

The metamodal organization of the brain

Alvaro Pascual-Leone* and Roy Hamilton

Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA

Introduction

Confronted with the question of how we perceive the world, we are often taught that we have a series of distributed systems structured according to the sensory modalities that they process. We talk about a visual system, a somatosensory or tactile system, an auditory system, and so forth. Certainly, the existence of specialized detectors or receptors for different sensory modalities grants us the opportunity to process different forms of energy and hence capture different 'views' of the world in parallel. Some experiences are uniquely unimodal. Hue can only be experienced by sight, tickle can only be felt by touch, and pitch can only be differentiated by audition. Nevertheless, our perceptual experience of the world is richly multimodal as eloquently elaborated by Barry Stein and Alex Meredith (Stein and Meredith, 1993). We are able to extract information derived from one sensory modality and use it in another; we can, for example, know a shape by touch and identify it correctly by sight. This reminds us of Molyneux's question, and raises the broad issue of internal versus experiential influences in the organization of the brain. Furthermore, we are able to integrate into a richer percept the impressions generated by different sensory modalities.

Such intersensory perceptual phenomena (Stein and Meredith, 1993) are many and there is no question that the experience in one sensory modality influences the experience in another. Think, for example, of listening to music over the radio or while watching an orchestra perform. The melody played by the violins seems to 'sound' much clearer when we see the instrumentalists and watch their fingering and bowing than when we do not. The 'ventriloquism effect' broadly refers to this phenomenon on which much of our knowledge of the world and an entire entertainment industry is based (Howard and Templeton, 1966; Stein and Meredith, 1993). Multimodal association areas that contain multisensory cells neurons are thought to provide a neural substrate for integrating ('merging') sensory experiences, modulating the saliency of stimuli, assigning experiential and affective relevance, and providing the substrate for the true perceptual experience of our rich world (Stein and Meredith, 1993).

However, studies on early blind subjects and visually deprived sighted subjects raise questions about the organization of the brain in parallel unimodal sensory systems that are eventually integrated in multimodal association cortical regions. One may argue that early blindness represents a pathological state resulting in substantial cross-modal brain plasticity (Rauschecker, 1995; Hamilton and Pascual-Leone, 1998; Kujala et al., 2000), but the findings in visually deprived sighted subjects are difficult to account for with such an argument. After providing a historical backdrop for the topic and reviewing the experimental data, we will hypothesize that the brain might actually represent a metamodal structure

*Corresponding author: A. Pascual-Leone, Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA. Tel.: +1-617-667-0203; Fax: +1-617-975-5322;
E-mail: apleone@caregroup.harvard.edu

organized as operators that execute a given function or computation regardless of sensory input modality. Such operators might have a predilection for a given sensory input based on its relative suitability for the assigned computation. Such predilection might lead to operator-specific selective reinforcement of certain sensory inputs, eventually generating the impression of a brain structured in parallel, segregated systems processing different sensory signals. In this view, the ‘visual cortex’ is only ‘visual’ because we have sight and because the assigned computation of the striate cortex is best accomplished using retinal, visual information. Similarly, the ‘auditory cortex’ is only auditory in hearing individuals and only because the computation performed by the temporal, perisylvian cortex is best implemented on cochlear, auditory signals. However, in the face of visual deprivation, the ‘striate cortex operator’ will unmask its tactile and auditory inputs to implement its assigned computation using the available sensory information.

Molyneux’s question

In 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 (Degenaar, 1996). Probably motivated to some degree by the fact that his own wife was blind, Molyneux posed the following question to his English contemporary:

Suppose a man born blind, and now adult, and then taught by his touch to distinguish between a cube and a sphere of the same metal, and the same bigness, so as to tell, when he felt one and the other, which is the cube, which is the sphere. Suppose then, the cube and the sphere placed on a table, and the blind man to be made to see. Query, whether by sight, before he touched them, he could distinguish, and tell, which is the globe, which is the cube?

Molyneux’s question has served as the touchstone for over three centuries 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. Molyneux himself came to the conclusion that the blind subject of his thought

experiment would not be able to equate his tactile experience to visual percepts. Locke considered Molyneux’s query in his 1690 *Essay Concerning Human Understanding*, and stated that “the blind man, at first, would not be able with certainty to say which was the globe, which the cube . . . ”

Molyneux was certainly not the first to ponder the relationship between vision and touch in the mind. In a famous passage in his *Dioptrics* (1637), Rene Descartes considers how a blind man might build up a perceptual world by tapping objects around him with a stick. He first considers a sighted person using a stick in darkness, and says:

. . . without long practice this kind of sensation is rather confused and dim; but if you take men born blind, who have made use of such sensations all their life, you will find they feel things with perfect exactness that one might almost say that they see with their hands . . .

Descartes goes on to argue that normal vision resembles a blind man exploring and building up his sense by successive probes with his stick. In 1709, Bishop George Berkeley agreed that there was no necessary connection between a tactile world and a sight world, that a connection between them could only be established through experience. Over a century and a half later, William James argued similarly 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 (James, 1890).

Not all great thinkers agreed that Molyneux’s question can be answered in the negative. The respected and versatile scholar Gottfried Wilhelm Leibniz wrote a critical commentary on Locke’s empirical approach to visual and tactile perception. Leibniz argued that while visual and tactile sensations of forms are different, the accompanying concepts underlying their perceptions are the same or share something critical in common. Leibniz makes an explicit distinction between images and ideas, and argues that a person blind from birth would be capable of distinguishing a sphere from a cube using his understanding and the knowledge acquired through the sense of touch with the aid of exact ideas of the forms of both objects. Francis Hutcheson,

another Irish philosopher, gave a similar answer to Molyneux's question. According to Hutcheson, we can, by virtue of our ideas about form, judge by touch what the visual extension of a touched object will be when we open our eyes, although we cannot tell by touch which color we will see.

Surgical answers to a philosophical debate

Molyneux's question was approached experimentally in 1728, when William Cheselden, an English surgeon, removed the cataracts from the eyes of a 13-year-old boy born blind. Cheselden's celebrated case was, by no means the first successful operation of its kind: the earliest reported dates from A.D. 1020, of a 30-year-old man operated upon in Arabia, and several other cases were reported between that first operation and the one performed by Cheselden. Cheselden's commentary on the case, however, stands out for its consideration of the changes in percept experienced post-surgically by the patient.

