Cortical plasticity associated with Braille learning

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Blind subjects who learn to read Braille must acquire the ability to extract spatial information from subtle tactile stimuli. In order to accomplish this, neuroplastic changes appear to take place. During Braille learning, the sensorimotor cortical area devoted to the representation of the reading finger enlarges. This enlargement follows a two-step process that can be demonstrated with transcranial magnetic stimulation mapping and suggests initial unmasking of existing connections and eventual establishment of more stable structural changes. In addition, Braille learning appears to be associated with the recruitment of parts of the occipital, formerly 'visual', cortex (V1 and V2) for tactile information processing. In blind, proficient Braille readers, the occipital cortex can be shown not only to be associated with tactile Braille reading but also to be critical for reading accuracy. Recent studies suggest the possibility of applying non-invasive neurophysiological techniques to guide and improve functional outcomes of these plastic changes. Such interventions might provide a means of accelerating functional adjustment to blindness.

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I n 1688, the Irish philosopher William Molyneux posed a question in a letter to John Locke that would capture the attention of cognitive psychologists and philosophers of mind for more than three centuries. Probably motivated to some degree by the fact that his own wife was blind, he asked his English contemporary to imagine that a congenitally blind person had learned to distinguish between and name a sphere and a cube by touch alone, and then to imagine that this person had suddenly recovered the faculty of sight. Would this individual, Molyneux wondered, be able to distinguish both objects by sight and to say which is the sphere and which is the cube[1]?

Molyneux's question served as the touchstone for 300 years of debate over the role of experience in the development of perception and the existence of innate or acquired cross-modal relationships between the senses. William James[2] argued that perceptions of space across different modalities have intrinsically different properties that make it impossible for cross-modal information to be relayed between sight and touch without experience. He noted, for example, that visual space is projective and non-Euclidean, whereas tactile space is Euclidean. More contemporary, experimental approaches to Molyneux's problem have included observation of surgically treated cataract patients[3,4], visual deprivation in animals[5] and the use of 'sensory substitution systems' that represent visual scenes and objects tactually[6]; all have failed to provide unequivocal evidence with which to answer Molyneux's 300-year-old conundrum. This review further examines the relationship between visual and tactile infor-mation processing in the context of plastic cortical changes that seem to occur in blind Braille readers.

Because the processing of visual information encompasses a significant portion of the brain, peripheral blindness represents a deafferentation of input to large areas of the cortex. Such deafferentation imposes great demands on other sensory systems to make compensatory adjustments in the absence of sight, particularly in the context of our vision-dependent society. Blind individuals must develop the ability to extract crucial spatial information from the modalities of touch and hearing. One particularly complicated compensatory tactile ability acquired by many blind individuals is Braille reading.

The acquisition of Braille-reading skill also poses an interesting problem of neural logistics, because it imposes a marked increase in afferent and efferent demands onto a restricted body space (the pads of Braille-reading fingers). Blind Braille readers must discriminate, with exquisite sensitivity and accuracy, subtle patterns of raised and depressed dots with the pads of their fingers and translate this spatial code into meaningful information. Faced with the complex cognitive demands of Braille reading, it appears that striking adaptive changes occur in the human brain (Fig. 1).

Enlarged somatosensory representation of braille-reading fingers

Evidence from both animal and human models suggests that somatosensory representation of a body part can be selectively remodeled by new tactile experiences, and that repeated use

