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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. Other studies have also shown that visual cortical areas can be activated by somatosensory input in blind subjects but not those with sight. 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 and non-invasive 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. Task disruption by focal stimulation has been interpreted as a sign that the stimulated region is functionally important for performance. When applied to occipital regions in subjects with normal sight, transcranial magnetic stimulation (TMS) can transiently suppress visual perception of letters and extrafoveal targets, an effect thought to occur by interference with visual calcarine and association cortical areas at depths of 1.5–2.25 cm below the scalp surface. 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\textsubscript{R}, EB\textsubscript{L}) and of embossed Roman letters in sighted volunteers (SV\textsubscript{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 electroencephalographic 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\textsubscript{R} group, 95.0 ± 3.0% for EB\textsubscript{L} group, and 95.5 ± 2.0% for the SV\textsubscript{R} group (Wilcoxon tests, non-significant).

In the EB\textsubscript{R} and SV\textsubscript{R} groups there was a significant effect of stimulated scalp position on the error rate (P ≤ 0.001). In the EB\textsubscript{R} group, mid-occipital stimulation induced more errors than the control condition (stimulation in the air) (P ≤ 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\textsubscript{R} and SV\textsubscript{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\textsubscript{R} group, as with the EB\textsubscript{L} group, mid-occipital stimulation induced more errors than control stimulation in the air (P ≤ 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, 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\textsubscript{R}, 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 ≤ 0.001, OR = 2.49, CI = (1.77, 3.51)) and contralateral occipital (P = 0.001, OR = 1.84, CI = (1.30, 2.62)) positions induced more errors than the control condition (Fig. 2). The UV\textsubscript{R} group had higher error rates overall and a higher proportion of errors with stimulation of lateral occipital positions than the EB\textsubscript{R} group. These differences are probably related to the higher stimulus intensities used in the UV\textsubscript{R} 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

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**Table 1 Clinical characteristics of the early blind subjects**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age of blindness</th>
<th>Cause of blindness*</th>
<th>Age of Braille reading (years)</th>
<th>Years of reading Braille</th>
<th>Visual perception</th>
<th>Daily reading (h)</th>
<th>Reading hand</th>
<th>Preferred hand</th>
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<tbody>
<tr>
<td>Early blind EB</td>
<td>44</td>
<td>M</td>
<td>3 months</td>
<td>Glaucoma</td>
<td>5</td>
<td>39</td>
<td>None</td>
<td>2</td>
<td>Both</td>
<td>Left</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>birth</td>
<td>Premat. retinitis</td>
<td>4</td>
<td>29</td>
<td>None</td>
<td>4</td>
<td>Both</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>F</td>
<td>4 years</td>
<td>Meningitis</td>
<td>6</td>
<td>57</td>
<td>None</td>
<td>6</td>
<td>Both</td>
<td>Right</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>F</td>
<td>birth</td>
<td>Premat. retinitis</td>
<td>6</td>
<td>41</td>
<td>Bright lights</td>
<td>2</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>F</td>
<td>birth</td>
<td>Glaucoma</td>
<td>5</td>
<td>39</td>
<td>None</td>
<td>2</td>
<td>Both</td>
<td>Right</td>
</tr>
<tr>
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<td>41.00</td>
<td></td>
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<tr>
<td>s.d.</td>
<td>9.42</td>
<td></td>
<td></td>
<td></td>
<td>0.84</td>
<td>10.10</td>
<td></td>
<td>1.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Premat., premature; cong., congenital.

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**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.

**Figure 1 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.
somatosensory information in sighted mammals occurs at cortical association sites. It is possible that connections between parietal and visual association areas mediate the transfer of somatosensory information to the occipital cortex in blind subjects. 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 evoked potentials in the $S_V$ and 12.40 ± 3.38 in the $E_B$ groups) did not induce sensations of missing or extra dots in any of the subjects tested.

In the $S_V$ 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, 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. 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 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 ($E_B$, 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 (F2) and to the contralateral sensorimotor area (overlying Brodmann areas 4, 3, 1 and 2). 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 (SVs, mean age 51.0 ± 11.5 years, 4 right handed and 1 ambidextrous) and in the blind group reading Roman letters (EBs) TMS was delivered randomly to midline occipital (O2), 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 investigators36,37), we could not study sighted volunteers identifying Braille letters. To ensure a similar overall prestimulation accuracy level in both groups, the blind (EBs) subjects were presented with a higher number of possible letters to choose from (26 letters) than the sighted (SVs) 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 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 group identified letters 1–3 in 1.0 ± 0.2, 2.1 ± 0.3 and 3.1 ± 0.3 s and the EB 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, EB, and SV 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 (UVs 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 position were not stimulated; and there were no trials without TMS. The parameters used in the UV 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. 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 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 were developed to assess the effects of stimulated scalp position on error rates in EB, EB, SV, and UV groups, and to examine the differences between blind and sighted subjects reading Roman letters. Significance was defined as P ≤ 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?

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