い、課題の成績の変化と、賦活の経時的変化を検討した。歩行運動訓練後に、ブランチング課題の成績のみが有意に改善し（$p<0.005$）、この課題遂行中の左側運動前野($p<0.007$)の酸素化ヘモグロビンの有意な増加が見られた。高齢者における歩行訓練は、前頭葉に特異的な認知機能を改善したことから、加齢に伴う前頭葉機能の低下防止の手段として、歩行訓練が有効である可能性を示唆する。

研究成果の刊行に関する一覧

書籍

1. Miyai I. Cortical networks associated with locomotion in man and patients with hemiparetic stroke. In Swinnen SP, Duysens J eds. Neurobehavioral determinants of interlimb coordination, Kluwer Academic Publishers, MA, 2004, p.109-128
2. 宮井一郎. 外部環境における脳の可塑的変化. 内山靖編. 環境と理学療法. 医歯薬出版. 2004, P.58-72.
3. 宮井一郎. 脳機能賦活法-脳卒中に対する神経リハビリテーションを中心に. 財団法人長寿科学振興財団編. 老年期痴呆の克服を目指して. pp185-193, 医学書院, 2005.
4. 畠中めぐみ, 宮井一郎. 脳卒中患者の転倒要因と転倒予防のための介入. 泉キヨコ編. エビデンスに基づく転倒・転落予防. P133-138, 中山書店, 2005.
5. 宮井一郎. 脳卒中に対する神経リハビリテーション. 武田雅俊編. 現代老年精神医療. p242-247, 永井書店, 2005.
6. 宮井一郎.脳卒中から回復する. のばそう健康寿命 - 老化と老年病を防ぎ、介護状態を予防する - . p.185-194, 長寿科学振興財団, 2005
7. 久保田競, 宮井一郎編.脳から見たリハビリ医療.ブルーバックス,講談社, 2005.
8. 宮井一郎. fMRI, fNIRSによる運動機能の評価.里宇明元,才藤栄一,出江紳一編.リハビリテーション医学の新しい流れ. P.94-99, 先端医療技術研究所, 2005

雑誌

1. Miyai I. Locomotor training with partial body weight support in patients with Parkinson's disease and stroke: Its efficacy and neural mechanisms. Geriatrics and Gerontology International 2004;4:S205- S206.
2. Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T, Kubota K. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. Neuroimage 2004;23: 1020-26.
3. Miyai I, Hatakenaka M, Kubota K. Effect of body weight support on cortical activation during gait in Parkinson's disease. Program No. 882.17. 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience
4. Hatakenaka M, Miyai I, Kubota K. Impaired motor skill learning in patients with stroke: A functional NIRS study. Program No. 533.20. 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience
5. Harada T, Okagawa S. Kubota K. Jogging improved performance of a behavioral branching task: implications for prefrontal activation. Neurosci. Res. 2004; 49: 325- 337.
6. Harada T, Ebe K, Kozato A. Shimizu K. Amita T Kubota K, The anterior portion of the prefrontal cortex was bilaterally activated during bipedal walking to a goal. Program No. 187.3 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2004.
7. Kubota K, Ebe K, Kozato A, Hashimoto Y, Kimura K, Shimizu K, Amita T, Oda I, Konishi I. Working memory in car driving and the anterior and dorsolateral prefrontal cortex. Program No. 432.2 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2004.
8. Shimizu S, Taira M, Nose I, Kubota K. Cortical motor areas related to the association of a selected button press and use of either hand: An FMRI study. Program No. 995.5 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2004.

9. Miyai I, Suzuki M, Hatakenaka M, Kubota K. Effect of body weight support on cortical activation during gait in patients with stroke. Exp Brain Res, 2005, published online first (DOI:10.1007/s00221-005-0123)
10. Yagura H, Miyai I, Suzuki T, Yanagihara T. Patients with Severe Stroke Benefit Most By Interdisciplinary Rehabilitation Team Approach. Cerebrovasc Dis 2005;20:258-263. (DOI: 10.1159/000087708)
11. Yagura H, Hatakenaka M, Miyai I. Does therapeutic facilitation add to locomotor outcome of BWSTT in nonambulatory patients with stroke? A randomized controlled trial, Arch Phys Med Rehab 2006, in press
12. Mihara M, Miyai I, Hatakenaka M, Suzuki M, Kubota K. Sustained frontal activation during gait in patients with ataxia. Program No. 865.11. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience
13. Hatakenaka M, Miyai I, Mihara M, Kubota K. Frontal regions involved in learning and retention of motor skill: a functional NIRS study. Program No. 980.2. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience
14. Suzuki M, Miyai I, Ono T, Kubota K. Preparatory activities in the frontal cortex associated with human walking: an fNIRS study. Program No. 864.1. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience
15. Harada T, Miyai I, Suzuki M, Kubota K. Frontal activation patterns during walking are influenced by daily physical activity in the elderly. Program No. 864.3. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience
16. 宮井一郎. 神経リハビリテーションにおけるfNIRSの応用. Medical Now 2004;52: 33-36.
17. 宮井一郎. 脳卒中のリハビリテーション. JSA news第11号. 2004.
18. 宮井一郎. コクランレビューUp To Date. Amphetamines for improving recovery after stroke (Cochrane Review). The Cochrane Library 4, 2003.分子血管病 2004;3(2)223-228.
19. 宮井一郎. 脳卒中のリハビリテーション. JSA news第12号. 2004.
20. 宮井一郎, 久保田競. 脳卒中リハビリテーションにおけるNIRS機能画像.臨床精神医学 2004;33(6):767-772.
21. 宮井一郎. 脳卒中のリハビリテーション. 神経内科2004;60(6):608-615.
22. 宮井一郎. 脳卒中による機能障害や能力障害の治療と訓練. Aging & Health 2004;13(2):16-19.長寿科学振興財団
23. 宮井一郎. 神経リハビリテーションと脳循環代謝. 脳循環代謝2004;16(3):189-193.
24. 宮井一郎. 体重免荷トレッドミル歩行訓練の有効性.カレントテラピー 2004;22(11):72-78.
25. 宮井一郎.トレッドミル強制歩行による中枢神経系の賦活 - 脳卒中での知見と脊髄障害への応用の展望 - .脊髄脊椎ジャーナル2004;17(11):1024-34.
26. 宮井一郎.光イメージングによる脳損傷後の機能回復の評価. 神経内科 2004;61(5):445-453.
27. 三原雅史, 畠中めぐみ, 宮井一郎. 脳卒中後の神経機能回復と糖尿病- 神経リハビリテーションの役割- . Diabetes Frontier 2004;15(6):842-845.
28. 古澤正道, 宮井一郎. リハビリテーション技術. Bobathアプローチ. 臨床リハ 2005;14(1):70-72.
29. 三原雅史, 畠中めぐみ, 宮井一郎. NIRSを用いたニューロリハビリテーションの評価と展望.分子脳血管病2005;4(1):53-59.
30. 三原雅史, 畠中めぐみ, 宮井一郎. 歩行機能の回復と大脳皮質運動関連領野の役割.理学療法ジャーナル2005;39(3):215-222.