When he first saw, he was so far from making any Judgement about Distances, that he thought all Objects whatever touched his Eyes, (as he expressed it) as what he felt, did his Skin; and thought no Objects so agreeable as those which were smooth and regular, though he could form no Judgement of their Shape, or guess what it was in any Object that was pleasing to him:

Despite his high intelligence and youth, the boy encountered profound difficulties with the simplest visual perceptions. He had no idea of space or size, and found it remarkably difficult to recognize and remember the visual form of objects, and had to constantly relate them to his previously acquired tactile impressions.

He knew not the Shape of any Thing, nor any one thing from another, however different in Shape, or Magnitude; but upon being told what Things were, whose Form he before knew from feeling, he would carefully observe, that he might know them again; but having too many Objects to learn at once, he forgot many of them; and (as he said) at first he learned to know, and again forgot a thousand Things a Day. One particular only (though it might appear trifling) I will relate; Having forgot

which was the Cat, and which was the Dog, he was ashamed to ask; but catching the Cat (which he knew by feeling) he was observed to look at her steadfastly, and then setting her down, said, So Puss! I shall know you another Time.

It has been similar with other patients in the 250 years since Cheselden's operation: nearly all had experienced the most profound, Lockean confusion and bewilderment. The best known and most influential account of these patients is provided by Von Senden (1932). Reporting on 60 cases, Von Senden attempted to investigate whether the tactile impressions of blind people provide them with any spatial awareness and he also sought to discover how spatial awareness develops in blind people who have been surgically treated.

Von Senden came to the conclusion that immediately after the operation the patients were able to distinguish objects one from the other and could localize them at a distance, but they could not identify any objects. When it appeared that they could identify objects, he attributed it to the fact that they were using other senses or had prior knowledge of the situation. Psychologists Richard Gregory and Jean Wallace dispute Von Senden's conclusions on the grounds of their own study of a blind person who had been operated on (Gregory and Wallace, 1963) and could recognize day-to-day objects, such as tables and chairs, immediately after the operation. Experimental approaches to Molyneux's problem have included visual deprivation in animals and the use of 'sensory substitution systems' which represent visual scenes and objects tactually (Morgan, 1977). However, we still lack unequivocal evidence with which to answer Molyneux's 300-year-old conundrum.

It seems clear from the experimental evidence as well as from a careful philosophical dissection of the question itself, that there are indeed two different problems posed: "... whether by sight, before he touched them, he could **distinguish**, and **tell**, which is the globe, which is the cube". In order to 'distinguish' Molyneux's hypothetical subject would merely need to differentiate the two stimuli on the basis of sight. In order to 'tell' the subject would have to learn by matching the newly experienced visual sensation to the old concept formed by touch alone. It is likely the subject would only be able

to ‘distinguish’, just as Chelshenden’s patient could differentiate between his cat and his dog by looking at them but needed to touch them to know (to ‘tell’) which one was actually the cat and which the dog. Hence, we may conclude that senses are merged perhaps at different levels. Knowledge (‘telling’) requires the high-order integration of what is perceived with what is recalled. Therefore, the patients of Von Senden and others actually experienced a visual agnosia, the inability of using information in one sensory modality (vision) to access metamodal knowledge. Obviously, not knowing how to use specific sensory information for knowledge does not imply that merging of the senses does not occur.

How merged are the senses?

The notion of information from different sensory modalities being merged and even being processed together in the same brain areas is far from new¹. The medieval model of the mind contained within it the concept of a ‘sensus communis’, a place in the brain where information from all modalities was summed into an integrated whole that could be utilized by the higher cognitive faculties of reason and memory. Since medieval ‘neuroscientists’ could not believe something as grand as consciousness could emerge from the mere physical tissues of the brain, this so-called ‘common sense’ was thought to be located in the lateral ventricles, which early anatomists collapsed into a single ventricle. The sensations merged in the *sensus communis* yielded images, and thus, fantasy and imagination were often located here as well. The second or middle ventricular space was the site of cognitive process: reasoning, judgment, and thought; the third was the site of memory (Gross, 1998). With the exception of some minor alterations, the multimodal view of sensory processing remained popular among intellectuals throughout the Middle Ages and Renaissance. For example, in his *Treatise on Man* (1662), Renee Descartes, proposed that sensory information from different modalities

¹ Much of the information discussed in the following section is derived from Charles Gross’ superb book on the history of the Neurosciences. The readers are encouraged to read this source (Gross, 1998).

meets in the pineal gland, and that information from one sensory modality interacts with information processing from another modality (Descartes, 1976).

Unimodal models of sensory processing did not emerge until it had become clear that different brain regions were responsible for mediating different functions. Localization of cognitive processes to particular regions of the brain began in early 19th century with Francis Gall and J.C. Spurzheim, who postulated that there were “about thirty-five affective and intellectual faculties” in the brain (Gall and Spurzheim, 1835). In one of the best known misapplications of an essentially good idea, Gall and Spurzheim subsequently founded the study of phrenology. The central ideas of their phrenological system were that the brain was an elaborately wired machine for producing behavior, thought, and emotion, and that the cerebral cortex was a set of organs with different functions. They postulated that the faculties of the brain were localized in specific organs of the cerebral cortex and that the development or prominence of these faculties was a function of their activity, such that the amount of activity would be reflected in the size of the cortical organ. They thus reasoned that the size of each cortical organ, and hence the prominence of mental faculties would be reflected by the prominence of cranial bumps on the overlying skull (Gall and Spurzheim, 1835).

Phrenology had wide appeal, especially in England and the United States, and among many leading intellectuals, but met considerable opposition from the religious, political, and scientific establishments of the day. The most important and influential scientific critique of Gall came from Pierre Fluorens, later professor of natural history at the Sorbonne in Paris. Starting in the 1820s and continuing for over 20 years, he carried out a series of experiments on the behavioral effects of brain lesions, particularly in pigeons. Fluorens reported that lesions of the cerebral hemisphere had devastating effects on willing, judging, remembering, and perceiving but that the site of lesions seemed irrelevant: all regions of the hemispheres contributed to these functions. The only exception was vision, in that unilateral, focal lesions produced only contralateral blindness (Clarke and Jacyna, 1987; Gross, 1998). Despite the fact that these holistic results tended to eclipse Gall’s ideas of discreet localization, the overall impact of Fluorens’

rens' work was to support Gall's broader notion that cognitive function could be localized to the cerebral cortex. By the third quarter of the 19th century, Gall's general ideas had been confirmed by Broca's demonstration of an association between damage of the frontal lobes and aphasia, and again by Fritsch and Hitzig's experiments on stimulation of the motor cortex (Gross, 1998). Thus while the practice of phrenology is no longer held in high esteem as an index of mental faculties, the notion of cognitive function being subdivided and routed to different regions of the brain has remained a central idea in neural science and a fundamental principle in the clinical practice of neurology.