or stimulation of that portion of the body can lead to an enlarged cortical representation. The work of Merzenich and colleagues[7–11] using animal models suggests that these changes in cortical representation might underlie changes in perception. Recanzone et al.[12] found that the topographical and temporal response properties of cortical neurons of adult owl monkeys can be altered by training them behaviorally to discriminate the temporal features of a tactile stimulus. This finding strongly suggests that the changes in the activity of cortical neurons, including enlargement of cortical representation, are directly correlated with perceptual ability.
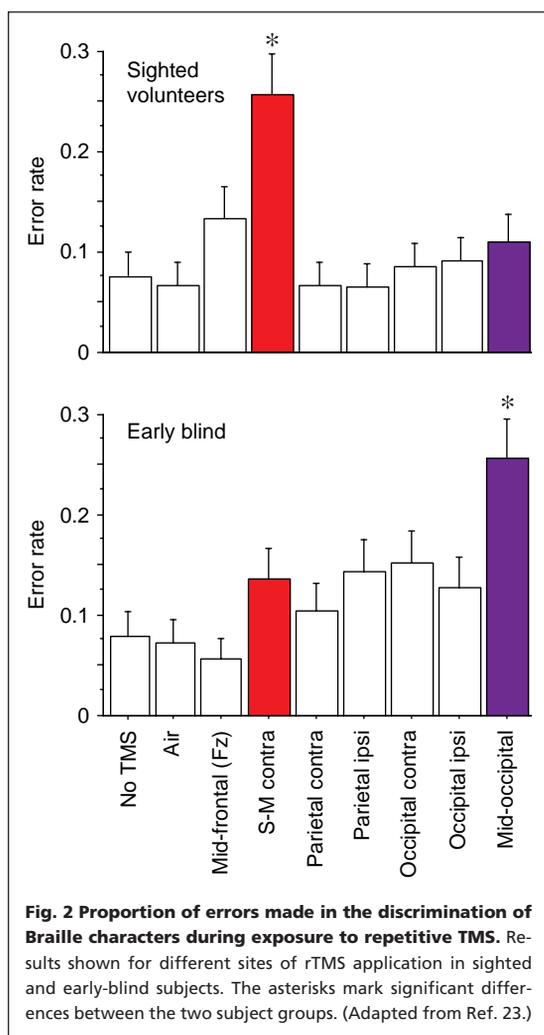
Recording somatosensory evoked potentials (SEPs) from the tips of the reading and non-reading index fingers of blind Braille readers, Pascual-Leone and Torres[13] demonstrated that sensory representation of the reading finger is enlarged when compared with the sensory representation of the homologous finger of their other hand, or with that of the

Fig. 1 Evidence of plasticity in sensory, motor and occipital cortex in early-blind subjects after learning Braille. Representative examples are shown from the studies performed before (top) and at the end of one year of learning Braille (bottom). The different studies were conducted on different subjects using somatosensory evoked potentials (SEPs) to mechanical stimuli to the index finger pad, motor mapping with TMS of the potentials evoked in the first dorsal interosseus (FDI) muscle (the side-to-side mover of the index finger), and functional magnetic resonance imaging (fMRI) while reading Braille characters. (Adapted from Refs 13,18.)

finger of sighted and blind non-Braille-reading controls. These results are consistent with data demonstrating enlargement of the somatosensory barrel cortex of binocularly deprived mice[14]. The use of transcranial magnetic stimulation (TMS) to map the motor cortical areas representing the reading fingers of blind Braille readers reveals similar enlargement[15]. This finding is consistent with data demonstrating that rehearsal of complex motor tasks by sighted subjects results in long-term, experience-dependent reorganization of the adult primary motor cortex[16].

Braille reading by proficient blind users shows consistent activation in the primary sensorimotor cortex (SM1) that is more prominent on the side contralateral to the reading finger than on the ipsilateral side[17]. These data are consistent, firstly, with the finding that rapid modulation of the cortical-output maps in proficient blind Braille readers depends on preceding activity[18], and, secondly, with other studies of modulation of motor cortical outputs during fine motor-skill acquisition[19,20]. Longitudinal studies of the cortical outputs of blind subjects learning Braille reveal that this enlargement seems to have two phases: (1) a rapid, dramatic, and transient enlargement that is likely to be due to the unmasking of connections or the up-regulation of synaptic efficacy; and (2) a slower, less prominent but more stable, enlargement of the cortical representation of the reading finger that might represent structural plasticity[21]. This suggests that the acquisition of Braille-reading skills, similarly to acquiring other skills, involves transient rapid changes in efficacy of existing connections that lead the way for enduring structural changes with practice.

