of the radial component. The precise location of these precentral generators is not known, particularly since it has been shown that SMA does not receive short-latency somatosensory input directly from peripheral median nerve (Barba et al., 2003). Nevertheless, although the exact generator of N30 component cannot be determined, our findings indicate that PMC is closely linked to the generator of this SEP component.

Parkinson's disease or patients with parkinsonism in parallel with the reduction of Parkinsonian symptoms (Rossini et al., 1995; Pierantozzi et al., 1999). The increase of rCBF in SMA during voluntary movement in Parkinsonian patients was observed only in the "on" condition (Rascol et al., 1992). These studies might suggest that dopaminergic transmission in basal ganglia influenced the increase of frontal N30 component. The anatomical and functional model of basal ganglia comprises dense connections between basal ganglia and PMC (Alexander and Crutcher, 1990), a region of rCBF increasing after application of rTMS in this study.

In a previous study using the same parameters of rTMS as in the present report, Murase et al. (2005) found that rTMS over PMC improved the symptoms of patients with focal writer's cramp. They argued that very low-frequency rTMS reduced the usual overactivity in PMC that is observed in dystonia and that this contributed to the improvement in clinical symptoms. Since patients with hand dystonia have been reported to have enlarged N30 components of the SEP (Reilly et al., 1992), it might also have been expected that the N30 would be reduced by the same intervention.

At first sight, the present results in healthy subjects appear to be the opposite to those expected from the previous report since rTMS over PMC increased rCBF and increased N30. However, as noted above, an increase in blood flow is consistent with an overall reduction in physiological activity if this is caused by an increase in inhibition. Similarly, it is conceivable that an increase in N30 also reflects inhibition rather than facilitation, the opposite to the N30-decreasing effect of motor imagery (Cheron and Borenstein, 1992). As argued by Kujirai et al. (1993), inhibition of neurons may be accompanied by a decrease in membrane resistance, leading to larger current flows during synaptic activation. If so, then an inhibited neuronal population can respond to a given synaptic input with a larger surface SEP than control. Alternatively, it is possible that the enlarged N30 in dystonic patients could respond differently to rTMS than in healthy subjects. However, since Murase et al. (2005) did not examine the behavior of the N30 in their patients, this must await further studies.

In conclusion, the present study demonstrated that application of monophasic 0.2 Hz rTMS over PMC increased the amplitude of frontal N30 component of median SEPs, and this change was associated with increased rCBF of PMC and the prefrontal cortex. Our findings suggest that PMC play a role in central sensorimotor integration by influencing the incoming somatosensory input for motor control.

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References

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Allison, T., McCarthy, G., Wood, C.C., Jones, S.J., 1991. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. Brain 114, 2465–5203.

Asanuma, K., Urushihara, R., Nakamura, K., Kitaoka, K., Sei, H., Morita, Y., Shibasaki, H., Kaji, R., 2003. Premovement gating of somatosensory evoked potentials after tibial nerve stimulation. NeuroReport 14, 375–379.

Barba, C., Valeriani, M., Restuccia, D., Colicchio, G., Faraca, G., Tonali, P., Mauguiere, F., 2003. The human supplementary motor area-proper does not receive direct somatosensory inputs from the periphery. Data from stereotactic depth somatosensory evoked potential recordings. Neurosci. Lett. 344, 161–164.

Brooke, J.D., Staines, W.R., Cheng, J., Misiaszek, J.E., 1996. Modulation of cerebral somatosensory evoked potentials arising from tibial and sural nerve stimulation during rhythmic active and passive movements of the human lower limb. Electroencephalogr. Clin. Neurophysiol. 37, 451–461.

Cheron, G., Borenstein, S., 1992. Mental movement simulation affects the N30 frontal component of the somatosensory evoked potential. Electroencephalogr. Clin. Neurophysiol. 84, 288–292.

Cohen, L.G., Starr, A., 1987. Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. Brain 110, 451–467.

Cunnington, R., Iansek, R., Thickbroom, G.W., Laing, B.A., Mastaglia, F.L., Bradshaw, J.L., Phillips, J.G., 1996. Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease. Brain 119, 815–822.

Desmedt, J.E., Bourguet, M., 1985. Color imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. Electroencephalogr. Clin. Neurophysiol. 62, 1–17.

Enomoto, H., Ugawa, Y., Hanajima, R., Yuasa, K., Mochizuki, H., Terao, Y., Shiio, Y., Furubayashi, T., Iwata, N.K., Kanazawa, I., 2001. Decreased sensory cortical excitability after 1 Hz rTMS over the ipsilateral primary motor cortex. Clin. Neurophysiol. 112, 2154–2158.

Fink, G.R., Frackowiak, R.S., Pietrzyk, U., Passingham, R.E., 1997. Multiple nonprimary motor areas in the human cortex. J. Neurophysiol. 77, 2164–7214.

Hoffman, R.E., Cavus, I., 2002. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am. J. Psychiatry 159, 1093–1102.

Kanetaka, H., Matsuda, H., Asada, T., Ohnishi, T., Yamashita, F., Imabayashi, E., Tanaka, F., Nakano, S., Takasaki, M., 2004. Effects of partial volume correction on discrimination between very early Alzheimer's dementia and controls using brain perfusion SPECT. Eur. J. Nucl. Med. Mol. Imaging 31, 975–980.

Kujirai, T., Sato, M., Rothwell, J.C., Cohen, L.G., 1993. The effect of transcranial magnetic stimulation on median nerve somatosensory evoked potentials. Electroencephalogr. Clin. Neurophysiol. 89, 227–234.

Matsuda, H., Mizumura, S., Soma, T., Takemura, N., 2004. Conversion of brain SPECT images between different collimators and reconstruction processes for analysis using statistical parametric mapping. Nucl. Med. Commun. 25, 67–74.

Mima, T., Ikeda, A., Yazawa, S., Kunieda, T., Nagamine, T., Taki, W., Shibasaki, H., 1999. Somesthetic function of supplementary motor area during voluntary movements. NeuroReport 10, 1859–1862.

Munchau, A., Bloem, B.R., Irlbacher, K., Trimble, M.R., Rothwell, J.C., 2002. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. J. Neurosci. 22, 554–561.

Murase, N., Kaji, R., Shimazu, H., Katayama-Hirota, M., Ikeda, A., Kohara, N., Kimura, J., Shibasaki, H., Rothwell, J.C., 2000. Abnormal premovement gating of somatosensory input in writer's cramp. Brain 123, 1813–1829.

Murase, N., Kaji, R., Urushihara, R., Nakamura, K., Mima, T., Ikeda, A., Murayama, N., Igasaki, T., Sakata-Igasaki, M., Shibasaki, H., Rothwell, J.C., 2005. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. Brain 128, 104–115.

Muri, R.M., Rosler, K.M., Hess, C.W., 1994. Influence of transcranial magnetic stimulation on the execution of memorised sequences of saccades in man. Exp. Brain Res. 1101, 521–524.

Papakostopoulos, D., Cooper, R., Crow, H.J., 1975. Inhibition of cortical evoked potentials and sensation by self-initiated movement in man. Nature 258, 321–324.

Peschina, W., Conca, A., Konig, P., Fritzsche, H., Beraus, W., 2001. Low frequency rTMS as an add-on antidepressive strategy: heterogeneous impact on 99mTc-HMPAO and 18 F-FDG uptake as measured simultaneously with the double isotope SPECT technique. Pilot study. Nucl. Med. Commun. 22, 867–873.

Pierantozzi, M., Mazzone, P., Bassi, A., Rossini, P.M., Peppe, A., Altibrandi, M.G., Stefani, A., Bernardi, G., Stanzione, P., 1999. The effect of deep brain stimulation on the frontal N30 component of somatosensory evoked potentials in advanced Parkinson's disease patients. Clin. Neurophysiol. 110, 1700–1707.

Ragert, P., Becker, M., Tegenthoff, M., Pleger, B., Dinse, H.R., 2004. Sustained increase of somatosensory cortex excitability 5 Hz repetitive transcranial magnetic stimulation studied by paired median nerve stimulation in human. Neurosci. Lett. 356, 91–94.

Rascol, O., Sabatini, U., Chollet, F., Celsis, P., Montastruc, J.L., Marc-Vergnes, J.P., Rascol, A., 1992. Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch. Neurol. 49, 144–148.

Reilly, J.A., Hallett, M., Cohen, L.G., Tarkka, I.M., Dang, N., 1992. The N30 component of somatosensory evoked potentials in patients with dystonia. Electroencephalogr. Clin. Neurophysiol. 84, 243–247.

Rossi, S., Tecchio, F., Pasqualetti, P., Ulivelli, M., Pizzella, V., Romani, G.L., Passero, S., Battistini, N., Rossini, P.M., 2002. Somatosensory processing during movement observation in humans. Clin. Neurophysiol. 113, 16–24.

Rossini, P.M., Bassetti, M.A., Pasqualetti, P., 1995. Median nerve somatosensory evoked potentials. Apomorphine-induced transient potentiation of frontal components in Parkinson's disease and in parkinsonism. Electroencephalogr. Clin. Neurophysiol. 96, 236–247.

Rossini, P.M., Babiloni, F., Babiloni, C., Ambrosini, A., Onorati, P., Urbano, A., 1997. Topography of spatially enhanced human short-latency somatosensory evoked potentials. NeuroReport 8, 991–994.

Rounis, E., Lee, L., Siebner, H.R., Rowe, J.B., Friston, K.J., Rothwell, J.C., Frackowiak, R.S., 2005. Frequency specific changes in regional cerebral blood flow and motor system connectivity following rTMS to the primary motor cortex. NeuroImage 26, 164–176.

Satow, T., Mima, T., Yamamoto, J., Oga, T., Begum, T., Aso, T., Hashimoto, N., Rothwell, J.C., Shibasaki, H., 2003. Short-lasting impairment of tactile perception by 0.9 Hz-rTMS of the sensorimotor cortex. Neurology 60, 1045–1047.

Schluter, N.D., Rushworth, M.F., Passingham, R.E., Mills, K.R., 1998. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. Brain 121, 785–799.

Shimazu, H., Kaji, R., Murase, N., Kohara, N., Ikeda, A., Shibasaki, H., Kimura, J., Rothwell, J.C., 1999. Pre-movement gating of short-latency somatosensory evoked potentials. NeuroReport 10, 2457–2460.

Siebner, H.R., Rothwell, J.C., 2003. Transcranial magnetic stimulation. New insights into representational cortical plasticity. Exp. Brain Res. 148, 1–16.

Siebner, H.R., Tormos, J.M., Ceballos-Baumann, A.O., Auer, C., Catala, M.D., Conrad, B., Pascual-Leone, A., 1999. Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. Neurology 52, 529–537.

Siebner, H.R., Filipovic, S.R., Rowe, J.B., Cordivari, C., Gerschlager, W., Rothwell, J.C., Frackowiak, R.S.J., Bhatia, K.P., 2003. Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. Brain 126, 2710–2725.

Speer, A.M., Willis, M.W., Herscovitch, P., Daube-Witherspoon, M., Shelton, J.R., Benson, B.E., Post, R.M., Wassermann, E.M., 2003. Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: I. Effects of primary motor cortex rTMS. Biol. Psychiatry 54, 818–825.

Starr, A., Cohen, L.G., 1985. 'Gating' of somatosensory evoked potentials begins before the onset of voluntary movement in man. Brain Res. 348, 183–186.

Strafella, A.P., Paus, T., 2001. Cerebral blood-flow changes induced by paired-pulse transcranial magnetic stimulation of the primary motor cortex. J. Neurophysiol. 85, 2624–2629.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotactic Atlas of the Human Brain. Thieme Medical, New York.

Tamura, Y., Okabe, S., Ohnishi, T., N Saito, D., Arai, N., Mochio, S., Inoue, K., Ugawa, Y., 2004. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain 107, 107–115.

Tings, T., Lang, N., Tergau, F., Paulus, W., Sommer, M., 2005. Orientation-specific fast rTMS maximizes corticospinal inhibition and facilitation. Exp. Brain Res. 164, 323–333.