31. 島恵，荒井洋，宮井一郎．脳性麻痺時の歩行 - 痙直型両麻痺児について．理学療法ジャーナル 2005;39(4):327-334.
32. 宮井一郎.脳卒中をリハビリで治す．市民公開シンポジウム『脳卒中を知る』 - その克服に向けて - ．難病医学研究財団 2005, p.29-41.
33. 宮井一郎．回復期リハビリテーション - 期待と検証．全国回復期リハビリテーション病棟連絡協議会機関誌 2005;4(1):20-25.
34. 宮井一郎．看護部・コメディカル部門の育成と質の向上．リハビリ部門．脳卒中に対するリハビリを中心に．日本病院会雑誌 2005;52(5)654-664.
35. 畠中めぐみ，三原雅史，宮井一郎．近赤外線光イメージングの神経リハビリテーションへの応用.最新医学 2005:60(5):1018-1024.
36. 三原雅史，畠中めぐみ，宮井一郎．NIRSによる脳血管障害のリハビリテーションの評価.分子脳血管病 2005;4(3):303-308.
37. 三原雅史，畠中めぐみ，宮井一郎．脳機能評価と検査法の進歩- 脳機能評価法としての有用性．MRI．脳と循環 2005;10(3):185-189.
38. 宮井一郎.脳卒中-臓器別死因第一位の国民病の克服に向けて.脳卒中のリハビリテーション.カラントテラピー2005;23(10):68-73.
39. 宮井一郎.大都市圏の脳卒中医療と地域医療連携ー大阪南部エリアから.病院新時代 2005;22:11-17.
40. 宮井一郎.小脳障害の治療.リハビリテーション．Clinical Neuroscience 2005;23:1438-1440.
41. 宮井一郎．脳卒中後の運動麻痺回復の脳内機構と神経リハビリテーション-fNIRS研究を中心に-．認知神経科学 2005;7(3):211-216.
42. 宮井一郎．脳卒中患者の歩行障害への対応．リハ医学 2006;43(1):33-39.
43. 三原雅史、畠中めぐみ、宮井一郎．運動時の大脳皮質活動．体育の科学 2006;56(1):13-17.

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2. Harada T, Okagawa S. Kubota K. Jogging improved performance of a behavioral branching task: implications for prefrontal activation. Neurosci. Res. 2004; 49: 325–337.
3. Miyai I, Suzuki M, Hatakenaka M, Kubota K. Effect of body weight support on cortical activation during gait in patients with stroke. Exp Brain Res, 2005, published online first (DOI:10.1007/s00221-005-0123)
4. Yagura H, Miyai I, Suzuki T, Yanagihara T. Patients with Severe Stroke Benefit Most By Interdisciplinary Rehabilitation Team Approach. Cerebrovasc Dis 2005;20:258-263. (DOI: 10.1159/000087708)
5. Yagura H, Hatakenaka M, Miyai I. Does therapeutic facilitation add to locomotor outcome of BWSTT in nonambulatory patients with stroke? A randomized controlled trial, Arch Phys Med Rehab, in press

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Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study

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We investigated changes of regional activation in the frontal cortices as assessed by changes of hemoglobin oxygenation during walking at 3 and 5 km/h and running at 9 km/h on a treadmill using a near-infrared spectroscopic (NIRS) imaging technique. During the acceleration periods immediately preceded reaching the steady walking or running speed, the levels of oxygenated hemoglobin (oxyHb) increased, but those of deoxygenated hemoglobin (deoxyHb) did not in the frontal cortices. The changes were greater at the higher locomotor speed in the bilateral prefrontal cortex and the premotor cortex, but there were less speed-associated changes in the sensorimotor cortices. The medial prefrontal activation was most prominent during the running task. These results indicate that the prefrontal and premotor cortices are involved in adapting to locomotor speed on the treadmill. These areas might predominantly participate in the control of running rather than walking.

Keywords: Near-infrared spectroscopic imaging technique; Oxygenated hemoglobin; Deoxygenated hemoglobin

Introduction

Experimental studies have indicated that bipedal gait is controlled by the cerebral cortices including motor neurons in the medial portion of the primary motor cortex (Ferrier, 1876; Leyton and Sherrington, 1917; Penfield, 1950) as well as the spinal central pattern generators and multiple motor centers in the brainstem (Armstrong, 1988; Drew, 1988; Mori et al., 2001; Nutt et al., 1993). In human gait, a study using single photon emission computed tomography showed activation in the multiple areas including the supplementary motor area, medial sensorimotor cortex, striatum, and cerebellum (Fukuyama et al., 1997). A near-infrared spectroscopic (NIRS) imaging study revealed that walking at the pace of 1 km/h on a treadmill was associated with a bilateral increase of oxygenated hemoglobin (oxyHb) in the medial sensorimotor cortices and the supplementary motor areas (Miyai et al., 2001). However, it is unclear whether there is also a significant relationship between cerebral activation and physiological parameters of gait such as speed and cadence. It is also not known how the rostral regions in the frontal cortices, such as the prefrontal and the premotor cortex, are involved in locomotor control, In the elderly, walking improved the performance of cognitive tasks involving prefrontal executive functions, such as a switching task, a response compatibility task, and a stopping task to abort a preprogrammed action (Kramer et al., 1999). A study has shown that habitual jogging improves a branching task combining the main visuospatial delayed-response and subroutine go/no-go task associated with the anterior prefrontal function (Harada et al., 2004; Koechlin et al., 1999). In patients with hemiparetic stroke, enhanced premotor activation in the affected hemisphere was associated with locomotor recovery (Miyai et al., 2002, 2003). Thus, we hypothesized that the prefrontal and premotor cortices are involved in the control of human walking and running. To test this hypothesis, we evaluated cortical activation patterns associated with locomotor speed as assessed by relative changes of oxyHb and deoxygenated hemoglobin (deoxyHb) levels using an optical imaging technique. Our results indicated that the prefrontal–premotor regions and sensorimotor cortices are activated differentially during walking and running and that the prefrontal activation is prominent, especially during running.

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Methods

Subjects and tasks

A total of nine, right-handed, healthy subjects (seven males, two females; mean age ± SD, 28.1 ± 7.4 years; range 22–46 years) without known neurological abnormalities participated in the experiments. This study was approved by the Ethical Committee of Bobath Memorial Hospital, and a written informed consent was obtained from each subject. The subjects performed three types of locomotor tasks (walking at 3 and 5 km/h, and running at 9 km/h) on a treadmill (Model 3200; SportsArt Ind., WA). Fig. 1 illustrates the temporal sequence of the task design.

Each locomotor task consisted of a 90-s task period and a 60-s rest period (30-s rest before and after each task period) for three repetitions. Subjects were instructed to stand still on the treadmill belt for 30 s, and then a verbal instruction to 'start' was given. The treadmill reached the target speed at 13 s later from the start at 3 km/h walking (Fig. 1-1), at 17.5 s later at 5 km/h walking (Fig. 1-2), and at 28 s later at 9 km/h running (Fig. 1-3), and the speed was steady until 120 s after the start when the treadmill was stopped. In the running task, each subject began to run 45 s after the starting locomotion when treadmill speed reached 6 km/h. During walking and running, subjects swung their arms without excessive efforts. Each subject was asked to stand still on the treadmill during the rest period. The order of the three treadmill speeds was randomized, except that running at 9 km/h was not chosen as the first task for safety reasons. All tasks were recorded on videotape (SONY; DCR-PC120, Tokyo, Japan) to calculate the cadence (steps/min). Blood pressure (mm Hg) and heart rate (beats/min) were measured immediately before and after each task. Arterial oxygen saturation was also monitored using a pulse oxymetry.

NIRS imaging

The details of the NIRS imaging system (OMM-2001, Shimadzu, Kyoto, Japan) using continuous wave laser diodes with wavelengths of 780, 805, and 830 nm were described previously (Miyai et al., 2001). We used a 42-channel system with 28 optodes, consisting of 12 light-source fibers and 16 detectors. A custom-made holder cap for the optodes was attached to the scalp and a weight balancer for the fibers enabled stable measurement during walking and running. The interoptode distance was set at 3.0 cm. The location of the optodes on the skull covering an area of 13 × 15 cm in the frontoparietal regions is schematically shown in Fig. 2A.

