Functional relevance of cross-modal plasticity in blind humans

Leonardo G. Cohen, Pablo Celnik, Alvaro Pascual-Leone,
Brian Corwell, Lala Faiz, James Dambrosia, Manabu Honda,
Norihiro Sadato, Christian Gerloff, M. Dolores Catalá & Mark Hallett

Reprinted from Nature, Vol. 389, September 11, 1997 Issue

Functional relevance of cross-modal plasticity in blind humans

Leonardo G. Cohen[*], Pablo Celnik[*†], Alvaro Pascual-Leone[‡], Brian Corwell[*], Lala Faiz[*], James Dambrosia[§], Manabu Honda[*], Norihiro Sadato[‖], Christian Gerloff[*], M. Dolores Catalá[‡] & Mark Hallett[*]

* *Human Cortical Physiology Unit, and § Biometry and Field Studies Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892-1428, USA*

† *Department of Neurological Rehabilitation, Fundación de Lucha contra las Enfermedades Neurológicas Infantiles, University of Buenos Aires, Argentina*

‡ *Instituto Cajal, Universidad de Valencia, Valencia, Spain, and Laboratory for Magnetic Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA*

‖ *Biomedical Imaging Research Center, Fukui Medical School, Matuoka, Fukui 910-11, Japan*

Functional imaging studies of people who were blind from an early age have revealed that their primary visual cortex can be activated by Braille reading and other tactile discrimination tasks[1]. Other studies have also shown that visual cortical areas can be activated by somatosensory input in blind subjects but not those with sight[2–7]. The significance of this cross-modal plasticity is unclear, however, as it is not known whether the visual cortex can process somatosensory information in a functionally relevant way. To address this issue, we used transcranial magnetic stimulation to disrupt the function of different cortical areas in people who were blind from an early age as they identified Braille or embossed Roman letters. Transient stimulation of the occipital (visual) cortex induced errors in both tasks and distorted the tactile perceptions of blind subjects. In contrast, occipital stimulation had no effect on tactile performance in normal-sighted subjects, whereas similar stimulation is known to disrupt their visual performance. We conclude that blindness from an early age can cause the visual cortex to be recruited to a role in somatosensory processing. We propose that this cross-modal plasticity may account in part for the superior tactile perceptual abilities of blind subjects.

Invasive[8,9] and non-invasive[10–12] cortical stimulation can transiently disrupt specific cognitive functions, such as naming objects. Trains of stimuli are more effective than single stimuli in inducing these effects[13–15]. Task disruption by focal stimulation has been interpreted as a sign that the stimulated region is functionally important for performance[9]. When applied to occipital regions in subjects with normal sight, transcranial magnetic stimulation (TMS)[16] can transiently suppress visual perception of letters[17] and extrafoveal targets[18], an effect thought to occur by interference with visual calcarine[17] and association cortical areas at depths of 1.5–2.25 cm below the scalp surface[19]. We have applied TMS to different scalp locations (Fig. 1a) to interfere with the function of different cortical areas during tactile identification of Braille letters and embossed Roman letters in early-blind subjects (EB_B, EB_R) and of embossed Roman letters in sighted volunteers (SV_R).

Five early-blind subjects who are experienced Braille readers (Table 1) were given strings of 'grade I' non-contracted, non-word Braille letters to read, and five sighted volunteers and four of the early-blind subjects were given a tactile discrimination task requiring identification of embossed Roman letters. Letters were presented with a specially designed device in a window of 6.4 × 1.9 cm (Fig. 1b). Subjects were asked to identify and read aloud letter by letter as quickly and accurately as possible. Phonographic recordings of voice and electromyographic recordings from hand muscles involved in the reading task were monitored (Fig. 1c). Overall accuracy in reading performance before TMS was 94.8 ± 4.6% for the EB_B group, 95.0 ± 3.0% for EB_R group, and 95.5 ± 2.0% for the SV_R group (Wilcoxon tests, non-significant).