Tsuji, T., Rothwell, J.C., 2002. Long lasting effects of rTMS and associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. J. Physiol. 540, 367–376.

Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation. Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr. Clin. Neurophysiol. 108, 1–16.

特集　大脳機能の神経生理学的研究の進歩

誘発電位・事象関連電位を用いた研究*
—顔や表情認知の脳内情報処理—

齊藤崇子**／中島大輔***／飛松省三***

Key Words：face recognition, facial expression, N170, domain-specificity, expertise

はじめに

ヒトの脳は，階層的，並列的な処理によって網膜に到達する光情報から意味ある視覚世界を再構築(カテゴリー化)している．これによりヒトは，刻々と変化する外界の情報を視覚パターンとして認知し，適応的な行動に即座に役立てることが可能となる．われわれの物体認知能力は，その柔軟さだけでなく処理速度と正確さにおいても卓越している．ヒトは，入力から約200ms程度のわずかな時間で視覚的情報を統合し，その物体が何であるかを正確に識別している[1]．

顔および表情は，社会生活において重要かつもっとも見慣れた視覚パタンの一つである．日常場面で目にする他者の顔は，人物固有の顔の特徴(個性)に加え部分的特徴変化の複雑な組み合わせから形成されている．そのため，顔およびその表情の認知は物体認知のなかでも高度に特殊化された処理機構をもつと考えられている．

本稿では，主に視覚認知の点から顔や表情認知の基盤となる脳内メカニズムについて過去の行動学的，脳科学的知見を，事象関連電位(ERP)を中心として紹介し，顔認知をめぐる最近の研究動向を概観する．はじめに顔認知のしくみについて述べ，次に顔認知の特殊性を説明する二つの対立する仮説(モジュール説・熟達化説)を紹介する．最後に顔，表情認知に関連する心理学的モデルとERPについて概説し，それを受けた近年のERP研究の動向を述べる．

顔認知のしくみ

1．顔認知モデル

顔認知には，心理学的，神経科学的に代表的なモデルが存在する[2)3)]．

BruceとYoung[2)]は，心理学的知見および脳損傷患者における相貌失認の症例などに基づき，ヒトの顔認知処理を図1に示すI.～IV.の段階によって記述した．モデルによると，表情認知処理はII.の顔認知(人物同定)に並行して行われる．両者は同様に顔から得られる情報の処理過程であるが，それぞれの処理で抽出される情報が違う(人物同定が顔の動きや方向を無視して個人の恒常的情報を必要とするのに対し，表情認知は個人情報を無視し，顔の動作パタンを抽出する)ため，互いに独立した機構に基づくとされている．

神経科学的知見に基づき提唱されたHaxbyら[3)]のモデルは，基本構造は上述のBruceとYoung[2)]

* Brain information processing of faces and facial expressions.

** Takako SAITO, Ph.D.: 九州大学大学院芸術工学研究院音響部門〔〒815-0032 福岡県福岡市南区塩原4-9-1〕; Department of Acoustic Design, Faculty of Design, Kyushu University, Fukuoka 815-0032, Japan.

*** Taisuke NAKASHIMA, M.D. & Shozo TOBIMATSU, M.D.: 九州大学大学院医学研究院脳研臨床神経生理; Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

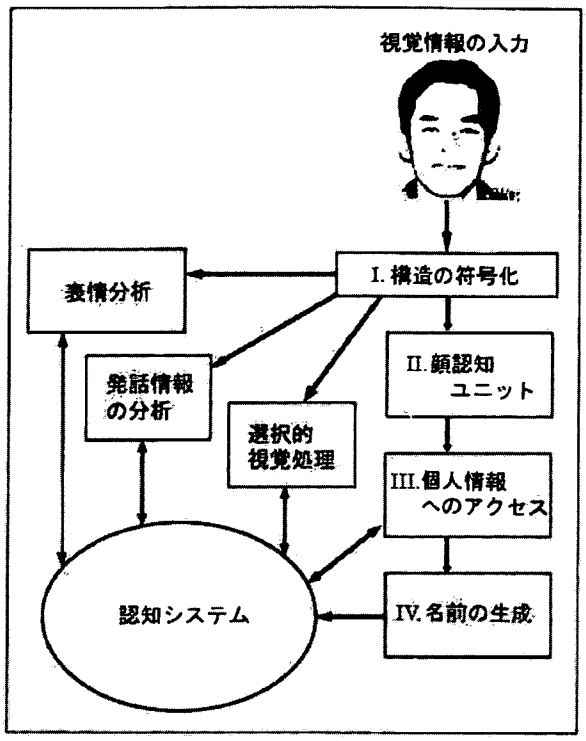

図1　Bruce & Young(1986)の顔認知モデル

に準じており，各認知過程にどのような脳部位の活動が関与しているかを対応づけて説明している(図2)．モデルの特徴として，顔の認知システムを後頭側頭領域に存在し視覚的分析を行う「コアシステム」と，他の神経システムとの連携により発話分析，表情認知，人物同定などの高次認知を行う「拡張システム」としてモデル化している点があげられる．

2．顔処理に関連する脳部位

a．顔処理の特殊性(モジュール説・熟達化説)

顔認知が固有のモジュールに基づく領域固有のものか否かについては，古くは1900年代半ばから議論されている[4]．機能的脳画像研究の隆盛によりこの問題は再び関心を集め，現在，顔認知研究における中心的な争点となっているが[5][6]，その内容は本質的には以前の議論と同様である．

モジュール説：顔認知能力はヒトにとって不可欠な能力であるため，専門化された神経経路を有すると考える研究者は多い[7]．この立場をとる研究者は，顔は領域固有のモジュールによって処理されていると主張する．顔認知と他の物体認知との質的差異に関する証拠は以下の4点に要約される[8]．

①新生児における顔への選好．

②顔特有の視覚処理を反映する心理学的現象の存在[7][9]．

③顔に選択性をもつニューロン(サルのIT野もしくは上側頭溝)，脳部位(ヒトの紡錘状回顔領野)，誘発電位N170，誘発磁場M170の存在．

④脳損傷患者において，顔と物体の認識に乖離のみられる症例の存在．

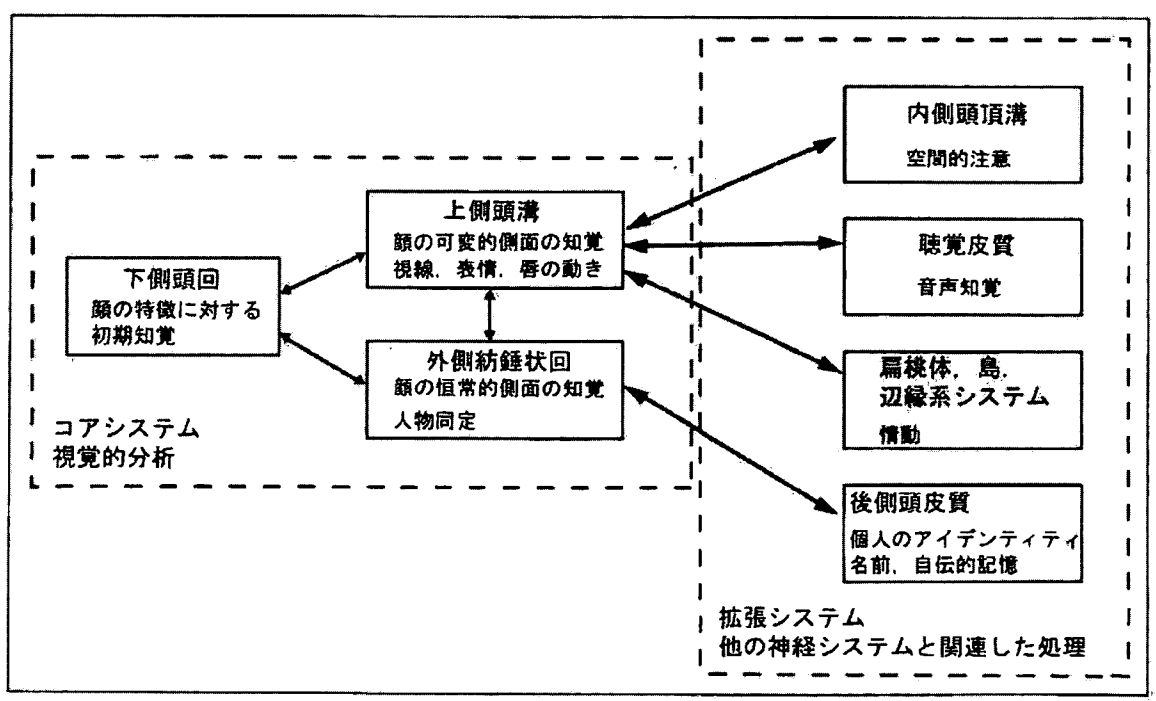

図2　Haxbyら(2000)の顔認知モデル

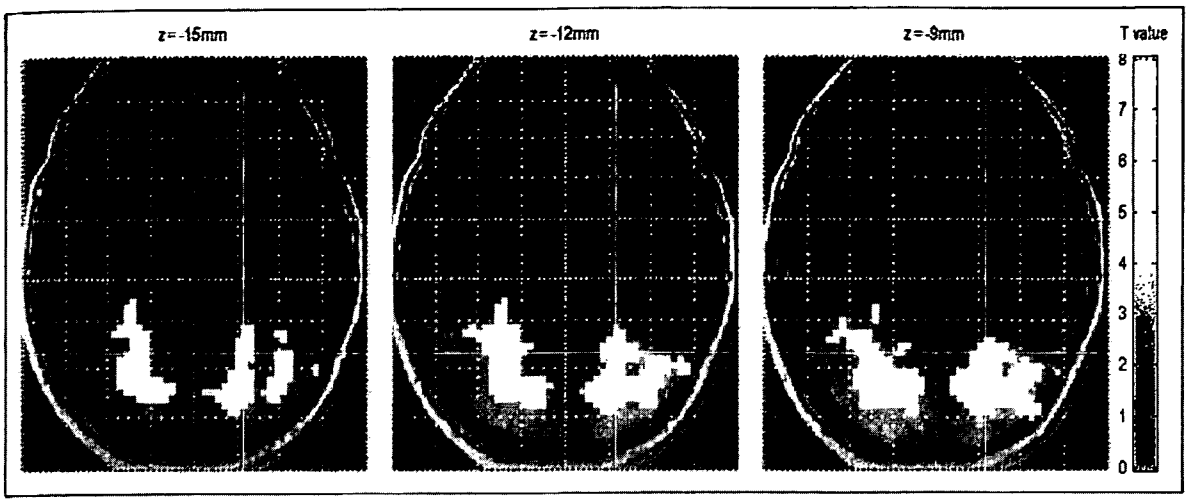

図3　顔認知時の機能的MRI画像の一例(n=1)
紡錘状回近傍で強い賦活を認める($p<.001$, uncorrected)(中島：未発表データ).