The last quarter of the 19th Century saw an intense search for localization of the sensory centers in the cortex. Interestingly, a notable shift occurred from the concept of function-specific centers to modality-specific brain regions. A major spur in the search for modality-specific cortical regions was Johannes Müller's doctrine of specific nerve energies. This doctrine had three elements. The first and most important was the revolutionary notion that persons are aware of the states of their sensory nerves, not of the state of the outside world itself. Secondly, when a given nerve type or nerve energy was excited, the same type of experience is produced no matter what the stimulus. The third element of this doctrine was that the same physical stimulus applied to different sense organs gives rise to different sensations. Hence, a similar blow to the eye and to the ear produce visual and auditory sensations, respectively (Müller, 1965). Subsequently Hermann von Helmholtz, the renowned physician, physicist, and psychologist, and a student of Müller, argued that the specificity of nerve energies could be attributed to the specific brain regions upon which they terminate. He compared nerves to wires through which impulses between modalities are essentially identical, but take on different meaning based on the portion of the brain to which they are routed. Emil Du Bois-Reymond, another of Müller's students, and the discoverer of the action potential, went one step further and claimed that if it were possible to cross-connect the auditory and optic nerves, we would see with our ears and hear with our eyes (Gross, 1998). Müller's doctrine of specific nerve energies thus became directed toward the cortex as the locus

of specific nerve energies. Under the influence of this doctrine, in the later part of the 19th century, neural pathways were traced from the sense organs into the brain to find the specific regions in which they ended. The cortex was divided up into separate centers or organs on the basis of the pattern of its structure, thereby yielding the techniques of cytoarchitectonics and myeloarchitectonics. Cortical lesions were made in animals to find the sensory centers, and in close parallel, attempts were made to correlate sensory losses in humans with sites of cortical damage. Nowadays, for each of the sensory modalities, we assume that there exists a hierarchically organized system that begins with specialized receptors that 'feed' unimodal, primary cortical. A series of secondary areas unimodally integrate different aspects of the processed information. Eventually, multimodal association areas integrate the processed signals with information derived from other sensory modalities. Certainly, top-down influence from multimodal association areas can change the function of 'hierarchically lower' unimodal cortical regions. Furthermore, in a modern-age experimental testing and refinement of von Helmholtz's and Du Bois-Reymond's hypotheses, Sur and colleagues have shown the enormous dependence of cortical development on external influences (Sur et al., 1990; Merzenich, 2000). Sur and colleagues rewired the brain of young ferrets so that the retinal nerves were directed to grow into the auditory thalamus, which was deprived of its normal auditory inputs. This intervention results in the emergence of a functional primary visual cortex in the brain area destined to develop into the primary auditory cortex (Sur et al., 1990; Roe et al., 1990; Sharma et al., 2000). The 'new' visual cortex is topographically organized and its neurons are selective for differently oriented visual stimuli and are arranged in visual orientation columns, much like it would be expected in the 'normal' primary visual cortex. Furthermore, this 'new visual cortex' shows behavioral functionality (Melchner et al., 2000). Using a variant of this original paradigm, Melcher and colleagues rewired cortical circuits on only one side of ferrets' brains, using inputs to the unaffected hemisphere as a control. They then trained ferrets on a task in which different responses elicited different rewards depending on whether the stimulus was visual or auditory. They found that when light

stimuli were presented in the portion of the visual field that is mediated only by rewired projection, the ferrets responded as though they perceived the stimuli to be visual rather than auditory. Literally, the rewired ferrets ‘see’ with the brain area that was meant to be the primary auditory cortex. Importantly, these animals do not become confused nor display behavior that might suggest synaesthetic merging of the senses. Rather, they appear to have developed a fully functional visual cortex with its appropriate, source-specific perceptual qualities.

This functional ‘redefinition’ of the ‘auditory’ cortex into a new ‘visual’ cortex requires rewiring of the retinal, visual inputs and depriving the medial geniculate nucleus in the thalamus of its cochlear, auditory inputs. Furthermore, the experiments by Sur and colleagues are successful in very young ferrets that are born very early in their neural development (Sur et al., 1990). Could it be, that in fact, in normal development, multimodal sensory inputs feed into all cortical regions and that external influences and predefined functional superiority of given cortical areas shape the brain? Could it be the case that the brain is actually metamodal, and that the impression of hierarchically structured unimodal systems is only the consequence of selection of functions by groups of neural networks that compete with each other in order to acquire specific processes? One might envision a cortical region with a functional role in spatial discrimination, that might therefore be predisposed to perform the kinds of processes that vision requires. In this setting, from early development onward, sight would be progressively selected as the input signal for such an ‘operator’. Eventually such an operator might appear to be ‘visual cortex’ by virtue of its dominant input, when in fact, under certain conditions, the presence of metamodal inputs could be unmasked. In the present article we advance such a hypothesis, based on a series of experiments in early blind subjects and visually deprived sighted volunteers.

Functional brain organization in the early and congenitally blind

Loss of vision due to injury to the eyes results in deafferentation of very large areas of the human cortex and poses striking demands on other sensory

systems to adjust to blindness in a society that relies heavily on vision. Blind subjects need to extract crucial spatial information from touch and hearing. Perhaps the most instructive approach to the experience of blindness is reading the several excellent accounts of the experiences of adults who became blind and had to adapt to their disability. One of the most compelling and lucid accounts of blindness, is John Hull’s autobiography ‘Touching the Rock’. Several passages should be underscored. For example, Mr. Hull relates how he ‘knows’ his youngest son, born after Hull became blind due to diabetes differently than he ‘knows’ his other children whom he saw being born and growing up. Another remarkable passage is the description of how he enjoys stepping outside in the rain. It is the sound that the rain makes on the different objects and planes that allows him to create a mental image of the space that surrounds him. Indeed, blind people often do not describe space, but rather describe specific objects and routes that can guide a listener around the room or from one place to another: “As you enter my house you will be able to feel the light switches on the left, by the door frame. If you then turn to the left and take a couple of short steps there will be a coat rack and next to it, on the right, you will feel the door opening to the kitchen . . . ”. There is a lack of more global space perception, and substitution with a percept that inches along, guided by touch.