One interpretation of these findings is that blind Braille readers extract more detailed information from the afferent input from the fingerpad, and that it is the sheer magnification of cortical representation that enables blind readers to excel at the complex discriminatory task of Braille reading.
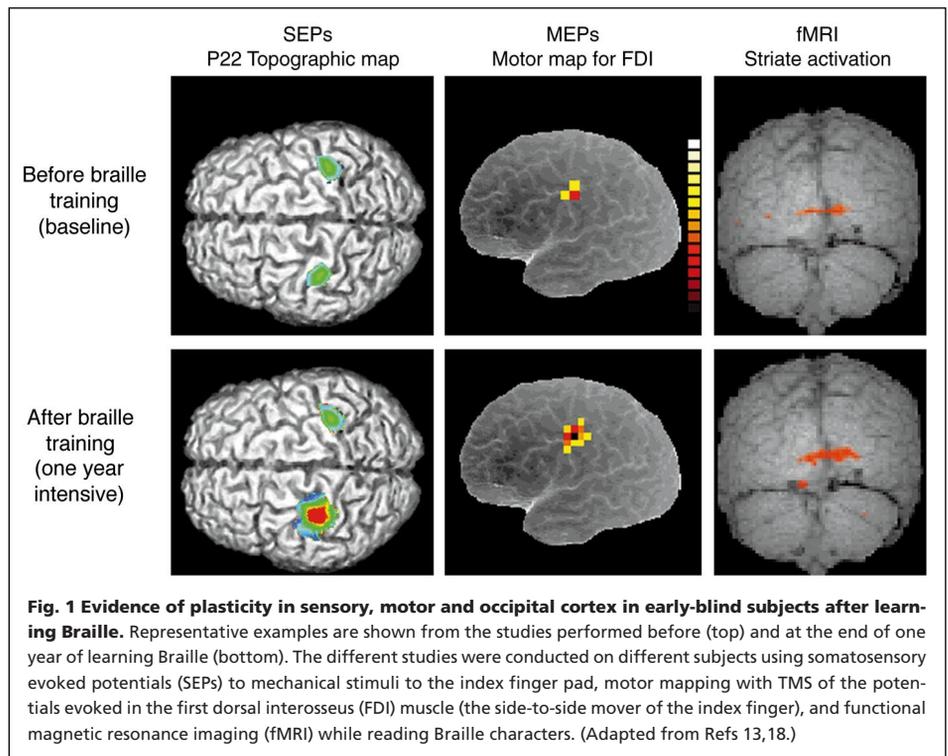
If this were the entire story, one would predict that producing a functional lesion, using TMS, of the sensorimotor cortex contralateral to the reading finger would render the Blind reader unable to decipher Braille stimuli[22]. One would also expect the relative size of the cortical representation of the reading finger to correlate with Braille-reading ability. Both of these predictions, however, appear to be incorrect. Although blind Braille readers did show some decrement in their ability to perform complex tactile discrimination tasks when TMS was applied to their sensorimotor cortex, they performed better than sighted subjects and blind subjects who could not read Braille and had received similar stimulation[23]. Furthermore, although the somatosensory cortical representations of particular portions of the body does enlarge as subjects develop skills using those somatic regions, sensorimotor cortical representations decrease in size as subjects gain mastery of those skills[19]. This suggests that motor skill acquisition is not singularly correlated with the size of somatosensory cortical representation. Phillips et al.[24] further demonstrated that representation of form in somatosensory afferents (the slowly adapting pathway in particular) becomes increasingly anisomorphic as it ascends the processing pathway. Those authors proposed that this increasing abstraction of representation might indicate that tactile input undergoes a critical transformation and redistribution that allows for the processing of fine spatial and temporal details of objects, and suggested that this would be important for Braille reading. This is consistent with the findings of Recanzone et al.[12], who revealed that changes in temporal response properties of cortical neurons were correlated with improved tactile performance. Taken together, this evidence strongly suggests that magnification of cortical representation is not the sole mechanism mediating the acquisition of Braille-reading skill in blind persons.

Fig. 2 Proportion of errors made in the discrimination of Braille characters during exposure to repetitive TMS. Results shown for different sites of rTMS application in sighted and early-blind subjects. The asterisks mark significant differences between the two subject groups. (Adapted from Ref. 23.)

If it is the case that the task of Braille reading requires the generation of complex spatiotemporal representations of tactile space, several questions become pertinent: (1) Are the mechanisms for this kind of spatial processing of haptic information the same as, or are they (as James[2] implied) fundamentally and irreconcilably different from those processing spatial information from sight?; (2) Can this spatial-information processing be accessed across modalities?; (3) If there is a relationship between spatial-processing mechanisms of haptic senses and spatial processing as it occurs in other modalities, is this relationship innate, or is it generated solely through multi-modal experience? In a very real sense, we find ourselves asking versions of Molyneux's ancient question revised to suit our use of the increasingly sophisticated tools of neural science.