Thus, 42 square grids of the NIRS topographic map consisted of seven rows and six columns and were labeled as Channels (Ch) 1 to 42. The light-source fiber next to the posterior one in the center row was located in the Cz position. An anatomical 3-D T1-weighted MRI scan was performed with marking the optode location on the skull by vitamin D capsules. In two subjects, the anatomical MRI was normalized to a standard stereotaxic space (Ashburner and Friston, 1999; Ashburner et al., 1997; Friston et al., 1995), using a Montreal Neurological Institute (MNI) brain template, which corresponds to the space described by Talairach and Tournoux (1988). The normalization was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Coordinates of each optode were then converted into MNI coordinates. Thus, the anterior commissure (AC) line (Picard and Strick, 2001) was approximately corresponded to the line between the second and third rows (i.e., Ch 37 and 38, Figs. 2B and C). Accordingly, the left and right PFC were covered by Channels 15, 16 and 22, 23, the left and right PMC by Channels 3, 4, 10, 11 and 31, 32, 38, 39 (Picard and Strick, 2001), the left and right m-SMC by channels 19, 20 and 26,27, and the left and right l-SMC by Channels 5, 6, 7 and 40, 41, 42, respectively (Fig. 2B). The lower limb areas in the PMC [Talairach and Tournoux's coordinates R (40, −4, 60) and L (−32, −8, 64)], as reported by Buccino et al. (2001), were found to be located in Channels 11 and 32.

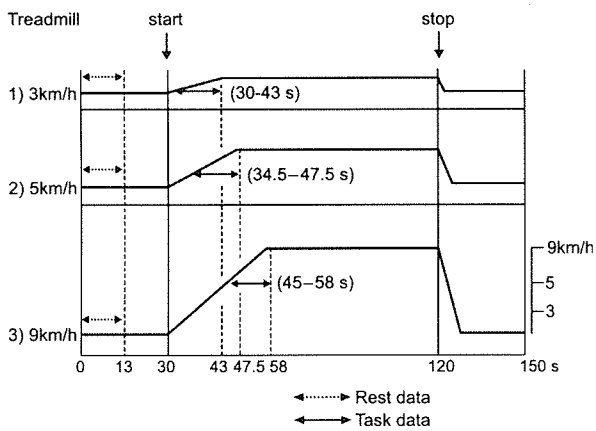

Fig. 1. Design for the sequence of three tasks with (1) 3 km/h walking, (2) 5 km/h walking, and (3) 9 km/h running. Subjects performed 150-s of locomotor tasks consisting of 30-s rest period before the locomotion, 90-s locomotion period, and 30-s rest period after task for three repetitions at each speed. Data were sampled for the 13-s period from 0 to 13-s as Rest data and for 13-s period just before reaching each constant speed as Task data. See text for details.

Data analysis

Changes of hemoglobin concentration were represented as mMol · cm. These data were sampled at the rate of 190 ms. Since previous findings (Hoshi et al., 2001; Strangman et al., 2002; Wolf et al., 2002) and our own findings (Miyai et al., 2001, 2002) have shown that oxyHb was the most sensitive marker for task-related hemodynamic changes, we used oxyHb levels for the assessment of regional cortical activation. We derived data and made calculations from 42 channels from the "ΔoxyHb during task period − ΔoxyHb during rest period." Task data were obtained from the 13-s period that immediately preceded reaching the constant speed because the period corresponded to data from start point of the task (30 s) to the point of plateau speed (43 s) at 3 km/h. To compare data in the comparable period, we analyzed data between 34.5 and 47.5 s at 5 km/h, and 45 and 58 s at 9 km/h, as indicated by solid arrows in Fig. 1. Rest data were obtained from the first 13 s of the rest periods (0–13 s), as indicated by a dotted arrow in Fig. 1. We obtained images depicting averaged changes of oxyHb from three cycles of each task, after adapting the linear interpolation to the 42-channel data recorded simultaneously from each channel. Our previous data suggested that even one cycle was sufficient to get reliable images (Miyai et al., 2001). Each channel was corrected to match the anatomical location on the brain surface, and the corrected maps were finally overlaid on anatomical MR images.

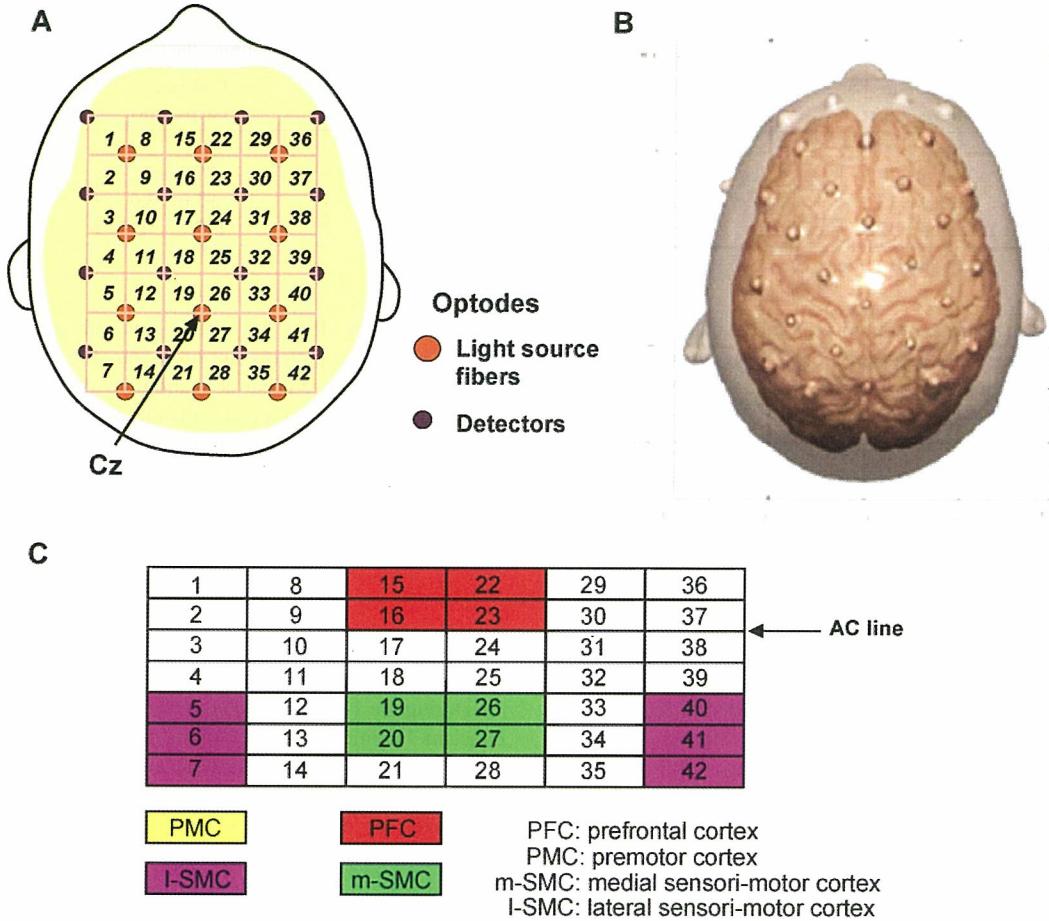

Fig. 2. Schematic for location of the optodes. (A) Twenty-eight optodes, constituting 12 light-source fibers and 16 detectors, were arranged on the scalp that enabled 42-channel measurement. (B) The anatomical location of the optodes exposed onto the normalized brain surface. (C) The channels covering the PFC are shaded in red, those covering the PMC in yellow, those covering the m-SMC in green, and those covering the l-SMC in purple. See text for details. AC indicates anterior commissure.

We calculated the regional activation ratio in each channel as defined by "ΔoxyHb in each channel" / "total ΔoxyHb from all 42 channels × 100%". The maximal value of regional activation ratio from the channels covering each region was used as an index for regional activation and was statistically analyzed. We performed a two-factorial repeated-measures ANOVA with the site of region as a between-subject factor and locomotion speed as a within-subject factor. Fisher protected least significant difference test was used as a post hoc test. Task performance (cadence) and physiological parameters (heart rate, blood pressure, and SaO_2) were analyzed by using an unpaired t test or one-factorial ANOVA. Statistical significance was set at $P < 0.05$.

Results

As locomotor speed increased from 3, 5, and then 9 km/h, cadence significantly increased linearly, and the heart rate and blood pressure increased slightly after 3 and 5 km/h walking, but the increase was greater after 9 km/h running. SaO_2 was affected by none of the tasks (Table 1). Fig. 3 illustrates representative data for temporal changes of oxyHb, deoxyHb, and totalHb during locomotor tasks at different speeds in the PFC, PMC, m-SMC, and l-SMC.