Braille reading provides blind subjects with the opportunity to read and write communication, thus greatly expanding their integration into society and their opportunities for employment. Braille reading requires the processing of tactile information into meaningful shapes. Subjects have to discriminate small patterns of raised dots with the pad of their index finger and extract spatial information through touch rather than vision. In order to accomplish this task, subjects move their index finger from side to side at a controlled speed so that the sensory skin receptors are maximally activated by the raised dots and as much information as possible is obtained. Therefore, learning to read Braille poses a great demand on sensory and motor representations from a rather small part of the body, the distant pad of the index finger, and stresses the spatial coding capabilities of tactile exploration. Blind, Braille readers do not have a lower peripheral sensory threshold

in the pad of the reading index finger than blind, non-Braille reading controls or sighted volunteers (Pascual-Leone and Torres, 1993). However, the sensory and motor representations of the reading index finger in the brain are significantly larger for Braille readers than for blind or sighted non-Braille readers (Pascual-Leone and Torres, 1993; Pascual-Leone et al., 1993). This enlarged sensorimotor representation in blind Braille readers develops slowly, over the course of months (Pascual-Leone et al., 1993, 1996) and is modulated by the preceding activity (Pascual-Leone et al., 1995). Therefore, changes in representation of the reading finger in the brain cortex seem to play a critical role in the acquisition of the Braille reading skill (Hamilton and Pascual-Leone, 1998).

Peripherally blind subjects also have very large areas of their brain cortex deafferented from input and hence parts of the former visual cortex are available to be recruited for the processing of tactile and auditory information. Indeed, proficient Braille reading by blind subjects activates the dorsal and ventral portion of the occipital cortex (Fig. 1A) (Sadato et al., 1996; Sadato et al., 1998). Furthermore, there is suppression of parietal operculum and activation of the ventral portion of the occipital cortex in blind subjects during tactile discrimination tasks, opposite to the pattern of activation observed in sighted subjects (Sadato et al., 1996, 1998). Studies using event-related potentials, cerebral blood flow, and magnetoencephalography also suggest occipital cortex activation by tactile stimuli activation in early blind humans (Hamilton and Pascual-Leone, 1998; Kujala et al., 2000). Participation of the striate 'visual' cortex in a tactile task seems related to the difficulty of the tactile discrimination regardless of whether there is a lexical component to it or not (Sadato et al., 1996). These findings suggest that the pathway for tactile discrimination changes with blindness. Indeed, in the congenitally blind, interference with the function of the occipital cortex during Braille reading using repetitive transcranial magnetic stimulation (rTMS) results in disruption of the Braille reading skill (Fig. 1B) (Cohen et al., 1997). Subjects were aware that they had felt Braille characters, but during rTMS to their occipital cortex were unable to discriminate them. In fact, some of the subjects reported phantom tactile sensations, feeling Braille dots that were not there or distortions of the

Braille symbols evoked by TMS. In sighted subjects, rTMS to the visual cortex does not interfere with the ability to detect or discriminate embossed roman letters by touch. Therefore, it would appear that Braille reading in the blind is an example of true 'cross-modal sensory plasticity' by which the deafferented, formally visual cortex, is recruited for demanding tactile tasks, thus enhancing the sensory discrimination abilities of the blind subjects and making the acquisition of tactile Braille reading skill possible.

Further support for the role of striate cortex in the perception of complex tactile stimuli comes from the findings in a most unfortunate patient (Hamilton et al., 2000). She had been blind since birth due to retinopathy of prematurity. She was a highly proficient Braille reader who used Braille at her work. She was a proof reader for the newsletter for the Spanish Organization for the Blind, and thus read Braille for 4–6 hours per day. At age 62, she had an acute neurological event that resulted in coma from which she recovered but was left unable to read Braille. She had no difficulties discriminating textures or identifying everyday objects by touch, but she was greatly impaired in tactile discriminations that required complex spatial decoding. She made frequent errors trying to identify even single Braille letters and she was completely unable to read Braille words. She described being able to 'feel' the Braille dots, but she could not 'make sense' of what she was touching. She complained that it felt "as if I had never learned Braille at all." Her neurological examination was otherwise unremarkable, and her MRI showed a bilateral occipital stroke (Fig. 2). Therefore, the findings in this case, emphasize the role that the occipital cortex plays in Braille reading in early blind subjects.

Cohen et al. argue for a critical period for this plasticity (Cohen et al., 1997), such that beyond age 14, the striate cortex is no longer recruited for the processing of tactile information. They base this argument on the study of late-blind subjects who became blind after age 15, in whom tactile stimulation failed to reveal activation of the striate cortex on PET, and in whom rTMS to the striate cortex did not interfere with reading of embossed Roman characters. Nevertheless there are a number of other potential confounders. For example, late blind individuals are often less skillful Braille readers, and

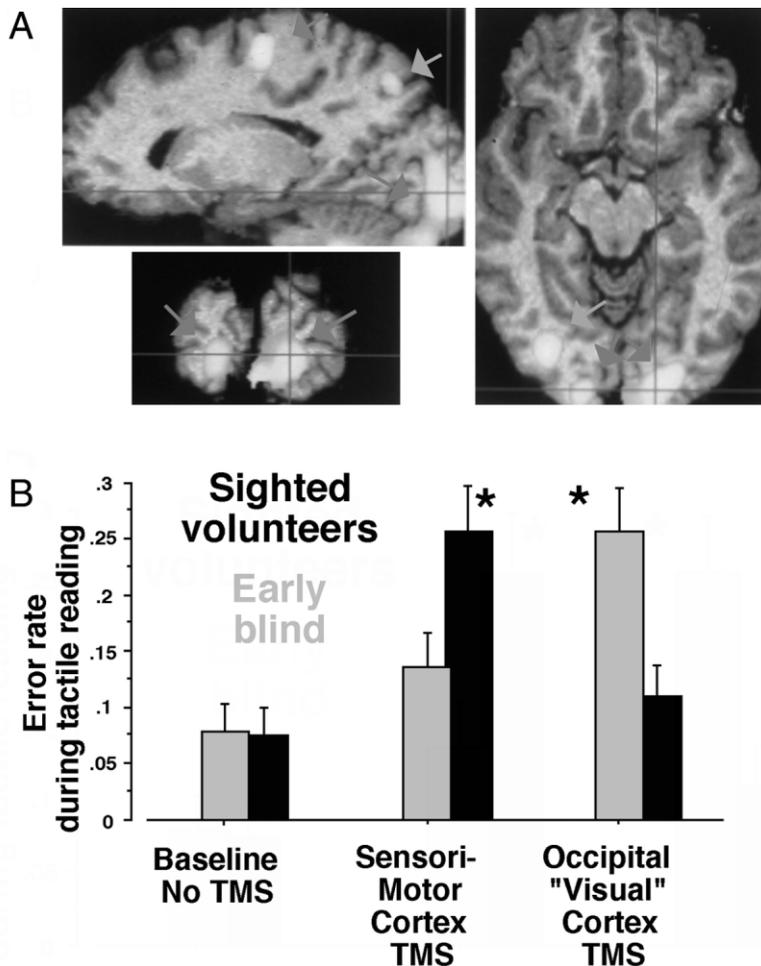


Fig. 1. (A) Modified from (Sadato et al., 1996, 1998). Activation of the occipital cortex in congenitally and early blind subjects during tactile Braille reading as demonstrated by positron emission tomography (PET). (B) Modified from (Cohen et al., 1997). Effects of repetitive transcranial magnetic stimulation (TMS) to the occipital or somatosensory cortex on tactile Braille reading ability in early blind subjects and on tactile perception of embossed Roman letter in sighted controls.

among the five subject studied, four had residual vision that could well affect the plastic changes that can take place in the brain.