Occipital cortex activation in early-blind Braille readers: true cross-modal plasticity

What becomes of those occipital portions of a blind individual's cortex that would otherwise have subserved visual processing? Can they be re-allocated to subserve new functions, or even different sensory modalities? The answer to the latter question, at least in the case of 'early-blind' Braille readers (subjects born blind or that had become blind before the age of 7), appears to be yes. Using positron emission tomography (PET) as a measure of cortical activation during tactile discrimination tasks, Sadato *et al.*[17] found that

blind subjects demonstrated activation of both primary and secondary occipital cortical areas (V1 and V2; Brodmann areas 17, 18, and possibly 19) during tactile tasks, whereas sighted controls showed deactivation in these regions. It is noteworthy that these areas are topologically remote from V4, which has already been shown to be influenced by tactile input[25]. This participation of the occipital cortex in a tactile task appears to be related to the difficulty of the tactile discrimination regardless of lexical information[16]. Studies by Uhl *et al.*[26,27] using event-related potentials and cerebral blood flow measures also suggest occipital cortex activation in early-blind humans. These findings indicate that in blind subjects the occipital cortex appears capable of reorganizing to accept non-visual sensorimotor information, possibly for further processing.

Recently, Cohen *et al.*[23] found that repetitive TMS (rTMS) applied to the occipital cortex was able to disrupt Braille-letter reading and the reading of embossed Roman characters in early-blind subjects. In this study, rTMS induced errors and distorted the tactile perceptions of blind subjects in both tasks. In the case of the Braille task, subjects knew that they were touching Braille symbols , but were unable to discriminate them (Fig. 2), reporting instead that the Braille dots felt 'different', 'flatter', 'less sharp and less well-defined'. Occasionally, some subjects even reported feeling additional ('phantom') dots in the Braille cell. In contrast, occipital stimulation had no effect on tactile performance in normal sighted subjects, whereas similar stimulation is known to disrupt their visual performance.

These findings support the hypothesis that the detection of tactile stimuli does not require striate cortex, but that perception (i.e. processing of the tactual information) does involve the striate cortex, at least in the early blind. It is not yet known whether this recruitment takes place purely in response to the haptic requirements of Braille reading or in response to cognitive demands of a higher order of tactile information processing. One possible approach to determine what kind of processing the recruited cortex actually does would be to look for a difference in occipital activation based on concrete versus abstract meanings of Braille words. In any event, current evidence suggests that Braille reading in the blind is an example of true cross-modal sensory plasticity by which the de-afferented, formerly visual, cortex is recruited for highly demanding spatial-tactile tasks, making the acquisition of the tactile Braille-reading skill possible.

Repetitive TMS at the appropriate stimulation intensity and frequency can also be used to generate increased cortical excitability longer-lasting than the duration of the TMS application itself[28–30]. In preliminary studies we applied trains of rTMS to the occipital cortex of five early-blind subjects and evaluated the effects of the stimulation on their Braille reading speed[21] (see Fig. 3). Following rTMS at parameters that enhance cortical excitability, subjects were able to read faster, although their reading speed was decreased by rTMS at 1 Hz – a frequency that has previously been shown to result in a lasting depression of cortical excitability[31]. Sham rTMS (a non-stimulating control condition) did not change the Braille reading speed in any of the subjects. These findings further support the notion that, for

blind Braille readers, the occipital cortex is recruited to sub-serve the tactile information processing of Braille reading.

If, however, the occipital cortex of the blind Braille reader is engaged in the processing of complex tactile information, what happens to the ability of this region to accommodate visual information? Although definitive data is yet to be collected, case studies of patients who have recovered from early blindness describe persistent difficulties in visual perception that may be related to these subjects' long-term use of 'visual' cortical areas for tactile information processing. The visual abnormalities described in the case-study literature include gross misjudgments of distance and perspective, and difficulty in identifying objects by sight without the use of other sensory modalities[3,4,32]. Moreover, sighted instructors at schools for the blind report similar abnormalities in visual perception after having undergone extended periods of being blindfold (A. Pascual-Leone, unpublished observations). These reported irregularities of visual perception include difficulties in gauging the speed of moving objects, inability to judge distances, impaired depth perception, and a sense of uncertainty about the identity of visual objects in the absence of other sensory cues. Although the ability of these temporarily blinded individuals has not been tested explicitly, the anecdotal evidence suggests that even transient loss of sight might disrupt visual information processing in the occipital cortex.