In the EB_B and SV_R groups there was a significant effect of stimulated scalp position on the error rate ($P \leq 0.001$). In the EB_B group, mid-occipital stimulation induced more errors than the control condition (stimulation in the air) ($P \leq 0.001$, odds ratio (OR) = 2.95, confidence interval (CI) = (1.96, 4.45)) (Fig. 2). In addition, stimulation of occipital positions occasionally elicited distorted somatosensory perceptions. Blind subjects reported a combination of negative ("missing dots", "dots felt faded"), positive ("phantom dots", "extra dots"), and confusing sensations ("dots don't make sense"). When comparing error rates in the EB_R and SV_R groups (blind and sighted subjects performing the same task) a logistic regression analysis showed a significant effect of group (OR = 3.55, CI = (2.17, 5.74)) and position (OR = 2.38, CI = (1.63, 3.47)) (Fig. 2). In the EB_R group, as with the EB_B group, midoccipital stimulation induced more errors than control (stimulation in the air) ($P \leq 0.001$, OR = 3.41, CI = (1.57, 7.40)). These findings support the view that the occipital cortex is functionally active despite decades of visual deafferentation[20,21], and is engaged in active and meaningful processing of tactile information related but not limited to Braille reading. The results of a similar Braille-reading protocol implemented by a different subset of investigators on a different group of early-blind subjects (UV_B, overall accuracy level pre-intervention, 95.4 ± 1.85%) (Table 1) also showed a significant effect of stimulated scalp position on the error rate (OR = 0.89, CI = (0.84, 0.95)). Stimulation of mid-occipital ($P \leq 0.001$, OR = 2.49, CI = (1.77, 3.51)) and contralateral occipital ($P \leq 0.001$, OR = 1.84, CI = (1.30, 2.62)) positions induced more errors than the control condition (Fig. 2). The UV_B group had higher error rates overall and a higher proportion of errors with stimulation of lateral occipital positions than the EB_B group. These differences are probably related to the higher stimulus intensities used in the UV_B group (see Methods).

Sensory processing for touch and vision seem to be segregated up to their arrival in primary reception areas (Brodmann areas 3, 1 and 2 for touch and 17 for vision). The early convergence of visual and

Table 1 Clinical characteristics of the early blind subjects

Subject	Age (years)	Sex	Age of blindness	Cause of blindness*	Age of Braille reading (years)	Years of reading Braille	Visual perception	Daily reading (h)	Reading hand	Preferred hand
Early blind EB										
1	44	M	3 months	Glaucoma	5	39	None	2	Both	Left
2	38	M	birth	Premat. retinitis	4	29	None	4	Both	Right
3	63	M	4 years	Meningitis	6	57	None	6	Both	Right
4	47	F	birth	Premat. retinitis	6	41	Bright lights	2	Left	Left
5	44	F	birth	Glaucoma	5	39	None	2	Both	Right
mean	47.20				5.20	41.00		3.20		
s.d.	9.42				0.84	10.10		1.79		
Early blind UV										
1	53	F	9 years	Glaucoma	9	43	None	4	Right	Right
2	52	F	birth	Congen. anophthalmos	6	42	None	1.5	Both	Right
3	47	F	birth	Premat. retinitis	5	42	None	2	Both	Right
4	42	M	2 years	Traumatic	6	38	None	4.5	Both	Right
5	53	F	birth	Premat. retinitis	5	48	None	5	Both	Right
mean	49.40				6.20	42.60		3.40		
s.d.	4.83				1.64	3.58		1.56		

* Premat., premature; congen., congenital.