A relationship between tactile discrimination ability and the amount of activation of the striate cortex in the blind is suggested by recent results in early and congenitally blind subjects. Behaviorally, early blind subjects show significant superiority to age-matched sighted controls in a gratings-orientation discrimination task (Fig. 3) (Van Boven et al., 2000). A gratings-orientation threshold was determined for the tip of several fingers using the Johnson, Van Boven, Phillips (JVP) Domes. Blind subjects had

a lower mean threshold of 1.04 mm (SD = 0.19) compared to 1.46 mm (SD = 0.46) for the sighted group ($F = 10.78$, $df = 1,28$, $P = 0.003$). Interestingly, there was a significant Group \times Finger interaction ($F = 3.03$; $df = 3,84$; $P = 0.034$) indicating that the extent of the difference in thresholds between the two groups was not the same across fingertips. Post hoc comparisons revealed that among the blind subjects, there were significant differences in threshold for the different fingers, such that their preferred Braille reading finger has the lowest threshold (Fig. 3). Sighted controls showed no threshold differences across fingers.

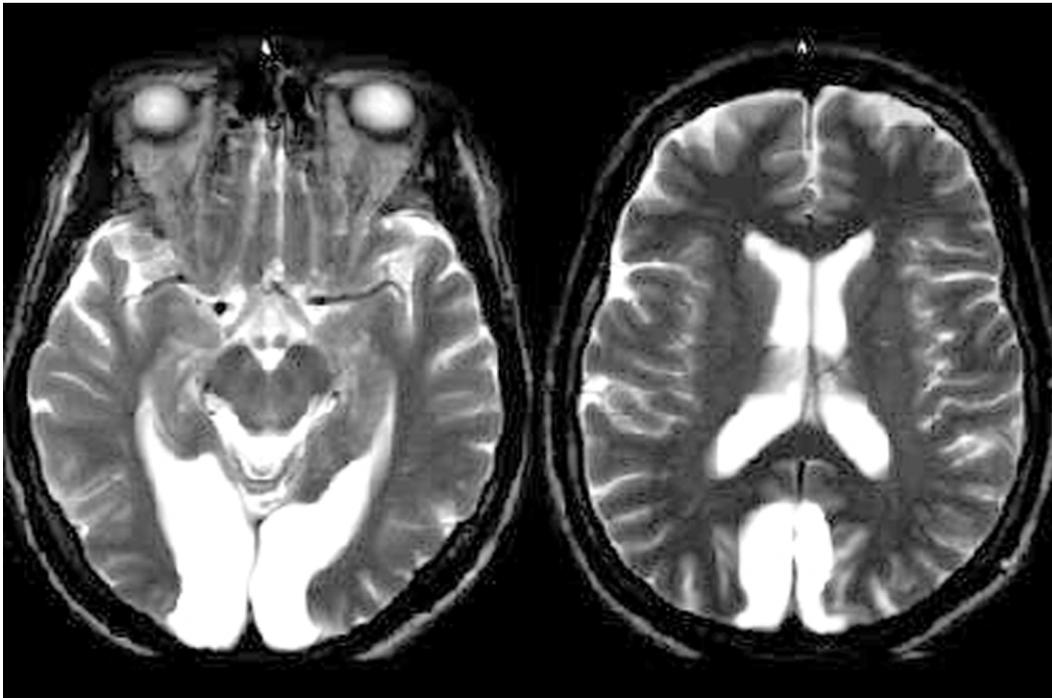


Fig. 2. Modified from (Hamilton et al., 2000). T2-weighted brain magnetic resonance imaging (MRI) of early blind woman with sudden onset of alexia for Braille. Note the large, bilateral occipital stroke in distribution of bilateral posterior cerebral arteries.

In these same 15 early blind subjects, we found a significant correlation between the amount of activation in striate and peri-striate cortex to tactile stimulation of the finger pads as measured by functional magnetic resonance imaging (fMRI) and the gratings-orientation thresholds for their different fingers (Kiriakopoulos et al., 1999). The blood-oxygen level dependent (BOLD) activation in occipital cortex was significantly greater during stimulation of the preferred reading finger than during stimulation of adjacent fingers in the same hand or of the homologous finger in the other hand (Fig. 3).

There are certainly alternative explanations as to how, in the blind, primary cortical areas that normally mediate vision can become responsive during tactile tasks. One possibility is that occipital activation in these tasks reflects mental imagery. Kosslyn and colleagues have repeatedly shown that visual imagery in normal subjects activates primary occipital cortical regions (Kosslyn, 1994). An argument could therefore be made that subjects who activate occipital networks during tactile tasks may, to some extent, be building visual representations of stimuli

encountered by touch. There are, however, a few pieces of evidence that suggest that visual imagery is not the phenomenon underlying activity across sensory modalities. In the absence of further evidence, it seems unlikely that early blind subjects, who in many cases have never had any vision whatsoever, are receiving top-down projections of visual percepts that then allow them to construct visual impressions of tactile stimuli. Furthermore, studies with late blind subjects, who often do remember the visual appearance of objects, suggest that these individuals may not activate occipital cortical networks during tasks, although this finding is still a topic of debate (Büchel et al., 1998).