Herein may be an answer to Molyneux's famous question. It seems that without visual input, the occipital cortex can be recruited to serve a role in tactile spatial processing, but this recruitment does not result in intrinsic cross-modal transfer of tactile information to potential visual sensations. On the contrary, visual–spatial association appears to be generated and maintained only by the simultaneous experience of both modalities, so that lifelong cataracts or even temporary loss of sight can impede an individual's ability to apply spatial information across sensory modalities. Thus, a blind individual suddenly gifted with sight might have abnormalities in visual perception, because the cortical space that would otherwise have been devoted to vision has been subsumed by the modality of touch. Such a person might lack the functional apparatus required for visual analysis and recognition of visual shapes, perhaps even to the point of being unable to distinguish correctly shapes like a sphere and a cube.

Using TMS to track the flow of spatial information in early-blind Braille readers

Having demonstrated that the visual cortex of early-blind Braille readers is activated by tactile discrimination tasks, questions such as how and when tactile information reaches the visual cortex may be pursued. TMS is a useful method with which to approach these questions. Appropriately delivered in time and space, TMS can transiently disrupt the arrival of the thalamo-cortical volley of afferent signals into the primary sensory cortex and thereby interfere with detection of peripheral somatosensory stimuli[33]. This disruptive effect will result in the subject's failure to detect the stimulus. In order to achieve this effect, the TMS cortical stimulus (CS) must be appropriately timed following the somatosensory peripheral stimulus (PS)[34]. Detection of the PS is
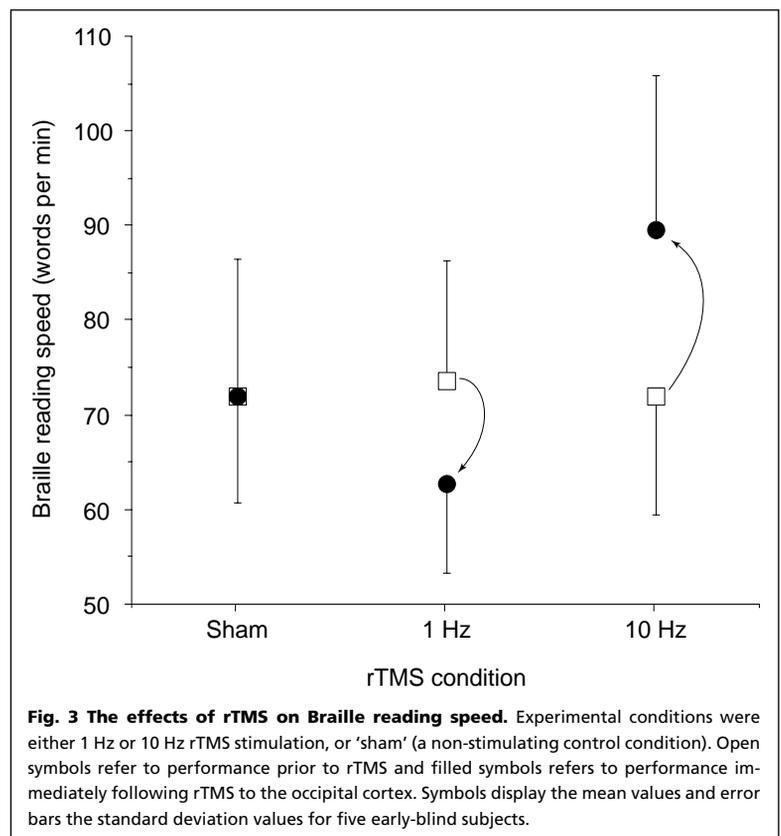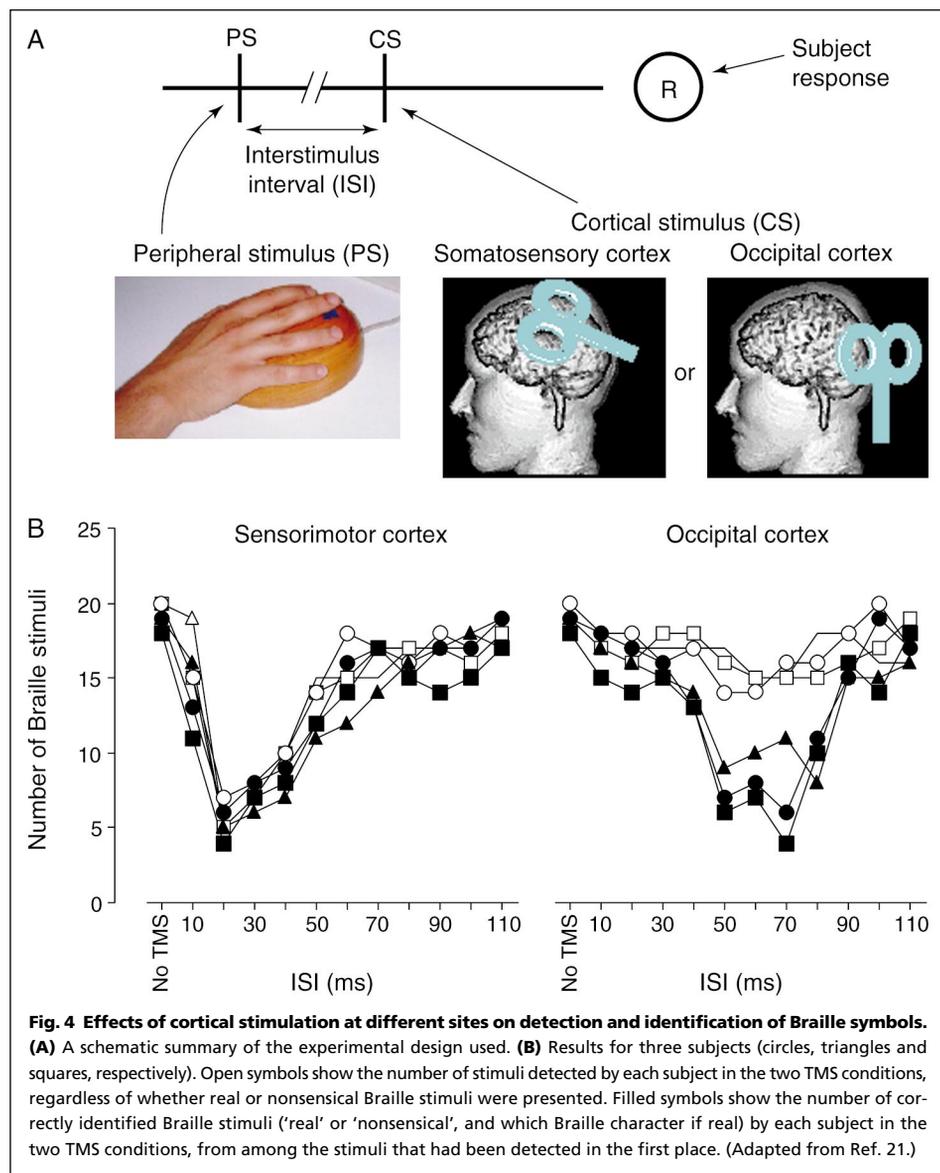

Fig. 3 The effects of rTMS on Braille reading speed. Experimental conditions were either 1 Hz or 10 Hz rTMS stimulation, or 'sham' (a non-stimulating control condition). Open symbols refer to performance prior to rTMS and filled symbols refers to performance immediately following rTMS to the occipital cortex. Symbols display the mean values and error bars the standard deviation values for five early-blind subjects.

disrupted only when the interval between PS and CS is 15–35 ms (Refs 33,34). In addition, topographic specificity can be demonstrated according to the known somatotopic organization of the primary somatosensory cortex. TMS must be delivered at the appropriate site for projection of index-finger afferents when the PS is applied to the index-finger pad, and no effect is demonstrable if the site of TMS is displaced by 1 or 2 cm in any direction[33]. These findings provide information about the timing of information arriving at the primary somatosensory cortex and the processing time in this region in normal subjects.