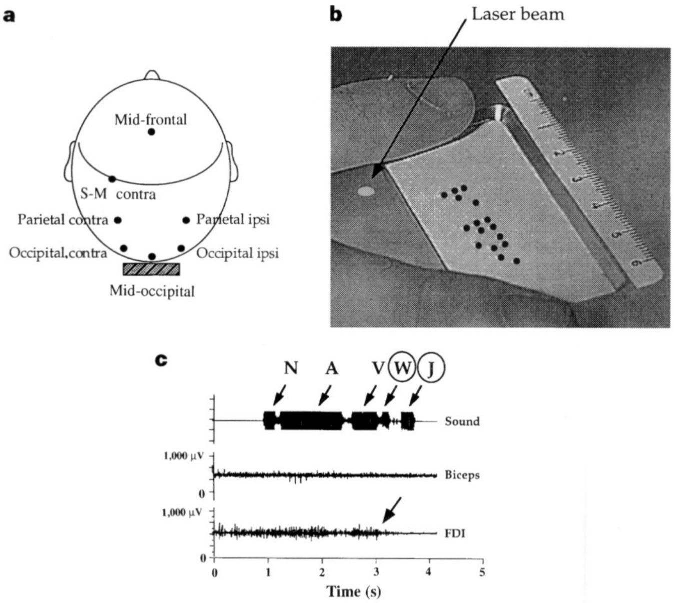

Figure 1 a, Schematic representation of the top of the head showing the scalp positions stimulated. The magnetic coil is shown positioned over the mid-occipital position. S-M, sensorimotor cortex; contra, contralateral; ipsi, ipsilateral. **b**, The index finger resting on a finger station. As the subject positioned the finger to read the first letter, the finger crossed a laser beam, triggering a 3-s period of TMS. **c**, Electromyographic activity from the first dorsal interosseous (FDI), which is a muscle active in tactile exploration required for the reading task, and biceps brachii (recorded for safety monitoring purposes), and phonographic recordings indicating the latency of letter identification (N, A, V, W and J). The reading task was completed approximately 3 s after the onset of stimulation (in this example, to the mid-occipital region of a blind subject; arrow in FDI channel). The circled letters, W and J., were read incorrectly.

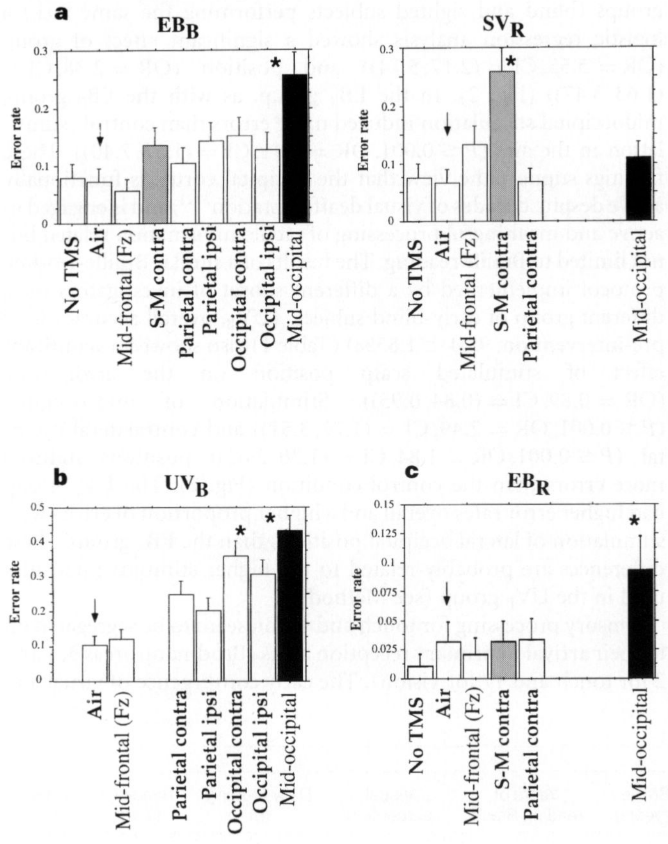

Figure 2 Error rates (mean ± s.e.) for stimulation of different positions in the four groups studied. Missing bars indicate that stimulation at that position was not performed in that specific group (see Methods). Black bars indicate error rates induced by stimulation of the mid-occipital position, and grey bars the error rates induced by stimulation of the contralateral sensorimotor cortex. In both groups of early blind subjects, stimulation of the mid-occipital position induced more errors in reading Braille and Roman letters than stimulation of any other position, whereas in the sighted volunteers stimulation of the contralateral primary sensorimotor region induced more errors than stimulation of any other position. Asterisks indicate scalp positions where significantly more errors occurred than control (air, marked with arrows). S-M, sensorimotor cortex; contra, contralateral; ipsi, ipsilateral. Asterisk, $P < 0.001$.

somatosensory information in sighted mammals occurs at cortical association sites[2]. It is possible that connections between parietal and visual association areas mediate the transfer of somatosensory information to the occipital cortex in blind subjects[22]. If so, what operations does the occipital cortex perform with the tactile information? In our experiment, speech was not affected by stimulation of any site, and errors were not corrected when subjects were given a chance to restate their choice after the end of stimulation. This indicates that errors were not due to interference with speech (output), but to disruption of discrimination processing. TMS over contralateral sensorimotor cortex and over parietal sites was relatively less effective in inducing errors than over mid-occipital areas (Fig. 2). Therefore, arrival of somatosensory information in primary somatosensory cortex (input) was relatively spared by TMS in blind subjects. Because primary input (somatosensory) and output (speech) were spared, the effects of mid-occipital TMS are thought to be related to interference with more complex discriminative operations performed by the occipital cortex in the blind. The occasional induction of complex sensations (phantom or extra dots) with occipital TMS supports this interpretation. Stimulation of sensorimotor regions that resulted in jerking of contralateral hand muscles (each TMS train produced 12.20 ± 4.43 motor