In the PFC, PMC, and m-SMC, oxyHb and totalHb levels began to increase bilaterally before starting the locomotor tasks especially at 9 km/h and reached to the peaks before the treadmill speed got steady. After reaching constant speed, these levels decreased and tended to return to the baseline or below the baseline levels during performing the locomotor tasks. After stopping locomotion, there were temporal drops in oxyHb levels before returning to the baseline levels. In the PFC, PMC, and m-SMC, the increase in oxyHb levels were the greatest at 9 km/h but appeared to be similar between 3 and 5 km/h. In the l-SMC, there were no increases in oxyHb levels at 3 km/h and slight increases at 5 and 9 km/h, probably due to prominent arm swings. Compared with changes of oxyHb levels, few changes were seen in deoxyHb levels as reported previously (Miyai et al., 2001, 2002, 2003). Accordingly, changes in totalHb levels were similar to those in oxyHb levels. To compare regional activation patterns at different speeds, changes of oxyHb levels before reaching the constant speed were chosen for the quantitative analyses and for developing the topographic maps. Fig. 4 shows an example of cortical activation patterns during locomotion at different speeds.

During walking at 3 km/h, activation mostly centered in the bilateral m-SMC. The left PMC appeared to be slightly activated while the other regions were not. During 5 km/h walking, the m-SMC activation appeared to be similar to that at 3 km/h. The left

Table 1
Averaged changes of heart rate, systolic blood pressure, diastolic blood pressure, and SaO_2 before and after performing the tasks, and cadence during the tasks

	Heart rate (beats/min)	Systolic BP (mm/Hg)	Diastolic BP (mm/Hg)	Cadence (steps/min)	SaO_2 %
before task	74.4 ± 9.9	118.7 ± 10.4	77.7 ± 8.2		
3 km/h	83.4 ± 12.3	118.2 ± 11.8	82.3 ± 12.0	77.7 ± 5.2	97.6 ± 0.5
5 km/h	91.9 ± 13.2	117.7 ± 11.5	81.8 ± 7.6	95.6 ± 3.0	97.6 ± 0.5
9 km/h	136.5 ± 12.5	136.6 ± 12.5	91.2 ± 10.1	145.7 ± 10.4	98.0

$n = 9$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

PMC activation was more prominent at 5 km/h than at 3 km/h. During 9 km/h running, the bilateral prefrontal cortices including the left medial and right lateral regions, as well as the PMC and m-SMC, were highly activated. Although the activations shown in Fig. 4 were stronger in the left side than in the right, such laterality of activation was inconsistent between subjects. However within subject, activation patterns were almost identical during three cycles of locomotor tasks at each speed. We also compared differences in regional activation between the left and right hemispheres and found no significant difference at any locomotion speed (Table 2).

Thus, we chose to use the averaged data from the left and right hemispheres for quantification.

Regional activation ratios during locomotion at different speeds are shown in Fig. 5. A two-factorial repeated-measures ANOVA revealed a significant main effect for site of region [$F(3, 64) = 4.383$, $P < 0.05$] and a significant interaction between locomotion speed and site of region [$F(6, 64) = 2.809$, $P < 0.05$] but no significant main effect for speed. This indicated that there were distinct activation patterns during locomotion at different speeds. Post hoc tests showed that activations in the PFC, PMC, and m-SMC were significantly greater than that in the l-SMC ($P < 0.05$). Furthermore, the PFC activation was significantly greater during running at 9 km/h than during walking at 3 and 5 km/h ($P < 0.05$). The PMC activation tended to be greater as the locomotor speed and cadence increased, but there was no statistical significance. There were few changes associated with the speed in the m-SMC.

Discussion

During the 13-s periods that immediately preceded reaching the constant locomotor speed on the treadmill, the PFC and PMC activation tended to increase as locomotor speed and cadence increased. Interestingly, the m-SMC activation appeared to be unchanged or decreased as the locomotor speed increased. In

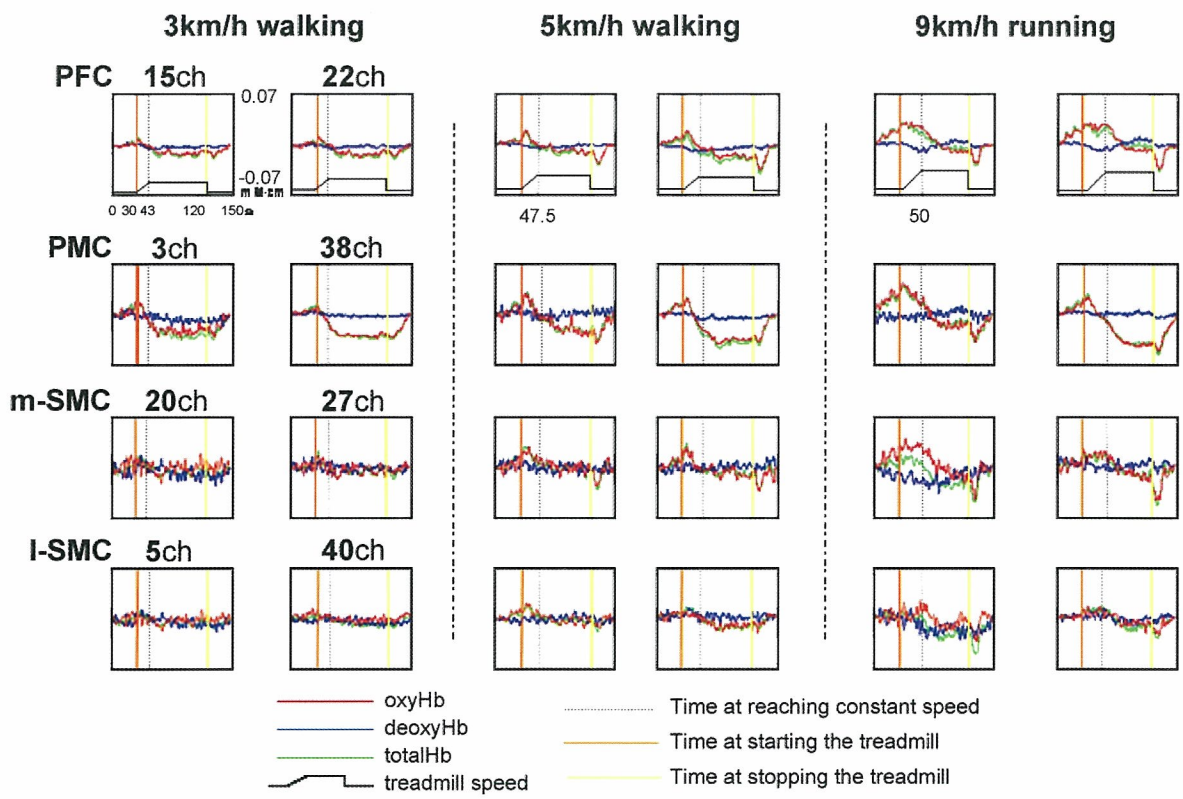

Fig. 3. Changes of regional hemoglobin concentration in the PFC, PMC, m-SMC, and l-SMC during locomotor tasks in a subject. Red lines indicate oxyHb levels (mMol · cm), blue lines indicate deoxyHb, and green lines indicate totalHb. Black lines indicate treadmill speeds. The orange vertical lines indicate the starting points of the locomotor tasks, dotted vertical lines indicate the time when the treadmill speed reached the plateau, and yellow vertical lines indicate the end point of the tasks. Each figure shows the averaged value of the three cycles.