More interestingly, it may be the case that occipital activation in the blind for tactile tasks does not represent visual imagery, but instead represents what can be thought of as ‘tactile imagery’. According to this hypothesis, top-down processes rather than afferent inputs may be driving occipital cortical response. Although such a model postulates a different ‘direction of flow’ of information from the bottom-up architecture being hypothesized, this view

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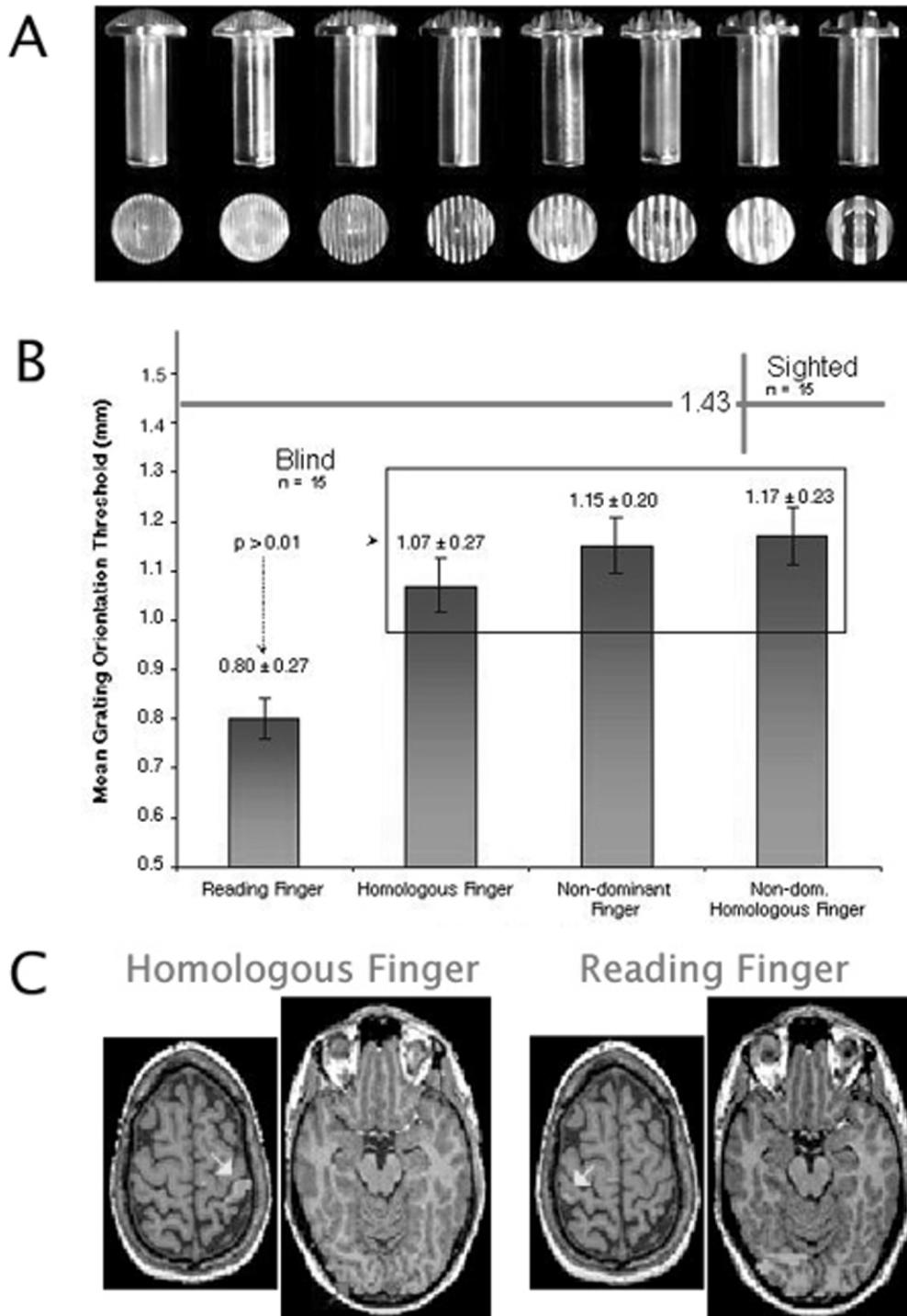


Fig. 3. (A) JVP Domes used for grating orientation discrimination testing. (B) Histogram displaying the thresholds for gratings orientation discrimination in early blind and sighted control subjects. Note the marked superiority (lower thresholds) of the blind subjects in general and in particular of their dominant Braille reading finger. Modified from (Van Boven et al., 2000). (C) Modified from (Kiriakopoulos et al., 1999). Representative example in one early blind subject of the differential activation of somatosensory and occipital cortex during tactile stimulation of the Braille reading finger and of the homologous finger in the other hand. Note the relative hypoactivity of the somatosensory cortex and the activation of the occipital cortex during stimulation of the reading finger.

is, nonetheless, entirely consistent with a metamodal model of the brain. The localization of tactile imagery to the occipital region would imply that complex reconstruction of aspects of a stimulus gained via touch are being represented in the occipital cortex, possibly because expert networks of neurons in that region of cortex have acquired, through competition, the ability to perform that operation.

Therefore, it seems that the occipital cortex in early blind and congenitally blind subjects is engaged in spatial tactile processing: it is both required for it and its activation is correlated with performance on behavioral measures. Is this the case in only the blind? It seems tempting to consider the possibility that such a role of the occipital cortex is present in all of us, sighted or blind, but that visual input masks detectable evidence of processing of information from other sensory modalities. If so, visual deprivation by blindfolding might unmask the metamodal role of the ‘visual cortex’.

The subjective experience of instructors for the blind in Spain

For a number of years, aspiring instructors for the blind in Spain were required to undergo a period of complete blindfolding “to get a first hand experience of what being blind really is like.” These future instructors of the blind lived at a boarding school and spent 1 week blindfolded. The blindfold was put on before getting up from bed in the morning and was worn all day until retiring for the night. The students were required to leave the blindfold on until they were in bed and the lights had been switched off. Most likely all of them cheated some, tampered with the blindfold and sneaked a peak into the light occasionally. However, this was likely held to a minimum since bright light bothered their eyes, which had adapted to darkness.

Most of these trainees report noticing improved abilities to orient to sounds and judge distance by sound by the end of the blindfolded week. For example, several describe becoming able to identify people quickly and accurately as they started talking or even as they simply walked by due to the cadence of their steps. Several learned to differentiate cars by the sounds of their motors, and one described the “joy of telling motorcycles apart by their sound.” A

few felt that they had become able to detect objects or furniture in their paths by the “echos of sounds”. Similarly, most of them noted an improved ability to differentiate surfaces and identify objects by touch during the 7 blindfolded days.