Table 2 Number of letters read in 3 s

	5 Braille letters EB$_B$		3 Roman letters SV$_R$		3 Roman letters EB$_R$	
	Unstimulated trials	Stimulated trials	Unstimulated trials	Stimulated trials	Unstimulated trials	Stimulated trials
Mean	3.80	3.73	2.38	2.44	2.80	2.86
S.d.	0.83	1.10	0.49	0.62	0.40	0.34

evoked potentials in the SV$_R$ and 12.40 ± 3.38 in the EB$_B$ groups) did not induce sensations of missing or extra dots in any of the subjects tested.

In the SV$_R$ group, there was a significant effect of stimulated scalp position on the error rate. Stimulation of the occipital cortex did not affect identification of embossed Roman letters or induce abnormal somatosensory perceptions. This result, in combination with the decrease of occipital activity on positron emission tomography in subjects performing a similar task[1], suggests that sighted individuals do not normally use the occipital cortex for identification of embossed Roman letters as the blind do for Braille and Roman letter reading. Stimulation of the contralateral sensorimotor cortex induced more errors than in the control condition ($P \leq 0.001$, $OR = 2.95$, $CI = (1.95, 4.48)$). Because the ability to interfere with a task is likely to depend on how well learned the task is, the hand movements induced by stimulation of the contralateral sensorimotor cortex may have exerted a more disruptive effect in the less-trained sighted readers than in the highly trained blind readers. Alternatively, sighted subjects may have spent more time than blind subjects in somatosensory processing, making the task more susceptible to disruption by TMS over the contralateral sensorimotor cortex.

The finding that the occipital cortex is an important component of the network involved in Braille reading supports the idea that perceptions are dynamically determined by the characteristics of the sensory inputs rather than only by the brain region that receives those inputs, at least in the case of early blindness[2,7]. These results show that cross-modal plasticity as identified electrophysiologically or by neuroimaging techniques in humans may be involved in functional compensation. □

Methods

Subjects. Study protocols were approved by the Institutional Review Boards of the National Institute of Neurological Disorders and Stroke and the University of Valencia, and TMS was used under a US Food and Drug Administration investigational device exemption. Subjects gave their written informed consent for the study. Blind subjects had normal brain magnetic resonance images and no progressive neurological disease. Sighted volunteers had normal neurological examinations and visual acuity better than 20/40.

Stimulation technique. Each train of TMS was triggered by the reading finger crossing a laser beam (Fig. 1b) and had a fixed frequency of 10 Hz and a duration of 3 s. TMS was delivered with a magnetoelectric stimulator (Cadwell Laboratories, Kennewick, WA) and an 8-shaped[23] water-cooled coil, each loop of which was 7 cm in diameter. The coil was held tangentially to the scalp with the intersection of both loops oriented sagittally. The stimulus intensity (normalized across subjects) was 10% above the minimal output of the stimulator required to induce a 50-μV electromyographic response from a relaxed muscle (first dorsal interosseous) involved in the Braille reading task when the stimulus was applied over the primary motor cortex.

Positions stimulated. See Fig. 1a. In the blind subjects (EB$_B$, see Table 1), TMS was delivered randomly to three occipital positions (midline, contralateral and ipsilateral to the reading finger, overlying Brodmann areas 17, 18 and 19; Oz, O1 and O2 of the international 10–20 system of electrode placement), two parietal positions (contralateral and ipsilateral, approximately overlying Brodmann area 7; P3 and P4), a midfrontal position (Fz) and to the contralateral sensorimotor area (overlying Brodmann areas 4, 3, 1 and 2)[24]. As a control condition, TMS was also delivered into the air (the sound of the stimulator was as loud as in actual brain stimulation, but no stimulation reached the brain). In the sighted volunteers (SV_R, mean age 51.0 ± 11.5 years, 4 right handed and 1 ambidextrous) and in the blind group reading Roman letters (EB_R) TMS was delivered randomly to midline occipital (Oz), contralateral parietal (P3 or P4), contralateral sensorimotor, and midfrontal (Fz) positions, and into the air. In both blind and sighted groups, reading was also done in the absence of TMS.