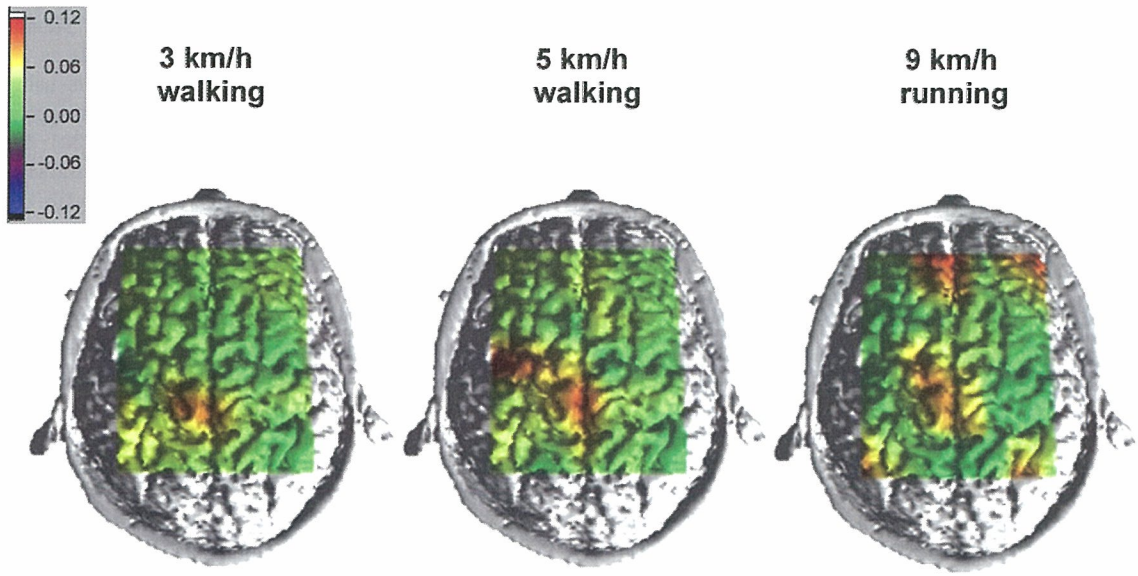

Fig. 4. Cortical mapping of locomotion tasks based on changes in oxyHb levels. The scale indicates the color coordinates of concentration changes (mMol · cm). See text for details.

contrast, several previous studies have demonstrated a linear correlation between regional cerebral blood flow (CBF) in the hand area of the human primary motor cortex and the rate or amplitude of finger tapping (Blinkenberg et al., 1996; Kawashima et al., 1999; Rao et al., 1996; Sadato et al., 1996) and power grip forces (Ehrsson et al., 2000). These areas may be related to repetitive rate or force. This discrepancy might be partially due to the fact that the locomotion is controlled by hierarchical mechanisms including the spinal central pattern generators and supraspinal multiple motor centers such as the cerebellum, subthalamic, and brainstem locomotor regions. The frontal lobes and basal ganglia loops are involved in higher motor control when one is faced with complex environmental conditions (Armstrong, 1988; Drew, 1988; Nutt et al., 1993). Therefore, it is possible that our failure to demonstrate a positive relationship between locomotor speed and the m-SMC activation might reflects a shift of the motor control center to the hierarchically lower or higher levels. Thus, control mechanism of locomotion might be different from that of hand movements or simple leg movements (Sahyoun et al., 2004).

The increases of oxyHb and totalHb levels in the PFC, PMC, and m-SMC were seen before starting the locomotor tasks especially at 9 km/h. We also reported similar findings in the previous study for cortical mapping of gait at 1 km/h (Miyai et al., 2001). It is possible that such phenomenon might be related to anticipatory or preparatory activities for locomotion (Kubota and Hamada, 1978; Tanji and Evarts, 1976) and that anticipatory or preparatory load might increase with the increment of locomotor speed to be executed. The increases in oxyHb levels after starting locomotor tasks were not sustained while subjects performed the tasks at the steady speed. Instead, the oxyHb concentration decreased to below baseline levels, especially in the PMC. This phenomenon might be at least partially explained by changes of neurovascular coupling (Hoshi et al., 2001; Wolf et al., 2002). Specifically, there might be a mismatch between CBF and the cerebral metabolic rate of oxygen ($CMRO_2$) when CBF decreased secondarily under the steady or decreased neural activities during the locomotion at the constant speed. In the PFC and the m-SMC, the oxyHb levels returned to the baseline while subjects kept performing the tasks, suggesting that these areas were most active during the acceleration phase of locomotion. Additionally, immediately after stopping the locomotor tasks at 5 and 9 km/h, there were drops (dips) in the oxyHb levels. These dips, although they occurred after completion of locomotion, appear to be similar to initial or early dips (Buxton, 2001; Mayhew et al., 2000; Thompson et al., 2003). Although the decrease in oxyHb levels can be explained either by decreased CBF, increased consumption, or decreased cerebral blood volume, it is also possible that neural activities related to discontinuation of the locomotion could produce a relative increase in $CMRO_2$ and consequent decrease in oxyHb levels. Similarly, within 3 s after the initiation of the hand motor task, the region where the concentration change of both oxyHb and deoxyHb was detected corresponded to the center of gravity of the motor response to transcranial magnetic stimulation,

Table 2
Regional activation ratios in the left and right hemispheres during locomotion at different speeds

	3 km/h		5 km/h		9 km/h	
	LH	RH	LH	RH	LH	RH
PFC	2.62 ± 1.68	2.64 ± 1.20	3.94 ± 1.83	2.67 ± 2.06	4.76 ± 2.59	4.39 ± 1.34
PMC	3.86 ± 2.00	3.29 ± 1.99	2.92 ± 1.53	3.77 ± 1.81	4.19 ± 2.65	3.86 ± 1.51
m-SMC	3.76 ± 1.43	4.34 ± 1.97	3.75 ± 1.95	2.98 ± 1.13	3.93 ± 1.77	3.29 ± 1.22
l-SMC	1.95 ± 1.18	1.86 ± 0.91	1.87 ± 1.30	2.23 ± 1.06	1.68 ± 1.74	1.76 ± 0.53

Data (%); average ± SD, LH indicates left hemisphere, RH; right hemisphere.

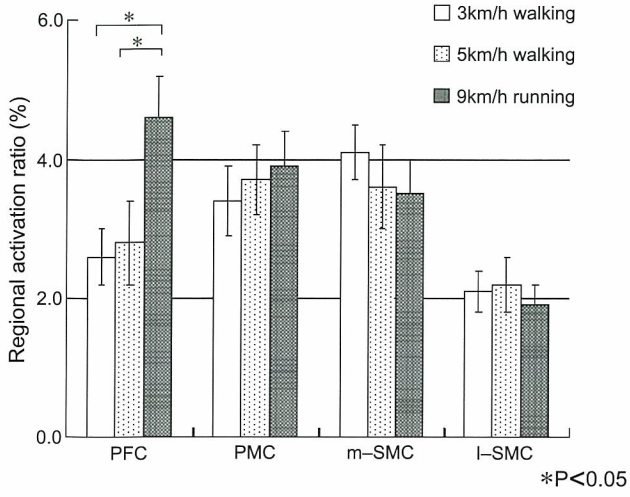

Fig. 5. The relationship between locomotor speed and regional cortical activation as assessed by the regional activation ratio. The data are mean ± SE (%). See text for details.

suggesting that cortical oxygen metabolism precedes the blood flow response (Akiyama et al., 2003). General changes in CBF associated with rises in blood pressure and heart rate are unlikely since there were distinct time courses of hemoglobin oxygenation among different cortical regions. However, these possibilities remain to be established in future studies.

Our data revealed that the PMC as well as the PFC are involved in control of locomotion at different speeds. It has been suggested that the dorsal PMC plays a role in the selection, planning, and execution of voluntary movements (Grafton et al., 1998; Kubota and Hamada, 1978; Weinrich and Wise, 1982), and in motor preparation (Boussaoud, 2001; Simon et al., 2002). Clinical studies have suggested that the PMC plays a crucial role in locomotor recovery after stroke (Miyai et al., 1999, 2002, 2003). Observation of foot movements activated the more dorsal sector in the ventral PMC than did observation of hand movements (Buccino et al., 2001). In the present study, the PMC activation during locomotion appeared to involve both the dorsal and ventral PMC. Thus, the PMC activation might reflect the neural mechanisms underlying the execution of bipedal movements for controlling locomotor speed in the acceleration phases of walking and running. For hand movements, the PMC might be involved in control of complex hand movements since precision grip also induces increased activities in the PMC as well as in the SMC compared with power grip (Ehrsson et al., 2000).