The same effect of blocking the detection of somatosensory stimuli can be demonstrated in blind, proficient Braille readers. Pascual-Leone and Torres[14] reported that detection of electrical stimuli applied to the pad of the index finger could be blocked by properly timed TMS stimuli to the contralateral sensorimotor cortex. Using a specially designed stimulator that resembled a Braille 'text' cell, electrical stimuli were applied, slightly above sensory threshold, to the index finger pad of the right or left hand in sighted controls and blind subjects. These peripheral stimuli were followed by TMS stimuli, at variable intervals and intensities, to different scalp positions targeting the sensorimotor cortex. With appropriate parameters of timing and spatial position, TMS resulted in the blocking of detection of the peripheral stimuli, such that the subjects were unaware of having received a peripheral stimulus preceding the cortical TMS stimulus.

We are using a similar approach to evaluate the timing and contributions of both the somatosensory and occipital cortex to the processing of tactile information in blind Braille readers[18]. Real or nonsensical Braille stimuli are presented with a specially designed Braille stimulator to the

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Fig. 4 Effects of cortical stimulation at different sites on detection and identification of Braille symbols. **(A)** A schematic summary of the experimental design used. **(B)** Results for three subjects (circles, triangles and squares, respectively). Open symbols show the number of stimuli detected by each subject in the two TMS conditions, regardless of whether real or nonsensical Braille stimuli were presented. Filled symbols show the number of correctly identified Braille stimuli ('real' or 'nonsensical', and which Braille character if real) by each subject in the two TMS conditions, from among the stimuli that had been detected in the first place. (Adapted from Ref. 21.)

Outstanding questions

- What are the neural mechanisms underlying the recruitment of the occipital cortex for tactile information processing in blind Braille readers?
- If cross-modal recruitment of the occipital cortex is crucial for the acquisition of Braille-reading skill in early-blind subjects, is the acquisition of Braille skill impaired in sighted individuals owing to the maintenance of dominant visual input?
- Other studies have implicated different areas of the brain in the ability of sighted subjects to match visual and tactile stimuli. Do blind and sighted subjects differ in the areas that are recruited for cross-modal information processing? If so, how?
- If reading words with concrete tactile and spatial meanings (e.g. 'sphere' or 'cube') were to lead to enhanced, diminished, or topologically separate activation in the occipital cortex of a blind Braille reader compared with that elicited by reading words with abstract non-spatial, non-tactile meanings ('justice' or 'wisdom'), how would this further elucidate the role of cognition in the current model of haptic–visual cross-modal plasticity?
- If the occipital cortex of blind Braille readers is recruited to process tactile information at the expense of visual information processing, is this sufficient evidence with which to answer Molyneux's question (see introduction)? If not, what further evidence would be needed?

pad of subjects' reading index fingers. Single-pulse TMS stimuli are applied to the left or right (as appropriate) sensori-motor cortex and striate occipital cortex at varying intervals following the presentation of the Braille stimuli (Fig. 4).

The current findings can be summarized as follows:

(1) TMS presented to the somato-sensory cortex disrupted detection of real and nonsensical Braille stimuli at inter-stimulus intervals of 20–40 ms. The subjects did not realize that a peripheral stimulus had been presented. In the instances in which the subjects did detect the peripheral stimulus, they were generally able to identify correctly whether it was real Braille or not and, if Braille, which symbol was presented.

(2) TMS to the striate cortex disrupted the processing of the peripheral stimuli at interstimulus intervals of 50–80 ms. Contrary to the findings with TMS to sensorimotor cortex, the subjects typically knew whether a peripheral stimulus had been presented or not, therefore no interference with detection was demonstrated. However, the subjects were unable to discriminate whether the presented stimuli were real or nonsensical Braille symbols, or which particular Braille symbol might have been presented. (This is therefore interference of perception.)

Thus, it appears that in early-blind subjects, the time interval between a tactile stimulus to the finger pad and a cortical stimulus that interferes with processing of the tactile information is different for cortical stimulation of the somatosensory and the occipital cortex. This time difference provides an insight into the temporal profile of information processing and the transfer of signals in early-blind subjects between somatosensory and striate cortex. Hypothetically, two alternative main routes can be considered: (1) parallel thalamo-cortical connections to somatosensory and striate cortices, and (2) cortico-cortical connections from somatosensory cortex to striate cortex. Although the details of these neural pathways are not yet fully understood, the existing body of data suggests that cortico-cortical connections mediate the cross-modal occipital activity in blind Braille readers (see Box 1).