Reading. Five blind subjects identified 25 Braille letters (out of 26 possible options) presented in 5 strings of 5 letters each for each scalp position stimulated. All sighted volunteers and 4 of the blind subjects identified 24 single Roman letters (out of 5 possible options) presented in 8 strings of 3 letters each for each scalp position stimulated. The question we addressed was whether the occipital activation associated with Braille reading is functionally relevant for task performance. Therefore, we included the control task in which both sighted volunteers and blind subjects identified embossed Roman letters, a task also involving form recognition of known objects. Because very few sighted subjects read Braille, and most of these use visual and not somatosensory input when learning Braille (an experience shared by other investigators[4,25]), we could not study sighted volunteers identifying Braille letters. To ensure a similar overall prestimulation accuracy level in both groups, the blind (EB_B) subjects were presented with a higher number of possible letters to choose from (26 letters) than the sighted (SV_R) subjects (5 letters). The reason for using strings of 3 letters in the sighted and 5 letters in the blind was that sighted subjects read at a slower rate than blind subjects. In unstimulated trials, the EB_B group identified letters 1–5 in 1.0 ± 0.4, 1.6 ± 0.4, 2.1 ± 0.5, 2.7 ± 0.5 and 3.2 ± 0.6 s after reading began; the SV_R group identified letters 1–3 in 1.0 ± 0.2, 2.1 ± 0.3 and 3.1 ± 0.3 s; and the EB_R group in 0.9 ± 0.0, 1.7 ± 0.2 and 2.6 ± 0.3 s. There were no significant differences in the number of letters read in trials with and without TMS (Table 2). Therefore the 3 s of TMS covered most of the reading time in the three groups. To keep the total number of TMS trains the same in the EB_B, EB_R and SV_R groups, subjects reading Roman letters were stimulated more times (8 as opposed to 5 for Braille letters at each scalp position) over fewer positions. The order of string presentations and stimulated positions were randomized across subjects. A.P.L. and M.D.C., who did not participate in testing the EB groups, used a similar protocol to study a different group of 5 early blind subjects (UV_B; Table 1). This study differed from that in the EB groups in that: TMS trains lasted for 5 instead of 3 s, and the intensity was 20% above motor threshold instead of 10%; contralateral sensorimotor positions were not stimulated; and there were no trials without TMS. The parameters used in the UV_B group (10 Hz, 20% above motor threshold, 5 s duration) are close to those now known to potentially induce seizures and should be used with extreme caution[26,27]. Errors were defined as wrong identification or inability to identify letters. Subjects were encouraged to report sensations felt after each TMS train.

Statistical analysis. A general linear model with a binary link function[28] was used to test the effects of string and letter while accounting for subject and stimulated scalp position with both groups reading Roman letters. Because no significant effects were found for letter and string, logistic regression models[29,30] were developed to assess the effects of stimulated scalp position on error rates in EB_B, EB_R, SV_R and UV_B groups, and to examine the differences between blind and sighted subjects reading Roman letters. Significance was defined as $P \leq 0.001$. Odds ratios (OR) and their confidence intervals (CI) are shown. To comply with safety regulations, we tested the minimal number of subjects required to answer the question posed according to prospective power analysis: does occipital stimulation affect identification of Braille letters by the blind?

Received 18 March; accepted 2 July 1997.