The PFC activation was most prominent during running. Running also induced the greatest changes in physiological parameters such as blood pressure and heart rate as well as cadence. Since electric stimulation of the medial prefrontal cortex induced the increase in blood pressure (Fulton, 1951; Kaada et al., 1949), it might be possible that high blood pressure and the PFC activation were related to each other. More importantly, the PFC has been shown to play a crucial role in attention (Averbeck et al., 2002; Büchel and Friston, 1997; Haxby et al., 1994; Koechlin et al., 2000; Wood and Grafman, 2003). This suggests that the PFC is likely to be involved in sustaining attention to keep up with the increase of the treadmill speed by maintaining the posture on the treadmill and by preparing the appropriate leg movements to adapt to the changes in treadmill speed. It might also be possible that the PFC activation is associated with the motor learning process of performing the running task in an unusual situation on the treadmill. The present study used oxyHb levels as a marker for cortical activation. Although NIRS experiments using rats with exposed cortex revealed evidence of robust changes not only in oxyHb but also in deoxyHb (Lindauer et al., 2001; Martin et al., 2002; Mayhew et al., 2001), oxyHb has been shown to be more sensitive to human cortical activities than deoxyHb, probably due to the higher signal-to-noise ratio associated with scattering of light through the scalp, skull and relatively inactive brain tissue (Strangman et al., 2002; Wolf et al., 2001). Further studies are necessary to investigate the relationships among the changes of oxyHb and deoxyHb, cerebral metabolism, and neural activities using multimodal approaches including NIRS, PET, fMRI, and transcranial magnetic stimulation.

Conclusion

Multiple motor areas including the PFC, PMC, and m-SMC were activated during the periods before reaching a constant speed of walking and running. The prefrontal and premotor cortex might be involved in controlling locomotion to adapt to the increasing speed in the acceleration phases.

Acknowledgments

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References

Akiyama, T., Ohira, T., Fukunaga, A., Niimi, M., Hiraga, K., Kawase, T., 2003. Analysis of Hb concentration change detected by TMS mapping oriented NIRS in the activated cerebral cortex during motor task. NeuroImage 19 (suppl) S28.

Armstrong, D.M., 1988. The supraspinal control of mammalian locomotion. J. Physiol. 405, 1–37.

Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7, 254–266.

Ashburner, J., Neelin, P., Collins, D.L., Evans, A.C., Friston, K.J., 1997. Incorporating prior knowledge into image registration. NeuroImage 6, 344–352.

Averbeck, B.B., Chafee, M.V., Crowe, D.A., Georgopoulos, A.P., 2002. Parallel processing of serial movements in prefrontal cortex. Proc. Natl. Acad. Sci. U. S. A. 99, 13172–13177.

Blinkenberg, M., Bonde, C., Holm, S., Svarer, C., Andersen, J., Paulson, O.B., Law, I., 1996. Rate dependence of regional cerebral activation during performance of a repetitive motor task: a PET study. J. Cereb. Blood Flow Metab. 16, 794–803.

Boussaoud, D., 2001. Attention versus intention in the primate premotor cortex. NeuroImage 14, S40–S45.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.-J., 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur. J. Neurosci. 13, 400–404.

Büchel, C., Friston, K.J., 1997. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cereb. Cortex 7, 768–778.

Buxton, R.B., 2001. The elusive initial dip. NeuroImage 13, 953–958.

Drew, T., 1988. Motor cortical cell discharge during voluntary gait modification. Brain Res. 457, 181–187.

Ehrsson, H.H., Fagergren, A., Jonsson, T., Westling, G., Johansson, R.S., Forssberg, H., 2000. Cortical activity in precision-versus power-grip tasks: an fMRI study. J. Neurophysiol. 83, 528–536.

Ferrier, D., 1876. The Functions of the Brain. Smith, Elder, London.

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., Kimura, J., Shibasaki, K., 1997. Brain functional activity during gait in normal subjects: a SPECT study. Neurosci. Lett. 228, 183–186.

Fulton, J.F., 1951. Frontal Lobotomy and Affective Behavior. W.W. NORTON COMPANY, Inc., New York, pp. 96–129.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., Frackowiak, R.S.J., 1995. Spatial registration and normalization of images. Hum. Brain Mapp. 2, 165–189.

Grafton, S.T., Fagg, A.H., Arbib, M.A., 1998. Dorsal premotor cortex and conditional movement selection: a PET functional mapping study. J. Neurophysiol. 79, 1092–1097.

Harada, T., Okagawa, S., Kubota, K., 2004. Jogging improved performance of a behavioral branching task: implications for prefrontal activation. Neurosci. Res. 49, 325–337.

Haxby, J.V., Horwitz, B., Ungerleider, L.G., Maisog, J.M., Pietrini, P., Grady, C.L., 1994. The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. J. Neurosci. 14, 6336–6353.

Hoshi, Y., Kobayashi, N., Tamura, M., 2001. Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. J. Appl. Physiol. 90, 1657–1662.

Kawashima, R., Inoue, K., Sugiura, M., Okada, K., Ogawa, A., Fukuda, H., 1999. A positron emission tomography study of self-paced finger movements at different frequencies. Neuroscience 92, 107–112.

Kaada, B.R., Pribram, K.H., Epstein, J.A., 1949. Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and cingulate gyrus. J. Neurophysiol. 12, 347–356.

Koechlin, E., Basso, G., Pietrini, P., Panzer, S., Grafman, J., 1999. The role of the anterior prefrontal cortex in human cognition. Nature 399, 148–151.

Koechlin, E., Corrado, G., Pietrini, P., Grafman, J., 2000. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proc. Natl. Acad. Sci. U. S. A. 97, 7651–7656.

Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M.T., MacAuley, E., Harrison, C.R., Chason, J., Vakil, E., Bardell, L., Boileau, R.A., Colcombe, A., 1999. Ageing, fitness and neurocognitive function. Nature 400, 418–419.

Kubota, K., Hamada, I., 1978. Visual tracking and neuron activity in the post-arcuate area in monkeys. J. Physiol. (Paris) 74, 297–312.

Leyton, A.S.F., Sherrington, E.S., 1917. Observation on the excitable cortex of the chimpanzee, orangutan, and gorilla. Q. J. Exp. Physiol. 11, 135–222.

Lindauer, U., Royl, G., Leithner, C., Kuhl, M., Gold, L., Gethmann, J., Kohl-Bareis, M., Villringer, A., Dirnagl, U., 2001. No evidence for early decrease in blood oxygenation in rat whisker cortex in response to functional activation. NeuroImage 13, 988–1001.

Martin, C., Berwick, J., Johnston, D., Zheng, Y., Martindale, J., Port, M., Redgrave, P., Mayhew, J., 2002. Optical imaging spectroscopy in the unanaesthetised rat. J. Neurosci. Methods 120, 25–34.

Mayhew, J., Johnstone, D., Berwick, J., Jones, M., Coffey, P., Zheng, Y., 2000. Spectroscopic analysis of neural activity in brain: increased oxygen consumption following activation of barrel cortex. NeuroImage 12, 664–675.

Mayhew, J., Johnstone, D., Martindale, J., Jones, M., Berwick, J., Zheng, Y., 2001. Increased oxygen consumption following activation of brain: theoretical footnotes using spectroscopic data from barrel cortex. NeuroImage 13, 975–987.

Miyai, I., Suzuki, T., Kang, J., Kubota, K., Volpe, BT., 1999. Middle cerebral artery stroke that includes the premotor cortex reduces mobility outcome. Stroke 30, 1380–1383.