とくに脳機能的には，ヒトの視覚皮質の特定の領域(紡錘状回)が顔をみる際に他の物体をみるときよりも活性化することが知られ，この領域は顔認知に特化した脳部位として「紡錘状回顔領野(Fusiform Face Area：FFA；図3)」と呼ばれる[5]．これらの証拠はみな，顔特異的な処理システムは顔認知がヒトの生存において根源的に重要であったために進化した可能性を示唆している．

熟達化説：顔処理のモジュール性についての数々の証拠は，顔が「特別である」と容易に解釈し得るものであるが，実のところその根拠は，「顔と顔認知には完全に固有の特徴と処理様式が存在する」というやや短絡的な仮定に基づいている．仮に顔がこれらの処理特徴をもっていたとしても，それらは他の物体カテゴリーにもありうる様式かもしれない．つまり，もし顔認知特有といわれる処理特徴や計算機構が顔特有でないとすれば，顔と顔以外の物体の処理は共通のシステムによって説明できるとも考えられる[8]．前節で述べた顔処理のモジュール説に論駁する以下のような反証も存在する[10]．

①新生児は，呈示刺激の上部に多くの要素を含むあらゆる視覚パタンを好む．

②顔に対して生じる心理学的効果は，経験を重ね熟達化した観察者では新規な物体カテゴリーに対しても起こる．

③顔選択性ニューロンは視覚経験に依存して他の物体カテゴリーにも反応する．さらに，熟達効果はFFA, N/M170においても当てはまる．

④相貌失認患者においてもFFAにおいて通常の顔に対する活性化が認められる．

この立場の研究者は，領域固有の処理機構を仮定せず，顔認知の特殊性は経験により熟達化した物体認知の反映であると主張している[6]．ヒトの顔認知の特殊性は，その能力が一般的な物体認知の基本レベルよりも「下位(sub-ordinate)」レベルで行われるために特殊であるとされる．このような階層的な認知処理システムの存在を提唱している研究者も多数存在する．ヒトは微妙な部分の変化や組み合わせから個々の顔を識別しているが，それと同様には個々の花や昆虫を区別できない．つまり，われわれが日常的に行う顔認知は，花や昆虫の専門家がそれらを識別するのに等しい高度な課題であるといえる．

b．顔認知に関連した事象関連電位：N170，N200，VPP

ERP研究において，顔認知は主に物体一般の視覚情報処理の時間的側面を理解するために有効であるとして多くの研究が行われている．

ERP研究では，物体カテゴリーは後側頭皮質頭皮上より記録される脳活動によって識別できる．ERP/MEG(脳磁図)でもっとも安定して得られる顔と物体画像認知時の差異は，刺激呈示後130～200ms後の後側頭部[9)11)~13)]，あるいは頭頂部[13)]において最大振幅となる成分で，前者は一般に「N170：顔認知成分」と呼ばれる[9)11)12)](図4)．また，下線状体外皮質の頭蓋内電極から顔関連ERPを記録したAllisonら(1994)は，刺激呈示後200ms

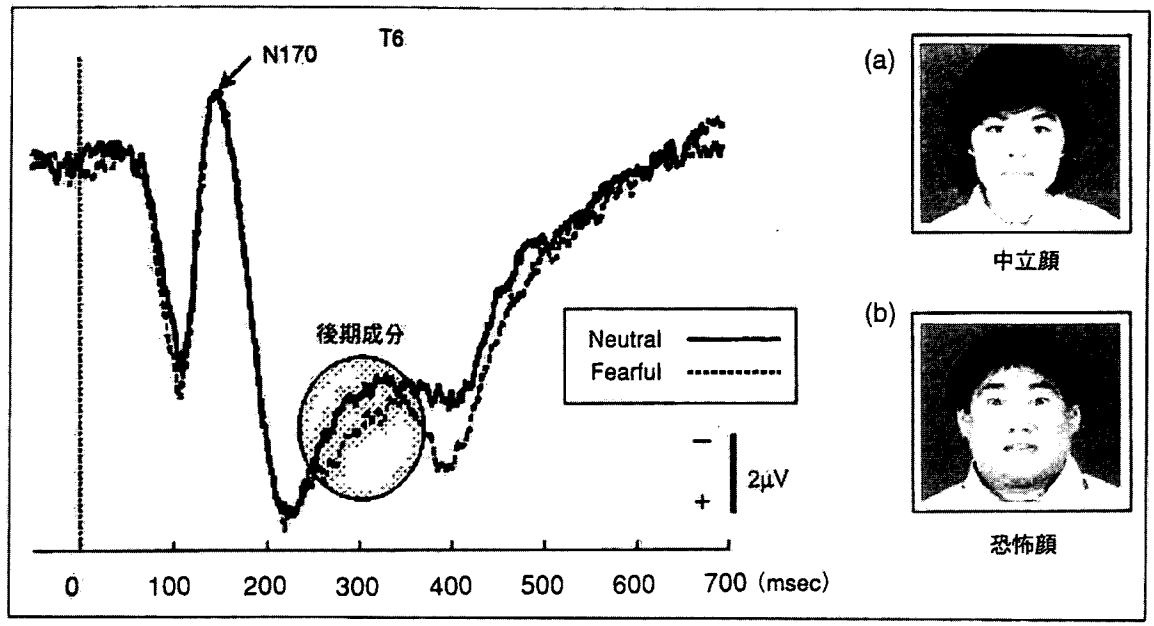

図4　顔・表情認知に関連する脳波(N170，後期陽性成分)

中立(a)あるいは恐れ表情(b)を300ms被験者に呈示し，頭皮上右後側頭部に装着した電極(T6)から得た脳波(10名の平均加算波計)．波形において，顔刺激呈示後潜時約170msに頂点をもつ陰性成分(N170)が確認できる．さらに，潜時250～300ms付近にみられる後期成分では中立と恐怖表情間に振幅差が認められる(中島：未発表データ)．

に左右紡錘状回および下側頭回から顔特異的な成分(N200)が認められると報告している[14]．

N170は後頭部P1成分(潜時約100ms)に続いて出現し，頭頂部より得られるP2あるいはvertex positive potential(VPP)[13]と呼ばれる成分と時間的に呼応して生じる．N170とVPPとは，その機能的な類似性に加え，時間的一致性，基準電極に対する極性の反転，頭皮上から推定される電流源の類似性などから同一双極子の両端をみているとの見方が強い[15]．なお，早期の顔特異的な反応が刺激呈示後60msから100msのP1成分[16]あるいはM1[17]成分に反映されるという報告もあるが，顔と物体で生じるこれら早期の差は概して低次レベルの視覚特徴の差であるという意見が一般的である[17]．

N170の発生源：N170の発生源は，後頭葉下部外側，紡錘状回，および上側頭溝近傍の3箇所のいずれかに推定されるとする報告が多い．

N170は顔特異成分か：N170が顔に特異的な事象関連電位を反映するか否かという問題については，顔認知処理全般の議論と同様にモジュール性，物体認知一般の両意見が存在し，得られる知見も各研究者の立場によって異なる[18][19]．

たとえばRossinら[18]では，顔，物体，文字画像に対するN170/VPPの潜時の差は認められず，左右半球の機能局在(顔：右優位，物体：差なし，文字：左優位)と左右差を除けばいずれのカテゴリーも後頭葉下部外側と紡錘状回後部に電流源が推定された．またPegnaら[19]は，刺激の低周波数成分を除去したバイナリー画像にノイズを加え，刺激間の視覚的見えを統制した際，顔，物体，文字画像のカテゴリー化におけるN170はそれぞれ個別の電流源が推定され，頭皮上から得られるN170成分には呈示される視覚画像の低次視覚特徴(空間周波数成分の影響や輝度差など)の処理が含まれると述べている．

しかしながら，N170(VPP)は多様な物体カテゴリーにおいて生じる電位ではあっても，その振幅は常に他の物体カテゴリーよりも顔に対して大きく，顔においてのみ顕著な方向依存性が認められる(倒立呈示において潜時が遅れ，振幅が増大する)という知見は多くの研究において一致している[20][21]．

ERP研究におけるN170の位置づけ：これらのことからN170は，下位レベルの視覚情報処理を含む物体認知の初期のカテゴリー化に関連した反応を反映する成分であると考えられる．N170とVPPの時間的特徴は，さまざまな物体の認知における後一側頭の腹側経路(what経路)の異なる

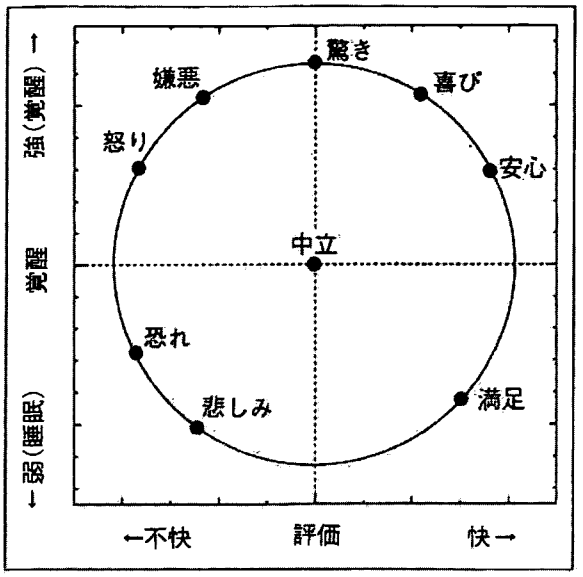

図5 表情の円環モデルと基本表情カテゴリー
表情認知の次元説を説明する二次元空間モデル.

下位プロセス(また領域)の活動を反映しており，顔を含む物体一般の視覚認知について明らかにしていくための有力な手がかりと考えられる[22].

表情認知モデル

表情認知研究においては，表情とそこから得られる感情的意味の対応づけを目的とした二つの代表的モデルが存在する(次元説，カテゴリー説；図5)．次元説では，表情は個々に独立した離散的なものではなく，いくつかの次元をもち，各次元でもつ値の組み合わせによって認識される連続的なものであるとされる．これに対しカテゴリー説では，表情には複数の基本的なパタンがあり，それらは独立した処理システムに基づくとされる．現在の脳機能画像研究やERP, MEG研究では後者の仮説に基づいた検討が主流である．

1．表情認知に関連した事象関連電位

表情の違いによるERPの差異は，頭頂部位において誘発される遅い潜時帯の陽性成分に反映されると報告されている[23]．後側頭部位においても，表情にかかわる電位変化が指摘されている[24]．Krolak-Salmonら[24]は，表情あるいは性別に注意を向けた課題での顔刺激に対するERPを比較し，表情に注意を向けた場合にのみ，後側頭部位(T5, T6)において中立顔と表情刺激間の振幅差(潜時約250～550ms)と，異なる表情刺激間での振幅差(潜時約550～750ms)が生じることを報告している．また，表情の情動価や覚醒度を評価させる課題では，N 170成分直後に生起する陽性電位(潜時約200～400ms)から，すでに中立顔と表情刺激間の振幅差がみられるとの報告もある[25].

表情認知の脳内処理過程については，動物実験や脳損傷患者の認知特徴，さらにヒトを対象とした機能的脳画像研究などにより検証されており，処理に関与する複数の脳部位が示されている．各基本表情の認知に関連する個別の脳部位が明らかとなっているが，とくに扁桃体，上側頭溝内側部，眼窩前頭皮質の3部位のネットワークがすべての表情の認知に関連する部位として重要であると考えられている[26].

2．現在のERP/MEG研究動向：物体認知処理の時間的特徴

1990年代までのERPおよびMEG研究においては，顔および物体認知処理におけるN170の役割そのものが研究の対象であったが，2000年代以降の研究では，刺激の入力から認知に至る早期の視覚情報処理過程を明らかにすることに関心が置かれるようになってきた[27][28]．これにより，われわれの脳がいつ，どのタイミングで個別の低次視覚特徴をまとめあげ，顔やそれ以外の物体認知を可能にしているのか，その時間的側面がより詳細に明らかにされつつある．これまでの報告で，顔および物体認知は刺激入力後100～130ms(P1もしくはN1)の活動を経て，その後150～170ms(N/M170)に至るまでの過程において，低次視覚情報処理→すべての物体カテゴリーに共通した全体構造の符号化→各物体カテゴリーに依存した形態の認知処理が行われることが示唆されているが，N170/ M170が顔の符号化を反映するという説と早期P1/N1/M100成分が既に物体のカテゴリー化に関与するという説があり，これ以降の研究による解明が期待される．

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文　献

1) Tobimatsu S, Celesia GG. Studies of human visual pathophysiology with visual evoked potentials. Clin Neurophysiol 2006；117：1414-33.