1. Sadato, N. *et al.* Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* **380,** 526–528 (1996).
2. Pons, T. Novel sensations in the congenitally blind. *Nature* **380,** 479–480 (1996).
3. Wanet-Defalque, M.-C. *et al.* High metabolic activity in the visual cortex of early blind subjects. *Brain Res.* **446,** 369–373 (1988).
4. Uhl, F., Franzen, P., Lindinger, G., Lang, W. & Deecke, L. On the functionality of the visually deprived occipital cortex in early blind persons. *Neurosci. Lett.* **124,** 256–259 (1991).
5. Uhl, F., Franzen, P., Podreka, I., Steiner, M. & Deecke, L. Increased regional cerebral blood flow in inferior occipital cortex and cerebellum of early blind humans. *Neurosci. Lett.* **150,** 162–164 (1993).
6. Kujala, T. *et al.* Visual cortex activation in blind subjects during sound discrimination. *Neurosci. Lett.* **183,** 143–146 (1995).
7. Rauschecker, J. P. Compensatory plasticity and sensory substitution in the cerebral cortex. *Trends Neurosci.* **18,** 36–43 (1995).
8. Penfield, W. & Roberts, L. (eds) *Speech and Brain Mechanisms* (Princeton Univ. Press, 1959).
9. Ojemann, G. A. Brain organization for language from the perspective of electrical stimulation mapping. *Behav. Brain. Sci.* **6,** 190–206 (1983).
10. Pascual-Leone, A., Gates, J. R. & Dhuna, A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* **41,** 697–702 (1991).
11. Cohen, L. G., Bandinelli, S., Sato, S., Kufta, C. & Hallett, M. Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. *Electroencephalogr. Clin. Neurophysol.* **81,** 366–376 (1991).
12. Pascual-Leone, A., Wassermann, E., Grafman, I. & Hallett, M. The role of the dorsolateral prefrontal cortex in implicit procedural learning. *Exp. Brain Res.* **107,** 479–485 (1996).
13. Luders, H. *et al.* in *Surgical Treatment of the Epilepsies* (ed. Engel, J.) 297–321 (Raven, New York, 1987).
14. Henderson, D. C., Evans, J. R. & Dobelle, W. H. The relationship between stimulus parameters and phosphene/brightness during stimulation of human visual cortex. *Trans. Am. Soc. Artif. Intern. Organs* **25,** 367–371 (1979).
15. Bridley, G. S. & Lewin, W. S. The sensations produced by electrical stimulation of the visual cortex. *J. Physiol. (Lond.)* **196,** 479–493 (1968).
16. Barker, A. T., Jalinous, R. & Freeston, I.L. Noninvasive magnetic stimulation of human motor cortex. *Lancet* (i), 1106–1107 (1985).
17. Amassian, V. E. *et al.* Suppression of visual perception by magnetic oil stimulation of human occipital cortex. *Electroencephalogr. Clin. Neurophysiol.* **74,** 458–462 (1989).
18. Epstein, C. M. & Zangaladze, A. Magnetic coil suppression of extrafoveal visual perception using disappearance targets. *J. Clin. Neurophysiol.* **13,** 242–246 (1996).
19. Epstein, C. M., Verson, R. & Zangaladze, A. Magnetic coil suppression of visual perception at an extracalcarine site. *J. Clin. Neurophysiol.* **13,** 247–252 (1996).
20. Rushton, D. N. & Bridley, G. S. in *Frontiers in Visual Science* (eds Cool, S. J. & Smith, E. L.) 574–593 (Springer, New York, 1978).
21. Schmidt, E. M. *et al.* Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. *Brain* **119,** 507–522 (1996).
22. Bruce, C., Desimone, R. & Gross, C. G. Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. *J. Neurophysiol.* **46,** 369–384 (1981).
23. Cohen, L. G. *et al.* Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. *Electroencephalogr. Clin. Neurophysiol.* **75,** 350–357 (1990).
24. Homan, R. W., Herman, J. & Purdy, P. Cerebral location of international 10-20 system electrode placement. *Electroencephalogr. Clin. Neurophysiol.* **66,** 376–382 (1987).
25. Pascual-Leone, A. *et al.* Modulation of motor cortical outputs to the reading hand of braille readers. *Ann. Neurol.* **34,** 33–37 (1993).
26. Wassermann, E. M. Risk and safety in repetitive transcranial magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol.* (in the press).
27. Chen, R. *et al.* Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroencephalogr. Clin. Neurophysiol.* (in the press).
28. McCullagh, P. & Nelder, J. A. (eds) *Generalized Linear Models* (Chapman and Hall, London, 1989).
29. Homser, D. W. & Lemeshow, S. (eds) *Applied Logistic Regression* (Wiley, New York, 1989).
30. Anderson, J. A. Separate sample logistic discrimination. *Biometrika* **59,** 19–35 (1972).

Acknowledgements. We thank our subjects for their cooperation; G. Dold and N. Dang for engineering support; E. Corthout, Ulf Ziemann, J. Classen and J. Grafman for comments; and B. J. Hessie for editing.

Correspondence and requests for materials should be addressed to L.G.C. (e-mail: lcohen@codon.nih.gov).