Miyai, I., Tanabe, C.H., Sase, I., Eda, H., Oda, I., Konishi, I., Tsunezawa, Y., Suzuki, T., Yanagida, T., Kubota, K., 2001. Cortical mapping of gait in human: a near-infrared spectroscopic topography study. NeuroImage 14, 1186–1192.

Miyai, I., Yagura, H., Oda, I., Konishi, I., Eda, H., Suzuki, T., Kubota, K., 2002. Premotor cortex is involved in restoration of gait in stroke. Ann. Neurol. 52, 188–194.

Miyai, I., Yagura, H., Hatakenaka, M., Oda, I., Konishi, I., Kubota, K., 2003. Longitudinal optical imaging study for locomotor recovery after stroke. Stroke 34, 2866–2870.

Mori, S., Matsuyama, K., Mori, F., Nakajima, K., 2001. Supraspinal sites that induce locomotion in the vertebrate central nervous system. Adv. Neurol. 87, 25–40.

Nutt, J.G., Marsden, C.D., Thompson, P.D., 1993. Human walking and higher-level gait disorders, particularly in the elderly. Neurology 43, 268–279.

Penfield, W., 1950. The Cerebral Cortex of Man: A Clinical Study of Localization of Function. MacMillan, New York.

Picard, N., Strick, P.L., 2001. Imaging the premotor areas. Curr. Opin. Neurobiol. 11, 663–672.

Rao, S.M., Bandettini, P.A., Binder, J.R., Bobholz, J.A., Hammeke, T.A., Stein, E.A., Hyde, J.S., 1996. Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. J. Cereb. Blood Flow Metab. 16, 1250–1254.

Sadato, N., Ibanez, V., Deiber, M.-P., Cambell, G., Leonardo, M., Hallet, M., 1996. Frequency-dependent changes of regional cerebral blood flow during finger movements. J. Cereb. Blood Flow Metab. 16, 23–33.

Sahyoun, C., Floyer-Lea, A., Johansen-Berg, H., Matthews, P.M., 2004. Towards an understanding of gait control: brain activation during the anticipation, preparation and execution of foot movements. NeuroImage 21, 568–575.

Simon, S.R., Meunier, M., Piettre, L., Berardi, A.M., Segebarth, C.M., Boussaoud, D., 2002. Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. J. Neurophysiol. 88, 2047–2057.

Strangman, G., Culver, J.P., Thompson, J.H., Boas, D.A., 2002. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. NeuroImage 17, 719–731.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Tanji, J., Evarts, E.V., 1976. Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. J. Neurophysiol. 39, 1062–1068.

Thompson, J.K., Peterson, M.R., Freeman, R.D., 2003. Single-neuron activity and tissue oxygenation in the cerebral cortex. Science 299, 1070–1072.

Wolf, M., Wolf, U., Toronov, V., Michalos, A., Paunescu, L.A., Choi, J.H., Gratton, E., 2002. Different time evolution of oxyhemoglobin and deoxyhemoglobin concentration changes in the visual and motor cortices during functional stimulation: a near-infrared spectroscopy study. NeuroImage 16, 704–712.

Weinrich, M., Wise, SP., 1982. The premotor cortex of the monkey. J. Neurosci. 2, 1329–1345.

Wood, J.N., Grafman, J., 2003. Human prefrontal cortex: processing and representational perspectives. Nat. Rev., Neurosci. 4, 139–147.

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Jogging improved performance of a behavioral branching task: implications for prefrontal activation

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Abstract

We studied the effect of habitual jogging on the performance of a frontal lobe functioning test. Fourteen subjects were divided into a jogging trained group (TG) or a jogging untrained group (NG). The TG jogged for 12 weeks, for 30 min, 2.6 times per week, while the NG did not. We administered a prefrontal branching task (BR) combining a Spatial Delayed-Response Test (DR) and a Go/No-Go Test (GNG). Each test alone and a Simple Reaction Time Test (SR) were given as controls. All tests were given three times at 6 week intervals over 12 weeks in both groups. In the TG, the tests were given two times after termination of the jogging. The maximal oxygen uptake ($\dot{V}_{O_{2max}}$) was measured in the TG during the 12 weeks. After 12 weeks, the correct performance rates in the BR task were more improved in the TG than in the NG. The control and reaction time tests were unchanged in both groups. The improved performance in the BR task in the TG decreased after stopping the jogging. The $\dot{V}_{O_{2max}}$ increased significantly during the 12 weeks of jogging in the TG. Thus, the habitual jogging improved performance in a prefrontal BR.

Keywords: Habitual exercise; Executive function; Aerobic exercise training

1. Introduction

Recent imaging studies have shown that alternating leg movements, such as occur in walking, running, and bicycling activate the primary motor region and the supplementary motor region. Fukuyama et al. (1997) showed, using single photon emission tomography (SPECT), that the primary sensorimotor area and the supplementary motor area were activated with back and forth walking along a 20 m long corridor. Miyai et al. (2001) showed, by an optical imaging technique using near-infrared spectroscopic topography (NIRS), that the concentration of the oxyhemoglobin was bilaterally increased in the medial primary sensorimotor region and the supplementary motor region during walking at 1 km/h on a treadmill. Christensen et al. (2000) showed, by positron emission tomography (PET), that during active bicycling the primary motor cortex, the primary sensory cortex, and the supplementary motor cortex are bilaterally activated. Further, a PET study showed that imagining an exercise increased the activity of the right superiodorsal sensorimotor area and the right supplementary motor area (Thornton et al., 2001). Finally, a gait imaging or passive performance of bicycling study showed activation of the primary sensory cortex, the primary motor cortex, and the supplementary motor cortex (Miyai et al., 2001; Christensen et al., 2000).

In the more rostral region of the cortex such as the premotor–prefrontal regions, there is only fragmentary evidence for active involvement in alternate leg movement. Ide et al. (1999) showed, by an NIRS technique, that concentrations of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin in the prefrontal region increased during bicycling at a submaximal work intensity. Thornton et al. (2001) showed that imagining freewheel bicycling activated the right dorsolateral-prefrontal cortex and the right premotor cortex. Suzuki et al. (2002) showed, by an NIRS technique, that during 9 km/h running on a treadmill, the oxyhemoglobin concentration of the prefrontal region was increased. Further, behavioral studies are available showing that the relation between exercise training and tasks requiring prefrontal–premotor executive controls. Walking-trained elderly subjects, compared with those with strength- or

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stretching-training, are reported to show shorter reaction times in tasks requiring prefrontal–premotor executive controls, such as the task-switching test, response-compatible test, and stopping test, together with an increase in the maximal oxygen uptake (Kramer et al., 1999). Moreover, it was reported that in clinically depressed older patients, an exercise-training program (walking, jogging, and cycling) of 4 months improved performance in visual memory on the Wechsler Memory Scale and the Stroop color-word test (Khatri et al., 2001). It appears that the prefrontal–premotor region may also be involved during alternate leg movement with associated cardiovascular function improvement induced by frontally-mediated regional changes.

Previous studies using animal model, in contrast to human studies, have shown direct evidence that exercise affects biochemical, anatomical and functional changes of the cortex. In the rat, it was shown that running on a running wheel induced increased productions of neurotrophic factor and neurogenesis with enhanced spatial learning (Van Praag et al., 1999; Cotman and Berchtold, 2002; Anderson et al., 2000; De Bruin et al., 1990; Fordyce and Farrar, 1991) and angiogenesis (Black et al., 1990; Swain et al., 2003). Thus, in the rat, running may affect various cortical areas of the brain through activity-dependent regulation. Therefore, we may expect that the human prefrontal cortex would experience similar use-dependent plastic changes due to exercise training. We assumed that in the human, the prefrontal–premotor regions, in addition to various sensory cortical regions, can be activated during running and habitual jogging may possibly improve prefrontal–premotor functions. The present study investigated in the young healthy subjects whether habitual jogging (running at a relatively slow and steady speed) and its practice may improve prefrontal–premotor function. We selected prefrontal–premotor tests that are well-established in the monkey, and are similar to those introduced by Koechlin et al. (1999) which activated the prefrontal polar cortex when other prefrontal areas are activated if separately performed. We coined the test or task using the same term with Koechlin as branching task (BR) which includes a Go/No-Go Test (GNG) during the delay period of the Delayed-Response Test (DR) (spatial working memory test with Go/No-Go trials). We found an improvement in the performance of the BR together with cardiovascular function improvement after jogging training. Our preliminary results were presented previously in an abstract form (Harada et al., 2001).