2) Bruce V, Young A. Understanding face recognition. Br J Psychol 1986 ; 77 : 305-7.
3) Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. Trends Cogn Sci 2000 ; 4 : 223-33.
4) Nachson I. On the modularity of face recognition-the riddle of domain specificity. J Clin Exp Neuropsychol 1995 ; 17 : 256-75.
5) Kanwisher N, McDermott J. Chun MM. The fusiform face area : A module in human extrastriate cortex specialized for face perception. J Neurosci 1997 ; 17 : 4302-11.
6) Gauthier I, Tarr, MJ, Moylan J, et al. Does visual subordinate-level categorization engage the functionally defined fusiform face area? Cogn Neuropsychol 2000 ; 17 : 143-63.
7) McKone E, Kanwisher N, Duchaine BC. Can generic expertise explain special processing for faces? Trends Cog Sci 2005 ; 11 : 8-15.
8) Tarr MJ, Cheng YD. Learning to see faces and objects. Trends Cogn Sci 2003 ; 7 : 23-30.
9) 後藤純信，鶴澤礼実，中島大輔，ほか．顔や表情認知の脳内情報処理．臨床脳波 2005 ; 47 : 701-8.
10) Gauthier I, Curby KM. A perceptual traffic jam on highway N170 interference between face and car expertise. Cur Direct Psychol Sci 2005 ; 14 : 30-3.
11) Bentin S, Allison T, Puce A, et al. Electrophysiological studies of face perception in humans. J Cogn Neurosci 1996 ; 8 : 551-65.
12) Eimer M. Effects of face inversion on the structural encoding and recognition of faces. Evidence from event-related brain potentials. Brain Res Cogn Brain Res 2000 ; 10 : 145-58.
13) Jeffreys DA. A face-responsive potential recorded from the human scalp. Exp Brain Res 1989 ; 78 : 193-202.
14) Allison T, Ginter H, McCarthy, et al. Face recognition in human extrastriate cortex. Cerebral Cortex 1994 ; 71 : 821-5.
15) Joyce C, Rossion B. The face-sensitive N170 and VPP components manifest the same brain processes : The effect of reference electrode site. Clin Neurophysiol 2005 ; 116 : 2613-31.
16) Halit H, de Haan M, Johnson, MH. Modulation of event-related potentials by prototypical and atypical faces. Neuroreport 2000 ; 11 : 1871-75.
17) Halgren E, Raij T, Marinkovic K, et al. Cognitive response profile of the human fusiform face area as determined by MEG. Cerebral Cortex 2000 ; 10 : 69-81.
18) Rossion B, Joyce CA, Cottrell, GW, et al. Early lateralization and orientation tuning for face, word and object processing in the visual cortex. Neuroimage 2003 ; 20 : 1609-24.
19) Pegna, AJ, Khateb, A, Christoph, MM, et al. Visual recognition of faces, objects, and words using degraded stimuli : Where and when it occurs. Hum Brain Mapp 2004 ; 122 : 300-11.
20) Eimer M. Effects of face inversion on the structural encoding and recognition of faces －Evidence from event-related brain potentials. Cogn Brain Res 2000a ; 10 : 145-58.
21) Itier RJ, Taylor MJ. N170 or N1? Spatiotemporal differences between object and face processing using ERPs. Cereb Cortex 2004 ; 14 : 132-42.
22) 山崎貴男，後藤純信，飛松省三．運動視および顔認知関連誘発電位．臨床脳波 2006 ; 48 : 413-18.
23) Vanderploeg RD, Brown WS, Marsh JT. Judgments of emotion in words and faces : ERP correlates. Intern J Psychophysiol 1987 ; 5 : 193-5.
24) Krolak-Salmon P, Fischer C, Vighetto A, et al. Processing of facial emotional expression : spatio-temporal data as assessed by scalp event-related potentials. Eur J Neurosci 2001 ; 13 : 987-94.
25) Marinkovic K, Halgren E. Human brain potentials related to the emotional expression, repetition, and gender of faces. Psychobiology 1999 ; 26 : 348-56.
26) Allison T, Puce A, McCarthy G. Social perception from visual cues : role of the STS region. Trends Cogn Sci 2000 ; 4 : 267-78.
27) Latinus M, Taylor MJ. Face processing stages : impact of difficulty and the separation of effects. Brain Res 2006 ; 1123 : 179-87.
28) Tarkiainen A, Cornelissen PL, Salmelin R. Dynamics of visual feature analysis and objectlevel processing in face versus letter-string perception. Brain 2002 ; 125 : 1125-36.
29) Yin RK. Looking at upride-down faces. J Exp Psychol 1969 ; 81 : 14-45.

Repetitive transcranial magnetic stimulation alters optic flow perception

Kenshi Tashiro[a], Katsuya Ogata[a], Takao Yamasaki[a], Tomomi Kuroda[a], Yoshinobu Goto[a,d], Shinji Munetsuna[e], Naoko Kinukawa[c], Jun-ichi Kira[b] and Shozo Tobimatsu[a]

Departments of [a]Clinical Neurophysiology, [b]Neurology, Neurological Institute, Graduate School of Medical Sciences, Faculty of Medicine, Kyushu University, [c]Department of Medical Information Science, Kyushu University Hospital, Higashi-Ku, [d]Department of Occupational Therapy, Faculty of rehabilitation, International University of Health and Welfare at Okawa, Okawa, Fukuoka and [e]Department of Brain Science and Engineering, Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, Japan

Correspondence to Dr Kenshi Tashiro, Department of Clinical Neurophysiology, Neurological Institute, Graduate School of Medical Sciences, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
Tel: +81 92 642 5543; fax: +81 92 642 5545; e-mail: ketashi@neurophy.med.kyushu-u.ac.jp

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Optic flow, the visual motion radiating from the center to side or opposite directions, is used to control human locomotion. Low-frequency repetitive transcranial magnetic stimulation (0.9 Hz, 10 min) was applied to the primary visual cortex (V1) and the extrastriate area (V5/MT) of 12 healthy participants to study effects of repetitive transcranial magnetic stimulation on coherent optic flow perception. Cz stimulation was used as control. Participants were instructed to correctly identify focus for dots with coherent optic flow motion. Ratios of reaction times between V1 and Cz or between V5 and Cz 40 min after repetitive transcranial magnetic stimulation significantly increased. These results suggest the prolonged inhibitory effect of low-frequency repetitive transcranial magnetic stimulation on optic flow perception. Low-frequency repetitive transcranial magnetic stimulation is a useful tool for exploring visuospatial cognition. *NeuroReport* 18:229–233 © 2007 Lippincott Williams & Wilkins.

Keywords: coherent motion perception, optic flow, prolonged effect, repetitive transcranial magnetic stimulation, visual cortex

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive method used to stimulate the human visual cortex in behaving participants. Single TMS over the occipital cortex induces flash-like light sensation, known as 'phosphenes' [1]. The minimum TMS intensity required to elicit phosphenes is defined as the phosphene threshold (PT). PT was demonstrated to remain temporally stable among participants. Visual imagery tasks decrease PT [2], and PT is lower in methylenedioxymethamphetamine (MDMA) users [3] and migraineurs [4]. Therefore, PT has been suggested to serve as an index of visual cortex excitability [5,6].

Recently, repetitive TMS (rTMS) has been widely used to modulate excitability of the regional cerebral cortex. Previous studies showed that the frequency of rTMS was an important factor. In general, low-frequency (LF) stimuli around 1 Hz reduce cortical excitability, whereas high-frequency (HF) stimuli >5 Hz facilitate excitability. The amplitude of pattern-reversal visual-evoked potentials (VEPs) in the first block and its habituation over sequential blocks decreases after LF-rTMS over the primary visual cortex (V1) in normal individuals [7]. In contrast, HF-rTMS in blind people has been reported to increase reading speed of Braille characters [8]. Several LF-rTMS studies have been previously conducted to investigate functions of the visual cortex. Stimulation of the occipital lobe increases PT [4,6], impairs visual mental imagery [9] and alters contrast detection [10].

Visual information is first carried to V1, and is subsequently processed through parallel pathways consisting of dorsal (spatial vision) and ventral (object vision) streams [11]. The extrastriate area (V5/MT) plays an important role in the dorsal pathway, and contributes to motion perception. The direction of locomotion can be determined from information defined by the optic flow (OF): that of self-motion can be directly perceived from the 'focus of radial outflow' in the OF pattern [12]. V5/MT is also a key structure for perception of OF [13]. In patients with Alzheimer's disease and mild cognitive impairment, OF perception is selectively impaired [14]. Previous studies have shown that motion priming was abolished [15], and motion after-effect duration was reduced [16] with HF-rTMS over V5/MT; however, there have been no studies on effects of LF-rTMS on coherent OF perception. Therefore, we investigated motion perception of OF after LF-rTMS over V1 or V5.

Methods

Participants

Seventeen healthy, right-handed participants (10 men and seven women; age range, 20–40 years; mean age, 25.1 years) with normal or corrected-to-normal vision participated in the experiments. All participants gave informed consent to the studies. The study was approved by the Ethics Committee of Kyushu University, and conformed with the tenets of the Declaration of Helsinki.

Phosphene threshold

On the first day of the study, PT and optimal position of TMS were determined. Participants sat on a chair in a dark

room, wore a blindfold and a swimming cap with a grid parallel to the medio-sagittal line and the interaural line to capture the accurate repositioning of the coil on the following days. We delivered paired pulse (interstimulus interval, 71 ms) TMS using a Magstim Rapid stimulator (Magstim Co., Whitland, Carmarthenshire, Wales, UK, maximal output 1.6 T) and a figure-of-eight coil (inner diameter, 70 mm) to determine PT. PT was defined as the minimal intensity of the stimulator output to evoke uniform phosphenes in at least two of three consecutive trials.

After dark adaptation for 10 min, PT of the right V1 was measured, which was completed in about 30 min. Subsequent light exposure for 5 min was given to avoid changes of visual cortex excitability owing to prolonged sensory deprivation [17]. After readaptation to darkness, PT of the right V5 was measured. We chose the right hemisphere because of its predominance in motion perception, as seen in VEP or PET studies [18,19]. The order to determine optimal positions and PTs for V1 or V5 was counterbalanced between participants.

The coil was initially positioned 1 cm laterally and 3 cm above the inion for V1, and 5 cm laterally and 3 cm above the inion for V5. Two participants did not perceive phosphenes until 80% of the stimulator output; they were excluded from the following experiments. If phosphenes were perceived, their optimal position in 1-cm steps, and optimal direction with 45° steps from upward to rightward directions, was determined.

Evaluation of optic flow perception

To assess OF perception, we used a Windows PC (NEC, Tokyo, Japan) and the 'presentation' software (neurobehavioral systems). Participants sat 57 cm away from a 15-inch monitor (30 × 22°) in a dark room. On the monitor with a black background, some of the 400 white dots, used as stimulus, were concentrated or expanded from the focus, whereas others move randomly (Fig. 1). Focus was set at 5° left or right from the center of the monitor. Participants were instructed to correctly identify the locations of focus as soon as possible by using computer mouse buttons with their thumbs. Luminance of the white dots was set at 48 cd/m^2, whereas that of the background was set at 0.1 cd/m^2; therefore, the contrast level was 99.6%. Ratios of dots (RODs) with coherent movement of 'concentrating' or 'expanding' varied at 11 steps from 5 to 70% in a random order. Each step consisted of 20 trials (1 session=20 trials × 11 steps). An OF stimulus was shown for 750 ms with an interstimulus interval of 1250 ms. Speed of dot movement was 5°/s. One session was completed in 10 min. Rate of correct choice and reaction time (RT) for each ROD were recorded.

Experimental procedures

Each experiment consisted of three sessions before, immediately after and 40 min after rTMS. rTMS (applied at a rate of 0.9 Hz for 10 min at PT intensity) was focused to Cz (control condition), to the right V1 or V5, on separate days in a counterbalanced order. Participants practiced the motion perception task 1 day before the experiment and performed one practice session before measurement on each experimental day.

Data analysis

We determined the threshold of motion perception (TMP), which was defined as the ROD yielding 81.6% of correct responses according to the Weibull's function (Fig. 2) for each participant. TMPs and mean RTs of V1 or V5 stimulations were standardized against values obtained with Cz stimulation. Effects of rTMS on TMPs and mean RTs were evaluated using two-way repeated measures analysis of variance (ANOVA) with time (before, immediately after and 40 min after rTMS) and site of stimulation (V1/Cz, V5/Cz) as within-subject factors. A post-hoc analysis was performed using a multiple comparison with Bonferroni correction. A P value less than 0.05 was considered significant for all statistical analyses.