Conclusions

Blind subjects demonstrate remarkable neuroplastic changes in response to the adjustment to blindness and the acquisition of Braille-reading skill. This reorganization appears to involve two distinct processes. First, there is enlargement of the somatosensory representation of the Braille reading finger, which probably reflects both rapid unmasking of existing cortical connections and slower, more enduring structural

Box 1. Two pathways to the occipital cortex

Thalamic somatosensory nuclei could send input to both the somatosensory cortex and the striate cortex. These theoretical multiple projections might be masked or degenerated in sighted humans but still functional in early-blind subjects, and might thus be responsible for the participation of areas V1 and V2 of the striate cortex in tactile information processing. Murata *et al.*[a] demonstrated the existence of weak non-visual input to cells of the newborn cat primary visual cortex. Such multi-modal neurons receive and process auditory and tactile information and are presumed to retain their projection to visual cortex.

Despite evidence suggesting that thalamo-cortical connections might mediate cross-modal plasticity, a growing body of evidence suggests that cortico-cortical connections between the somatosensory cortex and the visual cortex seem the most likely route of occipital cortex recruitment. A sequential pathway from striate to prestriate to inferior temporal cortex (ventral visual pathway) has been shown to play a role in the discrimination of visual shapes, including pictures, letter strings, faces and geometric shapes[b–e]. Murray and Mishkin[f] have suggested that the secondary sensory cortex (SII) for touch discrimination might be analogous to the posterior region of the inferior temporal cortex (area TEO) for visual pattern discrimination, and the insula might be analogous to the anterior part of the inferior temporal cortex (area TE). In the monkey, the posterior parietal 'association' cortex (Brodmann area 7) is interconnected with the visual 'association' cortex (dorsolateral Brodmann area 19) (Ref. g), and early visual deprivation in the monkey makes most neurons in area 7 and 19 responsive to somatic exploration[h]. In addition, diffuse reciprocal projections link area 19 to the primary visual cortex[i]. Korte and Rauschecker have also demonstrated increased numbers of auditory and multi-modal cells in the anterior ectosylvian cortex (AES) of cats with early blindness[j]. These findings suggest that the spatial information originally conveyed by the tactile modality in sighted subjects (SI to SII to insular cortex to limbic system) might be processed in the blind by the neuronal networks usually reserved for the visual, shape discrimination process (SI to area 7 to dorsolateral area 19 to V1 to occipito-temporal region to anterior temporal region to limbic system). This would explain the fact that tactile information processing in the somatosensory and occipital cortex in early-blind persons is not only different in timing but also in the type of contribution: detection versus identification of the stimulus, respectively.

Although the evidence for cross-modal plasticity between tactile and visual representations of space seems compelling and plausible models for the cortical connections involved have been proposed, this does not necessarily preclude the existence of other cross-modal mechanisms between visual and haptic perception. Most recently Hadjikhani and Roland[k] have demonstrated that the right insula–claustrum is active during cross-modal tactile–visual and visual–tactile matching tasks. The implication of these findings for blind Braille readers or for the recruitment of the occipital cortex for tactile processing has yet to be defined.

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changes. Secondly, at least in early-blind subjects, the occipital, 'visual' cortex appears to play a critical role in Braille reading. Cortico-cortical connections between sensorimotor and occipital cortex may be responsible for the recruitment of the occipital cortex in tactile information processing. These findings, which demonstrate the plastic capacity of the adult central nervous system, might also serve as a model to help account for other phenomena, such as the acquisition of new skills by normal subjects or the recovery of function after injury.

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From retinotopy to recognition: fMRI in human visual cortex

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Recent advances in functional magnetic resonance imaging (fMRI) have furnished increasingly informative and accurate maps of the retinotopy and functional organization in human visual cortex. Here we review how information in those sensory-based maps is topographically related to, and influenced by, more cognitive visuo-spatial dimensions, such as mental imagery, spatial attention, repetition effects and size perception.

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As cognitive science evolves, the initial psychological observations that established this field will increasingly be explained in terms of specific brain mechanisms. Such reductive explanations will undoubtedly take many forms, including those of electrophysiology, psychophysics and neuroimaging. Among these techniques, the neuroimaging of cognitive mechanisms in the human brain might be especially informative at present.