2. Methods

2.1. Subjects and training schedule

A total of 14 young, right-handed subjects with no history of neurological diseases or medications participated in this study (age, 27 ± 8; eight males and six females). Volunteers were solicited from the community of the City of Handa, and included one of the authors (T.H.). Written informed consent was obtained from all subjects. They had no previous experience with the employed tests and none were involved in exercise training. The subjects were divided into two groups: a jogging trained group (TG, $N = 7$: age, 29±9; five males and two females) and a jogging untrained group (NG, $N = 7$: mean age, 26 ± 6; three males, four females). The TG did jogging training for 12 weeks. In both groups, the BR and three control frontal tests (DR, GNG, and SR) were performed three times at 6 week intervals. The maximal oxygen uptakes ($\dot{V}_{O_{2max}}$) were also measured in the TG at 6 week intervals during training. After stopping the training, the TG further performed these the task and tests two more times at 6 week intervals. All measurements were performed after 2 days of no jogging to avoid possible jogging effects. Thus, the tests and $\dot{V}_{O_{2max}}$ measurements were performed before training at week 0, at week 6, and after training at week 12. After stopping the jogging in the TG, further tests were performed at weeks 18 and 24.

Subjects in the TG jogged with a heart rate monitor (Aculex Plus; Polar Co., Tokyo, Japan), maintaining the heart rate from 40 to 60% of the individual's maximal heart rate calculated from their predicted heart rate maximums (Karvonen et al., 1957). They jogged two to four times per week, for about 30 min per day. Table 1 presents each subject's values for their average performances during the early (0–6 weeks) and late (6–12 weeks) phases of training.

Before each jogging trial, the subjects were asked to draw a simple road map of their planned course to a final destination and to estimate the time (min) to completion, spending about 5 min. Immediately after the jogging was over, they were again asked to draw another, more detailed road map, including the jogged roads, main landmarks, etc., and to record the time actually jogged (min). This task took about 10 min. After 12 weeks of training, the subjects stopped jogging. One subject dropped out of the study program at week 18 due to a job transfer.

2.2. Tests employed

The BR was the main test employed and consisted of a main DR and a subroutine Go/No-Go Test with reversals (GNG). During the delay period of the DR, GNG trials were repeated twice. As control tests, a DR, GNG, and a SR were performed. During these tests, subjects sat about 50 cm away from the front of a desktop computer (PC9821; NEC, Tokyo, Japan; right side) with a 17 in. monitor and a lap top computer (PC98-21 Lt2; NEC, Tokyo, Japan; left side) placed on the table such that they could manipulate each mouse (cf. inset of Fig. 1; right bottom). The distance between the mice and the display screens was about 30 cm. The performance of each subject was videotaped (DCR-CX2000; Sony, Tokyo, Japan).

Fig. 1A–D illustrates a sequence of task and tests. Fig. 1A shows a BR. First, in the center of the right display, an instruction (in Japanese) to press the mouse with the right hand appeared. When the mouse was pressed, a Cue phase began

Table 1
Jogging performance of seven individuals in the trained group during 0–6 and 6–12 weeks

Weeks	Subjects	Training frequency (times per week)	Jogging duration (min per week)	Heart rate (beat/min)	Estimated training intensity (%)
0–6	1	3.2	96.1	142	61.4
	2	3.6	109.8	130	51.2
	3	3.6	110.0	138	60.2
	4	2.6	78.0	137	60.2
	5	2.0	60.0	119	50.0
	6	3.6	126.0	135	54.2
	7	3.6	118.8	132	55.1
	Mean ± S.D.	3.2 ± 0.6	99.9 ± 21.7	133 ± 7	56.0 ± 4.3
6–12	1	2.2	74.8	140	60.0
	2	2.2	88.8	123	46.7
	3	3.6	118.0	151	69.8
	4	2.1	77.7	128	48.1
	5	2.0	76.0	116	47.5
	6	3.2	112.0	129	49.8
	7	2.6	104.0	132	60.7
Mean ± S.D.		2.6 ± 0.6	93.0 ± 16.8	131 ± 11	54.7 ± 8.2

The training frequency per week, jogging time (min per week), average heart rate (beat/min), and estimated training intensity of their heart rate maximum (%) are shown.

0.5 s later. A Visual Cue for the DR appeared for 0.2 s in one of eight locations (circles of 3 cm in diameter, 6–9 cm from the center) peripherally arranged in a square fashion, as shown in a display figurine above the Cue and Match phases in Fig. 1A. During the succeeding delay period of 10 s, the subject had to look at the left display of the left computer, which showed an instruction (in Japanese) to press the left mouse to start two GNG trials successively. When the subject pressed the left mouse using the left hand while continuing pressing the right mouse with the right hand, 0.5 s later one of a pair of visual figures (3 cm × 3 cm, see inset of center bottom of Fig. 1, where these pairs are shown) appeared in the center of the display in the Cue phase, indicating a 'Go trial' or ' No-Go trial'. In the case of the Go trial, as shown in the first GNG trial in Fig. 1A, the subject released the mouse within 1 s, and a Feed back tone indicating a correct response was sounded (pleasant tone), and the display was colored green for 0.5 s. Alternatively, in the case of a No-Go trial, as shown in the second GNG trial in Fig. 1A, the subject withheld pressing the mouse for 2.5 s, then a Feed back tone and a display immediately appeared for 0.5 s. After the Feed back display, the trial was reset and an instruction for the second trial appeared. There were three pairs of figure patterns (inset of Fig. 1, center bottom) and the response association was reversed between the Go stimulus and the No-Go stimulus after seven successive correct trials were completed within one figure pair and it was then changed to the next figure pattern successively{(1) → (2) → (3)}. If the mouse was pressed for more than 1 s in the Go trial, or if it was released within 2.5 s in the No-Go trial, the performance was considered erroneous, the unpleasant tone was sounded, and the display was colored red for 0.5 s, indicating that the trial was reset. After the first GNG trial, the second GNG trial (only the No-Go trial is illustrated in Fig. 1A) had to be performed successively. After the two successive GNG trials, the subject returned to the main DR. Eight peripheral circles appeared simultaneously after the delay in the Match phase, as shown in a display figurine above the Match phase, and the subject pressed the display where the previously shown location of the DR Cue phase was presented 10 s earlier. After a 0.25 s delay, the Feed back display color changed to green (correct) or to red (incorrect) with the appropriate sounds (correct response, pleasant tone; incorrect response, unpleasant tone) for 0.25 s. After the Feed back display, the trial of the DR was reset and an instruction for the next trial appeared (correction method). Thus, one branching trial, that is, one main DR with two subroutine GNG trials, was conducted. The GNG trials were reversed after seven successive correct responses, changing associations between Cue figures and responses. The BR was concluded when there were 32 correct responses in the DR, 90 trials in the GNG, or 6 reversals. When there was an error response in either the DR or GNG trial(s), the same patterns were repeated (correction method). The test took about 10 min to complete.

Fig. 1B shows the performance in a DR, being identical to the main DR, after removing the subroutine GNG, as shown in Fig. 1A. An instruction (in Japanese) to press the mouse appeared and the subject pressed the mouse using the right hand. After pressing the mouse for 0.5 s, a Cue (circle, diameter: 3 cm) appeared for 0.2 s in one of eight locations arranged peripherally in a square fashion, as shown in a display figurine above the Cue phase in Fig. 1B. After 10 s of the delay period, eight circles appeared in the Match phase simultaneously, as shown in a display figurine above the Match phase in Fig. 1B. After pressing one circle location presented in the Cue phase, a Feed back display was presented. Then the trial was reset and an instruction