Results

Phosphene threshold

Fifteen of 17 participants perceived phosphenes, which tended to be on the contralateral side of rTMS, and most of them were white or light green. Two participants stimulated at V1 and four participants at V5 experienced moving phosphenes. Two of 15 participants conflicted with the schedule and one participant felt discomfort during rTMS; so, only the remaining 12 participants participated in the following rTMS experiments. Mean PTs were 58.9% for V1 and 57.5% for V5, respectively. Optimal direction of the handle of the magnetic coil was mostly rightward for V1, but rightward or oblique for V5.

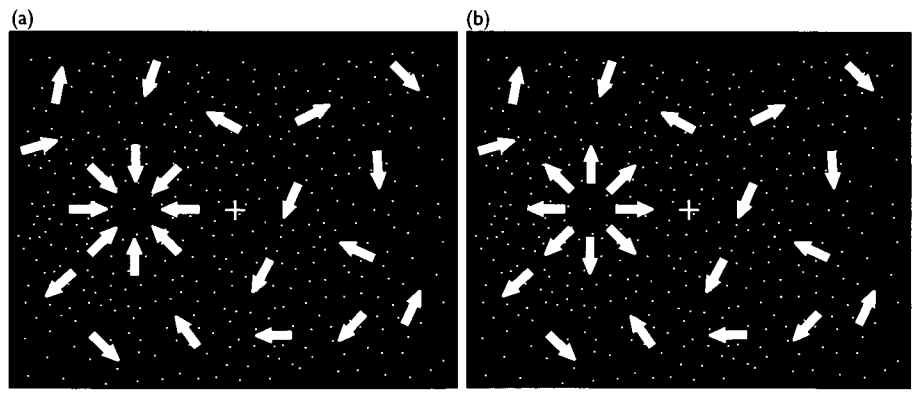

Fig. 1 Optic flow stimuli used in this study. Some of the 400 white dots used as stimulus were concentrated (a) or expanded (b) from the focus point. Participants were instructed to correctly identify locations of the focus that was left or right of the fixation point (cross).

Effect of repetitive transcranial magnetic stimulation on optic flow perception

Mean RTs at all levels of ROD and TMP for each stimulus site (V1/Cz, V5/Cz) are shown in Fig. 3. No significant temporal changes in RTs and TMPs were seen. We assumed that RTs could change mostly around TMP. Thus, we arbitrarily divided mean RTs into three subgroups: mean RTs around the threshold, subthreshold and suprathreshold (Fig. 4). Mean RT at threshold was calculated by averaging RTs at four ROD levels around TMP. Two-way ANOVA revealed a significant temporal increase in RT [$F(2,22)=4.943$; $P=0.017$], but neither a significant effect of stimulus site (V1/Cz vs. V5/Cz) nor a significant interaction between time and stimulus site was found. Multiple comparisons between time points revealed a significant decrease in RT between before rTMS and 40 min after rTMS ($P=0.023$). These results indicated that RTs for V1 and V5 stimulations increased 40 min after rTMS compared with Cz stimulation.

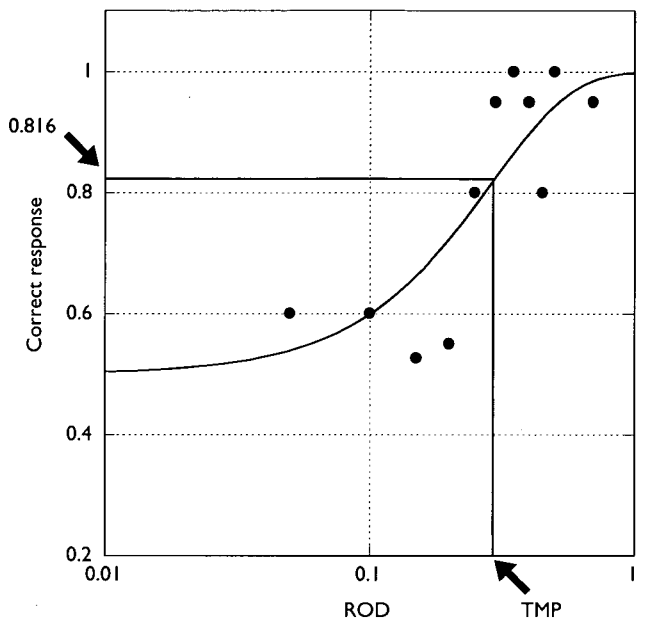

Fig. 2 Determination of the threshold of motion perception (TMP). TMP of a session (arrow) for each participant was defined as the ratio of dots (RODs) with coherent movement in stimuli yielding 81.6% of correct responses plotted according to the Weibull's function. The curve was fitted for 11 steps of ROD (filled dots). The correct response for each step was calculated for 20 trials.

Discussion

In this study, LF-rTMS over V1 or V5 inhibited OF perception, which lasted as long as 40 min as assessed by RT. We determined PT by paired TMS because of the difficulty in evoking phosphenes using single TMS in a preliminary study. Paired TMS reduced PTs as reported previously [1]. As we used rTMS with a single pulse, the intensity of rTMS was relatively low compared with paired pulse rTMS. Despite the subthreshold rTMS, we demonstrated an inhibitory effect of LF-rTMS on the visual cortex. This result was in good agreement with the results of previous studies showing that subthreshold LF-rTMS inhibited functions of the motor or visual cortex [6,20].

Significant differences were found in RTs but not in TMPs. This implied that RT might be more sensitive to cognitive changes than accuracy rate in rTMS studies [15]. So, how does RT really reflect motion perception? RT consists of visual perceptual and postperceptual (including motor response) processings; however, decision timing is not easy to specify. A recent magnetoencephalographic study [21] showed that accumulated activities in extrastriate areas identified the plausible timing of motion perception that was 150–200 ms before participants manually reacted to stimulation. Therefore, effects of LF-rTMS in our study may result from a decrease in rate or number of firing neurons in visual areas.

We also observed a significant inhibitory effect after 40 min rather than immediately after rTMS. In contrast, many rTMS studies revealed an immediate effect that lasted for a short period [7,20]. The mechanism of rTMS remains largely unclear, but the prolonged effect in our study may be related to long-term depression caused by synaptic changes or cell excitability changes [22].

OF is a stimulus related to motion perception and is important for locomotion or navigation [12]. A previous PET study [19] showed that V3 and other areas in addition to V5 and V1 were activated by OF. We demonstrated that rTMS

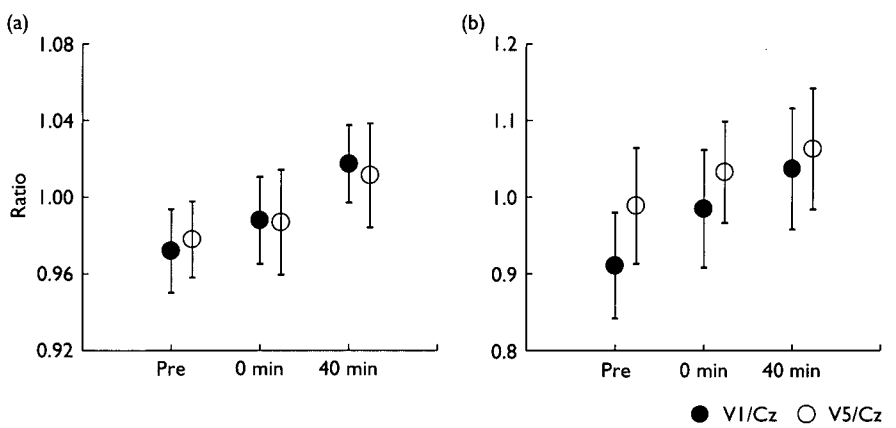

Fig. 3 Performance of motion perception: reaction time (RT) (a) and threshold of motion perception (TMP) (b). Mean RTs and TMPs of V1 or V5 stimulations were standardized against values for Cz stimulation. RTs and TMPs tended to be prolonged with time, but did not reach significant levels. Error bars indicate standard errors of means. Pre, before repetitive transcranial magnetic stimulation (rTMS); 0 min, immediately after rTMS; 40 min, 40 min after rTMS.

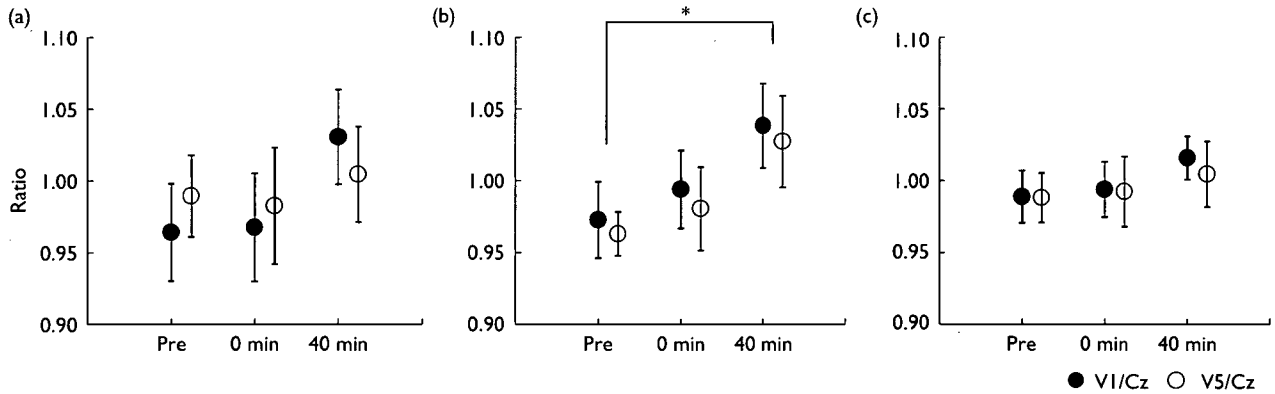

Fig. 4 Classification of reaction times into three groups: subthreshold (a), threshold (b) four steps around threshold of motion perception) and suprathreshold (c). Reaction times to the threshold level show clear changes compared with other groups, indicating a significant increase at 40 min after repetitive transcranial magnetic stimulation over V1 or V5. Error bars indicate standard errors of means. *Multiple comparisons between time points revealed a significant decrease in RT between before and 40 min after rTMS (P=0.023).

over V1 or V5 could modulate OF perception in similar manners, indicating that both V1 and V5 were important for OF perception. It is well known that visual information is processed step by step from V1 to V5/MT, and spreads to higher cortical areas. V1 and V5 stimulations may differentially affect OF perception. In fact, motion after-effect and visual motion priming were also disrupted by rTMS over V5 and not over V1 or posterior parietal cortices [15,16]. When single TMS was applied to V1 after V5, but not before V5, there was a marked decrease in quantity, and a change in quality of phosphenes elicited by V5 stimulation [23]. In addition, double-pulse TMS over V1 or V5/MT during a coherent motion task showed double dissociation in critical time windows, in which critical periods of V1 both preceded and followed that of V5/MT [24]. Although V5/MT obtains visual information through V1 feed-forward activity, back-projections from V5/MT to V1 are also critical for awareness of motion [23,24]. Thus, V1 and V5/MT differentially contribute to motion perception in a time-dependent manner. Although previous studies used single or paired TMS, LF-rTMS may result in modulation of motion perception through V1 as well as V5/MT.

OF is disturbed in patients with Alzheimer's disease and mild cognitive impairment [14], and VEPs to OF in Alzheimer's disease have also been reported to be impaired [25]. Subthreshold LF-rTMS over V1 or V5 in healthy participants can mimic visuospatial disturbance of such diseases as virtual brain lesions, as shown in this study.

Conclusion

LF-rTMS over V1 or V5 altered OF perception until 40 min after stimulation. This prolonged effect probably resulted from long-term depression. Therefore, LF-rTMS can be a useful tool for exploring visuospatial cognition.