Interestingly, at the end of the week, removal of the blindfold required a period of several hours for readjustment to a visual world, during which time these persons experienced difficulties in visual spatial information decoding. Frequently subjects experienced the greatest difficulties when attempting to cross the street after the blindfold had been removed: “it was difficult to judge the height of the curb and it was very anxiety provoking not to be confident about the time it would take for an approaching car to close in. I would question whether I had the time to cross the street safely because I could not judge the speed of the cars or how long it would take them to get to me”.

The blindfold experiment

In order to follow-up on these anecdotal reports by instructors for the blind in Spain in a systematic and controlled fashion, we are conducting a study in which normal sighted volunteers are visually deprived for 5 days (Maguire et al., 1999; Schlaug et al., 1999; Kauffman et al., 2000; Schlaug et al., 2001). During this time they are kept at the General Clinical Research Center (GCRC) at Beth Israel Deaconess Medical Center and are intensively trained in tactile and auditory spatial discrimination tasks. In addition to behavioral testing, subjects undergo serial fMRI studies to tactile and acoustic stimuli. Subjects are fitted with a specially designed blindfold that completely prevents all light perception. Potential tampering with the blindfold by the subjects is controlled with the use of a piece of photographic paper attached to the inside of the blindfold and analyzed for possible exposure to light at the end of the experiment. Non-blindfolded control subjects are blindfolded temporarily for all serial MRI and behavioral experiments.

MR Imaging is performed using a whole body 1.5 T Siemens Vision EPI system. A 3-D T1-weighted MR sequence ($1.0 \times 1.0 \times 1.0$ mm) is acquired for co-localization with functional images. A set of 18 functional MR images ($2.5 \times 2.5 \times 4$ mm) parallel

to the ACPC plane is acquired every 5 s for a total of 40 s/epoch. For the auditory fMRI studies, volunteers perform a tone matching task and a motor control task in counterbalanced order. Each task is repeated 8 times. The matching task consisted of a series of tones and subjects have to compare each tone with the previous one, stating whether it is the same or different using a button press. In the motor control task, subjects are instructed to alternate button presses between the two responses. For the tactile stimulation task, pairs of Braille symbols are presented to the pad of the right index finger and the subject has to report whether they are the same or different. A motor control task of alternating button presses is again used as control. Image analysis is done using the AFNI software package (2.2) using '3dvolreg' for motion correction. All images are spatially standardized into the Talairach space. A two-factorial 3D ANOVA analysis is performed on each of the two groups, i.e. blind-folded and control group, with the first factor being 'condition' (tone, rest) and the second factor being 'scan' (before, during, after blindfolding). The F-tests and planned contrasts are corrected for multiple comparisons.

Behaviorally, subjects have been tolerating the blindfolded period well, though all of them have developed visual hallucinations that generally met criteria for Charles–Bonnet syndrome (Maguire et al., 1999). All subjects lacked a history of psychopathology, sensory disorders, or ocular pathology, and all were readily cognizant of their complex, often colorful, hallucinations. Visual hallucinations began shortly after individuals were blindfolded. Subjects were instructed to keep a daily journal of their thoughts, dreams, and perceptions throughout the blindfolded period. Hallucinations were reported as incidences of intrusive visual hallucinations that varied in onset, duration, and content. Additionally, images also varied in complexity, ranging from Lilliputian figures to landscapes and cartoon figures. Hallucinations most often occurred during the subject's ambulatory movements, such as when walking to and from the rest room, and also between testing sites within the research unit. No obvious memory sources were associated with the hallucinations, nor did they have a tendency to repeat themselves.

One subject, a 24-year-old male, experienced a broader range of images, which commenced a few

hours after blindfolding and persisted for several hours after the blindfold was removed at the end of the study week. Hallucinations at first included flashing lights, mirrors, lamps, trees, and full landscapes. By the conclusion of the second day of blindfolding, the images grew in such complexity that the subject experienced difficulty walking due to the 'obstacles' he saw. While taking a walk outside, he reported seeing "a ground of dirt rows, mounds of pebbles, or little small stones that were running from upper left to lower right field of view and between them was running a small stream of water." Furthermore, the images became a constant presence to the subject, and by the end of the study week developed into ornate buildings of whitish green marble and cartoon-like figures. All of the hallucinations were recognized as such, and could consciously be cleared by the subject, if desired.

Another subject, a 20-year-old female, experienced an array of hallucinations that first appeared approximately 12 h after blindfolding and lasted throughout the course of the study week until moments before the blindfold was removed. The hallucinations seemed to appear suddenly and transform into a series of different images much like in a dream "a butterfly becomes a sunset, that becomes an otter, that becomes a flower, that becomes several different types of animals, and it all is kind of this big stream." Hallucinations varied in type from landscapes, such as cities, skies and sunsets, to objects that, as in the example transcribed above, frequently morphed into one another. The subject often described the visions as if looking at a kaleidoscope, with bright colors and shapes that moved in a continual rhythm: "if there is a sunset or a sunrise I couldn't look at the sun — because it was too bright . . . It would seem like all of this light would just collect where the sun was and I just couldn't look there . . . would get like a spot and it would turn into something else." The subject also stressed that the hallucinations were beautiful ("it is like art, sometimes they are much prettier I think than anything I've ever seen . . . I really wish I could paint.") and that motion was always involved.

However, the most exciting aspect of these results is that the serial fMRI studies of these subjects showed activation of the visual cortex during tactile and auditory stimulation of the fingers. These data