Acknowledgements

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References

1. Ray PG, Meador KJ, Epstein CM, Loring DW, Day LJ. Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. *J Clin Neurophysiol* 1998; **15**:351–357.
2. Sparing R, Mottaghy FM, Ganis G, Thompson WL, Topper R, Kosslyn SM, *et al.* Visual cortex excitability increases during visual mental imagery: a TMS study in healthy human subjects. *Brain Res* 2002; **938**:92–97.
3. Oliveri M, Calvo G. Increased visual cortical excitability in ecstasy users: a transcranial magnetic stimulation study. *J Neurol Neurosurg Psychiatry* 2003; **74**:1136–1138.
4. Brighina F, Piazza A, Daniele O, Fierro B. Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. *Exp Brain Res* 2002; **145**:177–181.
5. Boroojerdi B, Meister IG, Foltys H, Sparing R, Cohen LG, Topper R. Visual and motor cortex excitability: a transcranial magnetic stimulation study. *Clin Neurophysiol* 2002; **113**:1501–1504.
6. Boroojerdi B, Prager A, Muellbacher W, Cohen LG. Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. *Neurology* 2000; **54**:1529–1531.
7. Fumal A, Bohotin V, Vandenheede M, Seidel L, de Pasqua V, de Noordhout AM, *et al.* Effects of repetitive transcranial magnetic stimulation on visual evoked potentials: new insights in healthy subjects. *Exp Brain Res* 2003; **150**:332–340.
8. Hamilton RH, Pascual-Leone A. Cortical plasticity associated with Braille learning. *Trends Cogn Sci* 1998; **2**:168–174.
9. Kosslyn SM, Pascual Leone A, Felician O, Camposano S, Keenan JP, Thompson WL, *et al.* The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science* 1999; **284**:167–170.
10. Antal A, Kincses TZ, Nitsche MA, Bartfai O, Demmer I, Sommer M, *et al.* Pulse configuration-dependent effects of repetitive transcranial magnetic stimulation on visual perception. *Neuroreport* 2002; **13**: 2229–2233.
11. Livingstone M, Hubel D. Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science* 1988; **240**: 740–749.
12. Warren WH Jr, Kay BA, Zosh WD, Duchon AP, Sahuc S. Optic flow is used to control human walking. *Nat Neurosci* 2001; **4**:213–216.
13. Smith AT, Wall MB, Williams AL, Singh KD. Sensitivity to optic flow in human cortical areas MT and MST. *Eur J Neurosci* 2006; **23**: 561–569.
14. Mapstone M, Steffenella TM, Duffy CJ. A visuospatial variant of mild cognitive impairment: getting lost between aging and AD. *Neurology* 2003; **60**:802–808.
15. Campana G, Cowey A, Walsh V. Priming of motion direction and area V5/MT: a test of perceptual memory. *Cereb Cortex* 2002; **12**:663–669.
16. Theoret H, Kobayashi M, Ganis G, Di Capua P, Pascual-Leone A. Repetitive transcranial magnetic stimulation of human area MT/V5 disrupts perception and storage of the motion after effect. *Neuropsychologia* 2002; **40**:2280–2287.

17. Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia F, Muellbacher W, *et al.* Enhanced excitability of the human visual cortex induced by short-term light deprivation. *Cereb Cortex* 2000; **10**:529–534.
18. Niedeggen M, Wist ER. Characteristics of visual evoked potentials generated by motion coherence onset. *Brain Res Cogn Brain Res* 1999; **8**:95–105.
19. De Jong BM, Shipp S, Skidmore B, Frackowiak RS, Zeki S. The cerebral activity related to the visual perception of forward motion in depth. *Brain* 1994; **117**:1039–1054.
20. Romero JF, Anschel D, Sparing R, Gangitano M, Pascual-Leone P. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clin Neurophysiol* 2002; **113**:101–107.
21. Amano K, Goda N, Nishida S, Ejima Y, Takeda T, Ohtani Y. Estimation of the timing of human visual perception from magnetoencephalography. *J Neurosci* 2006; **26**:3981–3991.
22. Wang H, Wang X, Scheich H. LTD and LTP induced by transcranial magnetic brain stimulation in auditory cortex. *Neuroreport* 1996; **7**:521–525.
23. Pascual Leone A, Walsh V. Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 2001; **292**:510–512.
24. Silvanto J, Lavie N, Walsh V. Double dissociation of V1 and V5/MT activity in visual awareness. *Cereb Cortex* 2005; **15**:1736–1741.
25. Kavcic V, Fernandez R, Logan D, Duffy CJ. Neurophysiological and perceptual correlates of navigational impairment in Alzheimer's disease. *Brain* 2006; **129**:736–746.

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A distinct subgroup of chronic inflammatory demyelinating polyneuropathy with CNS demyelination and a favorable response to immunotherapy

Arnold Angelo M. Pineda [a], Katsuya Ogata [b], Manabu Osoegawa [a], Hiroyuki Murai [a], Hiroshi Shigeto [a], Takashi Yoshiura [c], Shozo Tobimatsu [b], Jun-ichi Kira [a,*]

[a] *Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[b] *Department of Clinical Neurophysiology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[c] *Department of Radiology, Kyushu University, Fukuoka 812-8582, Japan*

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Abstract

To explore subclinical central nervous system (CNS) involvement in chronic inflammatory demyelinating polyneuropathy (CIDP), we recorded somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) using transcranial magnetic stimulation, to measure central sensory conduction time (CSCT) and central motor conduction time (CMCT) and examined brain and spinal cord MRI in patients with probable CIDP based on the American Academy of Neurology AIDS Task Force criteria. Eighteen patients with probable CIDP (12 males and 6 females; mean age at examination±SD, 45.8±17.0 years; range, 17–72) were included in the study. Of the 13 patients who underwent SEPs, one had prolonged CSCT (8%) and of the 13 who underwent MEPs, four had abnormal CMCT (31%). Cranial MRI revealed five of 18 patients had abnormal scans, only one of which showed multiple ovoid periventricular lesions suggestive of demyelination while none showed any intramedullary lesion on spinal cord MRI. Thus, 6 of the 18 patients were considered to have subclinical demyelinative CNS involvement which had lower disability on Global Neurological Disability Score (GNDS) ($p=0.0061$), a male preponderance (0.0537) and a larger compound muscle action potential (CMAP) amplitude in the median nerve ($p=0.005$) than those without. The decrease of GNDS with immunologic therapies was nearly significant in the former ($p=0.0556$) but not in the latter. The results of the present study suggest that subclinical CNS involvement in CIDP is not uncommon in Japanese patients and that CIDP with subclinical CNS involvement is more demyelinative thus responsive to immunotherapies while those without have more axonal damage and less responsive to immunotherapies.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Motor evoked potentials; Somatosensory evoked potentials; Central nervous system

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be an autoimmune disorder of the peripheral nervous system (PNS). Although peripheral myelin is targeted by an autoimmune attack, central nervous system (CNS) involvement has been suggested in a fraction of CIDP patients with the presence of subclinical electrophysiologic and magnetic resonance imaging (MRI) abnormalities.

In two large series, CNS involvement was clinically observed in 5% and 8% of patients, respectively [1,2]. In the electrophysiological study by Ormerod et al. [3], six of 18 patients (33%) had unilateral or bilateral abnormalities in central motor conduction time (CMCT) on motor evoked potentials (MEPs). On brain MRI, a third to a half of CIDP patients have been reported to have brain lesions [3–6] whereas demyelinating lesions with typical appearance of multiple sclerosis (MS) are uncommon; for example, two of

* Corresponding author. Tel.: +81 92 642 5340; fax +81 92 642 5352.
E-mail address: kira@neuro.med.kyushu-u.ac.jp (J. Kira).

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26 patients (8%) in the series of Hawke et al. [6]. As non-specific brain lesions are frequently encountered on MRI, the electrophysiological methods may be more suitable for detecting demyelinative CNS lesions in CIDP. Therefore, the present study was undertaken firstly to explore subclinical CNS involvement in CIDP patients without clinically overt CNS signs, by electrophysiological methods such as MEPs and somatosensory evoked potentials (SEPs), and by brain and spinal cord MRI. Moreover, it was recently shown that in CIDP patients, treatment response to intravenous immunoglobulin (IVIg) administration was in part determined by degree of peripheral axonal involvement with poor response in those with greater axonal damage [7]. However, it is unknown whether CIDP patients with subclinical CNS involvement respond to immunotherapies well or not. Thus, secondly, we aimed to clarify the difference between patients with subclinical CNS involvement and those without.

2. Subjects and methods

2.1. Subjects

Eighteen consecutive patients with probable CIDP (12 males and six females; mean age at examination±SD, 45.8± 7.0 years; range, 17–72) based on the criteria of the American Academy of Neurology AIDS Task Force were included [8]. The demographic features of the patients are described in Table 1. The mean age of onset was 40.5± 20.7 years (mean±SD; range 17–72 years). The duration of disease ranged from 2 months to 36 years (mean±SD= 5.8±10.9 years). Seven presented with weakness while eleven with combined weakness and sensory impairment. At some stage in the clinical course, all of the patients showed distal limb weakness while sensory disturbance was present in 15. None of the patients had clinical signs of CNS involvement. The clinical courses were chronic progressive in 10 patients, relapsing–remitting in three, and monophasic in five. For the assessment of neuropathy, the Global Neurological Disability Score (GNDS) was used to initially assess the motor neurological disability, sensory loss and areflexia on a scale of 1 to 15 [9]. The GNDS scores before treatment were 12.5±3.0 (mean±SD, range: 6–15). On nerve conduction studies, motor nerve conduction velocities (MCV) were all reduced in all patients in at least more than one nerve. Sensory nerve conduction velocities (SCV) were normal in 5/18, unevoked in 7/18 and reduced in 6/18 in the median nerve and normal in 4/18, unevoked in 8/18 and reduced in 4/18 in the sural nerve. Protein levels in the cerebrospinal fluid (CSF) were elevated in 13 of 17 examined (>40 mg/dl) while none had CSF pleocytosis. All but one patient were subjected to immunotherapies and a 2-point decrease in the GNDS score was considered to be effective. Seven of 17 patients (41.1%) responded to immunotherapies; high-dose corticosteroids (prednisolone 40–60 mg/day with gradual taper) were effective in two of four patients who received it, IVIg was effective in three of five patients, and plasma exchange (PE) was effective in two of five. Three patients who received PE and IVIg showed no

Table 1
Demographic features of patients with CIDP

Patient No.	Sex	Age at onset (year)	Age at exam. (year)	Duration (months or years)	GNDS at peak	CSF cell/ protein (/μl, mg/dl)	Clinical course	Response to immunotherapies	Clinical symptoms		Evoked potentials			
									Predominant symptoms	Symmetrical involvement	MEP abnormality		SEP abnormality	
											CNS	PNS	CNS	PNS
1	M	58	65	8y	15	3/217	R	IVIg: +	motor>sensory	+	−	+	ND	
2	M	28	28	1y	11	5/100	CP	IVIg: +	motor>>sensory	+	+	+	−	+
3	F	58	59	4m	15	0/33	CP	IVIg: +	motor>sensory	+	−	+	−	−
4	M	17	17	1y	15	1/58	CP	PE: −	motor	+	−	+	ND	
5	M	47	52	5y	15	1/34	CP	IVIg, PE: −	motor>sensory	+	−	+	ND	
6	F	51	52	1y	11	3/178	CP	PE: −	motor>sensory	+	−	+	−	−
7	M	31	32	11m	9	0/320	CP	IVIg, PE: −	motor>sensory	+	−	+	−	−
8	F	48	52	5y	15	1/55	CP	PE: +	motor>sensory	−	−	+	−	−
9	M	12	18	6y	15	0/266	CP	PE: −	motor>sensory	+	−	−	ND	
10	M	11	45	34y	9	0/67	R	CS: +	motor	+	−	+	+	−
11	M	66	67	1y	15	3/290	CP	CS: −	motor>sensory	+	ND		−	−
12	M	36	42	6y	6	3/62	R	IVIg, PE: −	motor>sensory	+	+	+	−	+
13	M	69	69	2m	13	1/57	M	PE: +	motor>sensory	+	+	+	ND	
14	F	26	26	2m	11	1/157	M	CS: +	motor	+	ND		−	+
15	M	46	46	2m	15	2/127	M	CS: −	motor>sensory	+	ND		−	−
16	M	1	37	36y	8	2/27	CP	IVIg: −	motor>sensory	+	+	+	−	+
17	M	46	46	2m	13	ND	CP	ND	motor=sensory	+	ND		−	+
18	F	72	72	2m	15	1/28	CP	IVIg: −	motor>sensory	−	ND		−	−

M: male; F: female; m: months; y: years; CSF: cerebrospinal fluid; R: relapsing–remitting; M: monophasic; CP: chronic progressive; ND: not done; GNDS: Global Neurological Disability Score.
Response to immunotherapies given.
IVIg: intravenous immunoglobulin (IVIg), PE: plasma exchange (PE), CS: corticosteroids.
+: effective (2 or >2-point decrease in GNDS scores), −: no change (<2-point decrease in GNDS scores).

significant improvement. One patient did not undergo any treatment.

2.2. Somatosensory evoked potential recording

The SEPs were obtained by stimulating the median nerve at the wrist and the posterior tibial nerve at the ankle with frequencies of 5 Hz and 2 Hz respectively [10]. Recording electrodes were placed over Erb's point, seventh cervical vertebra, and C3′ or C4′ over the somatosensory cortex; for the lower extremities, the electrodes were placed over the 12th thoracic vertebra and Cz′. Fz was used as the reference of all electrodes. The amplifier used was a Neuropack 8 (Nihon kohden) with a bandpass of 5–2000 Hz and averaged at 500 for the uppers and 350 for the lowers. At least two trials were superimposed to establish reproducibility. The peak latencies of the responses were measured: N9 (Erb), N13 (C7) and N20 (sensory cortex) for median nerve SEPs and N20 (Th12) and P37 (sensory cortex) for tibial nerve SEPs. Central sensory conduction time (CSCT) was calculated as N20–N13 for the upper extremities while P37–N20 for the lower extremities. The normal values for SEPs in our laboratory are as follows: for the upper extremities, for median nerve stimulation, the mean for N13–N20 is 5.89 with an upper limit of 7.33 ms, while for the lower extremities, with posterior tibial nerve stimulation, the mean for N20–P37 is 16.88 ms with an upper limit of 21.83 ms, while for peroneal nerve stimulation, the mean for N13–P28 is 14.5 ms with an upper limit of 20.08 ms [10]. Latencies exceeding the mean+3SD from the established normal values for SEPs were considered abnormal.

2.3. Motor evoked potential recordings

Magnetic stimuli were applied to the motor cortex and the seventh cervical vertebra using an eight-shaped coil for the upper extremities while a double cone coil was used for stimulating the motor cortex for the lower extremities, and the lumbar root (L4) was elicited by the eight-shaped coil [11]. The target muscles were the abductor pollicis brevis for the hands and the abductor hallucis for the legs. The stimulator used was an SMN-1200 (Nihon kohden) with a stimulus intensity of 65% of stimulator output for the upper extremity and lumbar, and 90% was used for the vertex. The amplifier was a Neuropack 8 (Nihon kohden) and the bandpass of 50–3000 Hz. We assessed MEP latencies and amplitudes (qualitatively) and calculated the central motor conduction time (CMCT): CMCT=CML−PML (CML: cortical motor latency; PML: peripheral motor latency). Normal values: the normal mean central conduction used in our laboratory for the thenar muscle central conduction is 8.61 ms with an upper limit of 10.67 ms while for the plantar muscle the mean central conduction time is 16.94 ms with an upper limit of 21.04 ms [10]. Latencies exceeding the mean+3SD from the established normal values for MEPs were considered abnormal.

2.4. Magnetic resonance imaging

MRI was performed using 1.5 T units, Magnetom Vision and Symphony (Siemens Medical Systems, Erlangen, Germany) as described previously [12]. The typical imaging parameters for brain MRI were: axial T2-weighted turbo spin-echo imaging using TR/TE=2800/90 ms, flip angle=180°; axial turbo-FLAIR imaging using TI/TR/TE=2200/9000/110 ms, flip angle=180°; and sagittal and axial precontrast and axial and coronal postcontrast T1-weighted spin-echo imaging using TR/TE range=400–460/12–17 ms, flip angle range=80–90°. One excitation, with a matrix of 256×256, a slice thickness of 5 mm, and a slice gap of 2.5 mm was used for all brain studies. Gadopentetate dimeglumine at 0.1 mmol/kg body weight was administered intravenously for contrast-enhanced studies. The typical imaging parameters for the spinal cord were as follows: sagittal T2-weighted turbo spin-echo imaging using TR/TE range=2500–2800/90–116 ms, flip angle=180°, number of excitations=3–4; sagittal T1-weighted spin-echo imaging using TR/TE range=400–440/11–12 ms, flip angle range=90–170°, number of excitations=2–3; axial T2-weighted turbo spin-echo imaging using TR/TE range=3200–5360/99–116 ms, flip angle=180°, number of excitations=3–4; axial T1-weighted spin-echo imaging using TR/TE range=400–440/12 ms, flip angle range=90–170°, number of excitations=2. For sagittal imaging, a matrix of 256×256 or 512×512, a slice thickness of 4 mm and a slice gap of 0.4 mm were used, and for axial imaging, a matrix of 256×256 or 512×512, a slice thickness of 5 mm, and a slice gap range of 1.5–5 mm were used. Both brain and spinal cord MRI's were taken at the time of illness and were independently evaluated by two of the authors, one of whom (T. Yoshiura) is a neuroradiologist who was unaware of the diagnoses.

2.5. Statistical analysis

Statistical analyses were performed using the Mann–Whitney U test to determine significant differences in age at onset, duration of disease and CSF protein levels between the two groups and the differences in GNDS scores between those with CNS involvement and those without and between before and after treatment. Fisher's exact probability test was used for sex ratio and clinical course. The p values of <0.05 were considered to be significant.

3. Results

3.1. Electrophysiological findings

Five of the 13 patients who underwent SEPs had peripheral nerve involvement, one (Patient No. 10 in Table 1) having prolonged CSCT (8%). This patient had bilateral lower extremity involvement (peroneals) with CSCTs of 22.72 ms on the right and 23.52 ms on the left. Another patient (Patient No. 15) had unevoked N13 but prolonged N20 on median

nerve SEPs bilaterally and was not regarded as having definite CNS involvement, though the possibility of CNS involvement was not fully ruled out. Of the 52 limbs examined, 12 (23%) showed prolonged latencies (compared with the normal values previously mentioned) for Erb (N9), and the seventh cervical vertebrae (N13) for the upper extremities and fourth lumbar vertebrae (N17) and twelfth thoracic vertebrae (N20) for the lower extremities with posterior tibial nerve stimulation. Of the 13 patients who underwent MEP, 12 showed peripheral involvement and four had abnormal CMCT (31%) (Table 1). Three of these four patients had unilateral involvement (left upper extremity with a CMCT of 10.8 ms, right lower extremity with a CMCT of 23.5 ms and left lower extremity with a CMCT of 39.6 ms) while one patient had bilateral lower extremity involvement with CMCT of 26.6 ms on the right and 28.4 ms on the left. Five additional patients showed unevoked MEPs at cervical or lumbar stimulation but prolonged latency of MEPs at cortical stimulation, and were not considered to have definite CNS involvement, though the possibility of CNS involvement was not completely excluded. Of the 52 limbs examined, 31 (60%) showed prolonged latencies with Erb, cervical or lumbar stimulation as compared with normal values.

3.2. Magnetic resonance imaging findings

On brain MRI, five of 18 patients had an abnormal MRI scan; of these, four were aged 50 years or older. One patient (Patient No. 13 in Table 1, 69 years old) with abnormal CMCT, showed punctate T2 prolonged lesions in the cerebral white matter on MRI, which were considered to be non-specific. In the other three patients without CMCT or CSCT abnormalities, one (Patient No. 3, 59 years old) showed T2 prolonged lesions in the right putamen and caudate nucleus suggestive of old small infarcts while the other two (Patients No. 6, 52 years old and No. 8, 52 years old) had tiny spots of T2 prolonged lesions in the white matter on cranial MRI, which were also considered non-specific. Patient No. 17, a 46-year-old male, on fluid-attenuated inversion recovery (FLAIR) imaging, showed multiple ovoid lesions of increased signal intensity in the corpus callosum bilaterally, and in the left parietal and occipital lobes which appeared MS-like (Fig. 1).

3.3. Clinical characteristics of patients with subclinical CNS involvement

For comparison of clinical features, we divided the patients by electrophysiologic and MRI findings into two groups, those with and those without subclinical CNS involvement; patients were regarded as having subclinical

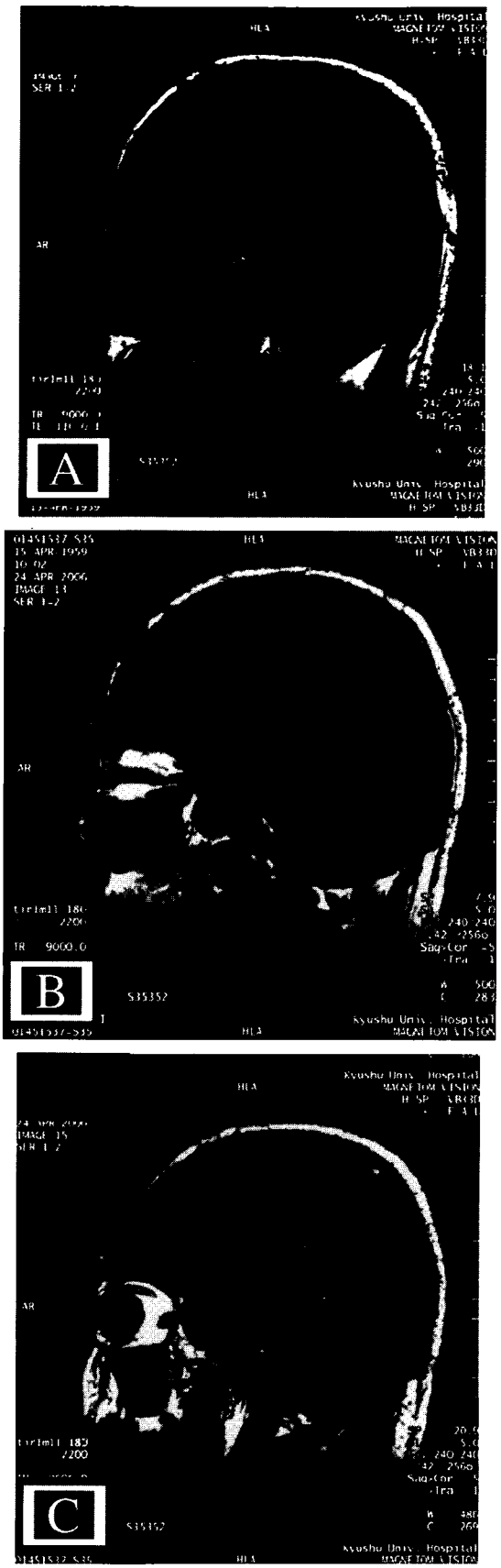

Fig. 1. Brain MRI of Patient No. 17. Sagittal fluid-attenuated inversion recovery (FLAIR) images (TR=9000 ms, TE=110 ms) of a 46-year-old male demonstrating multiple ovoid lesions of increased signal intensity in the corpus callosum, bilaterally, and in the left parietal and occipital lobes which appeared MS-like. [A] to [C]: right to left side of the patient.

demyelinative CNS involvement if they had prolonged CMCT or CSCT or MRI lesions suggestive of CNS demyelination (MS-like ovoid lesions). Based on the electrophysiological and MRI findings, six were considered to have subclinical demyelinative CNS involvement (Patient Nos. 2, 10, 12, 13, 16 and 17) and the other 11 were not. As shown in Table 2, the patients with subclinical CNS involvement showed a tendency of male preponderance ($p=0.0537$) and significantly lower GNDS scores before treatment ($p=0.0061$), as compared with those without CNS involvement. Most patients (83%) without CNS involvement showed a chronic progressive course while half of those with subclinical CNS involvement had either a relapsing–remitting or a monophasic course. In addition, the patients with subclinical CNS involvement had lower CSF protein levels than those without, but this was not statistically significant. In the peripheral nerve conduction study, CMAP amplitude in the median nerve was significantly larger in the patients with subclinical CNS involvement than those without ($p=0.005$). In addition, in half of CIDP patients without CNS involvement, tibial nerve CMAPs were unevoked while only one of six CIDP with subclinical CNS involvement were. Patients with subclinical CNS involvement showed a nearly significant decrease of GNDS scores after immunotherapy ($p=0.0556$) while the decrease of GNDS scores was not significant in those without CNS involvement (Table 2). GNDS scores after treatment were also significantly lower in the patients with subclinical CNS involvement than in those without ($p=0.0365$).

Table 2
Comparison of clinical findings between patients with subclinical CNS involvement by EP or MRI and those without

	CIDP with subclinical CNS involvement by EP or MRI ($n=6$)	CIDP without CNS involvement ($n=12$)
Male:female	6:0	6:6
Age at onset (mean±SD, years)	31.8±24.5	44.4±19.1
Duration of disease	2m–34y	2m–36y
(range, median)	3.5y	1y
Clinical course/onset		
Chronic progressive	3 (50%)	10 (83%)
Relapsing–remitting	2	1
Monophasic	1	1
GNDS before treatment	9.4±2.7*	13.8±2.2
GNDS after treatment	5.8±1.8*	11.1±4.6
CSF protein	62.6±26.1	146.9±107.5
Median nerve		
MCV, m/s	34.7±13.5	29.8±14.2
DL, ms	6.6±3.0	7.6±3.8
CMAP, mV	15.4±7.0*	5.8±3.2
Unevoked	0/6	0/12
Tibial nerve		
MCV, m/s	35.7±5.2	29.5±10.4
DL, ms	5.6±2.5	11.6±6.9
CMAP, mV	5.9±4.7	4.3±6.2
Unevoked	1/6	6/12

GNDS: Global Neurological Disability Score; CSF: cerebrospinal fluid; MCV: motor nerve conduction velocity; DL: distal latency; CMAP: compound muscle action potential. One patient from the CNS involvement group declined to have a lumbar puncture and also did not receive any immunotherapeutic intervention.
* $p<0.05$.

4. Discussion

The present study revealed subclinical CNS involvement suggestive of demyelination in Japanese patients with CIDP by combined electrophysiological and neuroimaging studies. We further described the distinct clinical features between those with and those without subclinical CNS involvement; CIDP patients with subclinical CNS involvement had lower disability and a more favorable response to immunological treatment than those without.

Although the frequent occurrence of peripheral conduction abnormalities in CIDP patients may well decrease the detection rate of CNS abnormality by EP, in the present study, about 30% of the CIDP patients demonstrated prolongation in either CMCT or CSCT, suggesting the presence of simultaneous CNS demyelination. The frequency of CNS abnormalities on EP in the present study is compatible with that reported in the previous studies [3,13]. However, though Mendell et al. [4] reported that approximately 40% of CIDP patients had MS-like periventricular, subcortical and brainstem lesions on MRI in their selected patient series, MS-like periventricular ovoid lesions were seen in only one patient in our series. Our findings are in accord with the report of Feasby et al. [5] that typical MS-like lesions are uncommon in CIDP. Our results are also compatible with those of Pakalnis et al. [13], who concluded that with a combined EP and MRI study, EP is more sensitive than MRI in detecting CNS demyelination in CIDP. Therefore, we consider that subclinical CNS involvement is not infrequent on EPs while typical MS-like lesions suggestive of demyelination on MRI are exceptional in Japanese patients. It is suggested that a combined peripheral and central nervous system demyelination is not rare, but the nature and mechanism of CNS demyelination in CIDP is probably distinct from those in MS.

Neither characteristic clinical features nor response to immunotherapies has yet to be described in CIDP patients with subclinical CNS involvement. In our series, although the number of patients is limited, it was shown that those with subclinical CNS involvement had a milder disease, and chronic progressive disease was less frequent compared with those without CNS involvement, and showed a favorable response to immunotherapies. Although therapeutic modalities were not controlled in the present study, it has been shown that IVIg, PE and corticosteroids have essentially the same efficacy in CIDP [14,15]. In previous studies, axonal loss, as shown by a decrease in CMAP or nerve biopsy, was correlated with a significantly poor response to immunotherapies such as IVIg [1,7]. In the present study, CMAP amplitudes in median nerve were significantly larger in CIDP patients with subclinical CNS involvement than those

without, while in the tibial nerve, unevoked response was more frequent in the latter than in the former. These findings, although seen in a small number of patients and a generalized conclusion should be drawn with caution, are still suggestive that CIDP patients without CNS involvement suffer more severe axonal pathology than those with subclinical CNS involvement. The high frequency of chronic progressive course in those without CNS involvement may also contribute to more severe axonal damage [7]. Such difference in pathology may in part explain the difference in treatment response between the two subgroups; CIDP with subclinical CNS involvement is more demyelinative and thus responsive to immunotherapies while CIDP without CNS involvement is more axonal and less responsive to such therapies. Fee and Fleming [16] reported that IVIg resolved CNS demyelinative lesions in a case of CIDP. Thus, subclinical CNS lesions are also likely to be caused by the same immune mechanism as that involved in PNS demyelination in this condition.

The presence of a combined central and peripheral inflammatory demyelinating neuropathy has long been proposed in the literature [3,4,6]. The results of our study support such a notion. Whether CIDP with subclinical CNS demyelination is distinct from CIDP without CNS involvement in etiology and mechanism remains to be elucidated, the combined use of MEP/SEP and brain MRI may help identify a subgroup of CIDP patients with combined central and peripheral demyelination. Future immunological and pathological studies in a larger group of patients and controlled therapeutic trials on this specific subgroup of CIDP patients are called for to further clarify the mechanisms behind this debilitating disease of the human nervous system.

References

[1] Bouchard C, Lacroix C, Plante V, Adams D, Chedru F, Guglielmi JM, et al. Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. Neurology 1999;52:498–503.

[2] Rotta FT, Sussman AT, Bradley WG, Ram Ayyar D, Sharma KR, Shebert RT. The spectrum of chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2000;173:129–39.

[3] Ormerod IEC, Waddy HM, Kermode AG, Murray NMF, Thomas PK. Involvement of the central nervous system in chronic inflammatory demyelinating polyneuropathy: a clinical, electrophysiological and magnetic resonance imaging study. J Neurol Neurosurg Psychiatry 1990;53:789–93.

[4] Mendell JR, Kolkin S, Kissel JT, Weiss KL, Chakeres DW, Rammohan KW. Evidence from central nervous system demyelination in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 1987;37 445–1291–4.

[5] Feasby TE, Hahn AF, Koopman WJ, Lee DH. Central lesions in chronic inflammatory demyelinating polyneuropathy: an MRI study. Neurology 1990;40:476–8.

[6] Hawke SHB, Hallinan JM, Mcleod JG. Cranial magnetic resonance imaging in chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 1990;53:794–6.

[7] Iijima M, Yamamoto M, Hirayama M, Tanaka F, Kastuno M, Mori K, et al. Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. Neurology 2005;64:1471–5.

[8] Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991;41:617–8.

[9] Birouk N, Gouider R, Le Guern E, Gugenheim M, Tardieu S, Maisonobe T, et al. Charcot–Marie–Tooth disease type 1A with 17p11.2 duplication; clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain 1997;120: 813–23.

[10] Suga R, Tobimatsu S, Kira J, Kato M. Motor and somatosensory evoked potential findings in HLTV-1 associated myelopathy. J Neurol Sci 1999;167:102–6.

[11] Tobimatsu S, Sun S-J, Fukui R, Kato M. Effects of sex, height and age on motor evoked potentials with magnetic stimulation. J Neurol Sci 1998;245:256–61.

[12] Su J, Osoegawa M, Matsuoka T, Minohara M, Tanaka M, Ishizu T, et al. Upregulation of vascular growth factors in multiple sclerosis: correlation with MRI findings. J Neurol Sci 2006;243:21–30.

[13] Pakalnis A, Drake ME, Barohn RJ, Chakeres DW, Mendell JR. Evoked potentials in chronic inflammatory demyelinating polyneuropathy. Arch Neurol 1988;45:1014–6.

[14] Dyck PJ, Litcy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 1994;36:838–45.

[15] Hughes RAC, Bensa S, Willison HJ, Van den Bergh P, Comi G, Illa I, Nobile-Orazio E, et al. Randomized controlled trial of intravenous immunoglobulin versus prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 2001;50:195–201.

[16] Fee DB, Fleming JO. Resolution of chronic inflammatory demyelinating poly-neuropathy-associated central nervous system lesions after treatment with intravenous immunoglobulin. JPNS 2003;8:155–8.

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Altered soleus responses to magnetic stimulation in pure cerebellar ataxia ☆

Tomomi Kurokawa-Kuroda [a,b,*,1], Katsuya Ogata [a,1], Rie Suga [a], Yoshinobu Goto [c], Takayuki Taniwaki [d], Jun-ichi Kira [b], Shozo Tobimatsu [a]

[a] *Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*

[b] *Department of Neurology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

[c] *Department of Occupational Therapy, Faculty of Rehabilitation, International University of Health and Welfare, Okawa, Japan*

[d] *Division of Respiratory and Neurology, Department of Medicine, Kurume University of Medicine, Kurume, Japan*

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Abstract

Objective: Transcranial magnetic stimulation (TMS) over the leg motor area elicits a soleus primary response (SPR) and a soleus late response (SLR). We evaluated the influence of the cerebellofugal pathway on the SPR and SLR in patients with 'pure' cerebellar ataxia.
Methods: SPRs and SLRs were recorded from 11 healthy subjects and 9 patients with 'pure' cerebellar cortical degeneration; 5 with spinocerebellar ataxia type 6 (SCA6), and 4 with late cortical cerebellar ataxia (LCCA). In addition, three patients with localized cerebellar lesions were tested.
Results: The SPR latency was significantly longer in patients than in controls, but primary responses in the tibialis anterior muscle were normal. The frequency of abnormal SLR was 38.9% in the supine position and 83.3% in the standing position. Two out of three patients with localized cerebellar lesions also showed abnormal SLR.
Conclusions: Altered SPRs in patients may result from a dysfunction of the primary motor cortex caused by crossed cerebello-cerebral diaschisis. In addition, our results suggest that 'pure' cerebellar degeneration involves the mechanism responsible for evoking SLR which is related to the control of posture.
Significance: SLR can be a useful neurophysiological parameter for evaluating cerebellofugal function.

Keywords: Soleus primary response (SPR); Soleus late response (SLR); Transcranial magnetic stimulation (TMS); Cerebellar degeneration; Posture

1. Introduction

Transcranial magnetic stimulation (TMS) of the motor cortex elicits signals that are transmitted by the corticospinal tract to the four limbs to evoke primary motor evoked potentials (MEPs). In the soleus (SOL) muscle, TMS elicits a primary response with a latency of about 30 ms followed by a late response with a latency of about 90 ms (Dimitrijević et al., 1992; Ertekin et al., 1995; Holmgren et al., 1990; Sammut et al., 1995; Valls-Solé et al., 1994). The soleus primary response (SPR) has been considered to be the direct activation of the corticospinal pathway (Lavoie et al., 1995; Wochnik-Dyjas et al., 1998), and is enhanced by standing or voluntary contraction (Ackermann et al., 1991; Valls-Solé et al., 1994). The soleus late response (SLR), on the other hand, is more prominent when the tibialis anterior (TA) is activated weakly (Ertekin et al., 1995;

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* Corresponding author. Address: Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel.: +81 92 642 5543; fax: +81 92 642 5545.
E-mail address: kurokawa@neurophy.med.kyushu-u.ac.jp (T. Kurokawa-Kuroda).

[1] These authors contributed equally to this work.

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