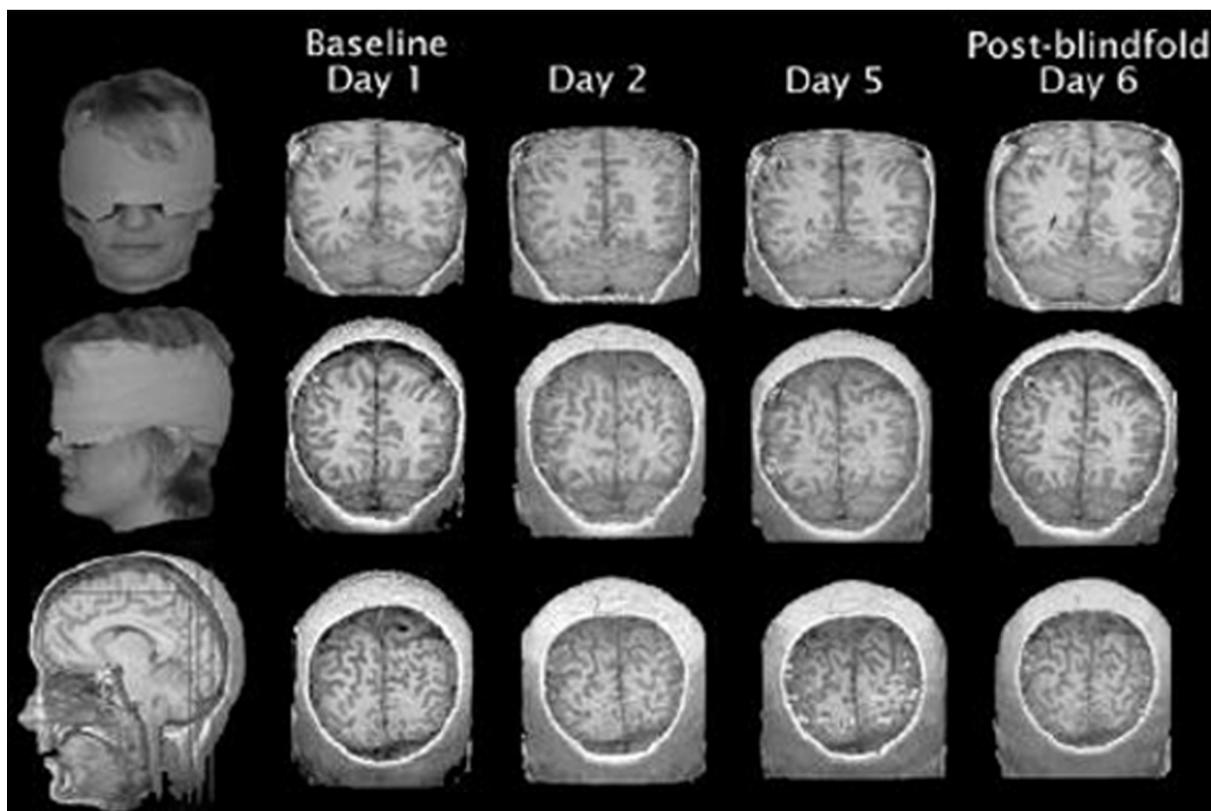


Fig. 4. Representative example of the changes in BOLD activation on functional brain MRI over the course of 5 days of complete visual deafferentation through blindfolding. Note the increasing activation of occipital cortex, including striate cortex by the fifth day of blindfolding and the dramatic return to baseline following removal of the blindfold for a single day (despite testing with the blindfold on).

suggest that the appearance of visual hallucinations in these subjects may be the result of modifications made by the visual cortex in processing both tactile and other non-visual sensory information. As illustrated in Fig. 4 over the course of the blindfolded period, the striate and peri-striate cortex becomes increasingly activated during the tactile stimulation. On the first day of the blindfolding period there is activation in the contralateral somatosensory cortex, but none in the occipital cortex. On the second and particularly on the fifth day of blindfolding the activation in the somatosensory cortex is less, but there is increasing BOLD activation in occipital, ‘visual’, regions. Similarly, activation of striate cortex during auditory stimulation is seen at the end of the blindfold period and was absent prior to the blindfolding or in the control subjects (Schlaug et al., 1999, 2001).

Strikingly, the occipital activation with tactile or auditory stimulation disappears 12–24 h following removal of the blindfold (Fig. 4), even though for the purpose of the fMRI the subjects wear the blindfold again. In other words, removing the blindfold and being exposed to the seeing world for 12–24 h is sufficient to revert all changes induced by the 5 days of blindfolding.

A TMS experiment (Kauffman et al., 2000) serves to explore the behavioral significance of the findings (Fig. 5). At the last day of blindfolding, rTMS to the occipital cortex of the volunteers significantly disrupts their newly acquired tactile Braille symbol discrimination ability. The findings are similar to those found in early blind subjects. The sighted, non-blindfolded control subjects do not show such results. Interestingly, and in accordance with the fMRI results, 1 day after removal of the blindfold,

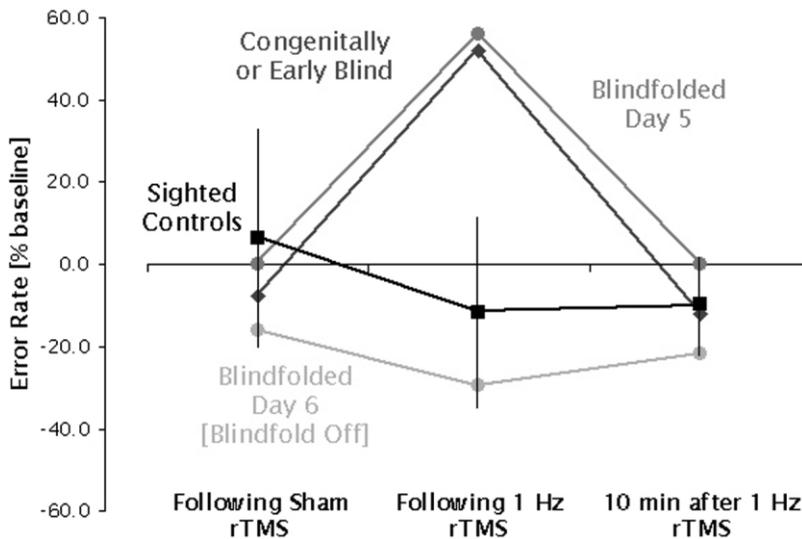


Fig. 5. Modified from (Kauffman et al., 2000). Representative example of the effects of repetitive TMS to the occipital cortex onto the tactile Braille symbol discrimination ability in a subject after 5 days of complete visual deafferentation through blindfolding. Note the comparison with a subject undergoing the same experimental procedures but never blindfolded and with a congenitally blind control.

disruption of the occipital cortex by rTMS no longer impairs tactile Braille reading ability.

These results suggest that the occipital cortex had become recruited for processing tactile and auditory information when it was deafferented of visual input. However, as soon as visual input became available, even transiently, the induced changes rapidly reversed to baseline. The speed of these changes is such that establishment of new connections is not possible. Therefore, it must be assumed that tactile and auditory input into 'visual cortex' is present in all of us and can be unmasked if behaviorally desirable.

Anatomical support

Such a hypothesis requires some anatomical support. One might expect that multimodal sensory responses of neurons in primary 'visual' cortex ought to be demonstrable and that tracing studies would have already revealed pathways relating information from the medial lemniscus, somatosensory thalamus, medial geniculate, or other structures to the striate cortex. In fact, the evidence is rather scarce.

A number of possible explanations can be discussed to account for the paucity of supporting evidence from animal models, including, for example,

choice of the animal models and anesthetic agent. Most importantly, however, the competitive selection among expert systems that may determine the functional specificity of cortical modules would be expected to powerfully suppress less suitable inputs. Hence, experiments in selectively sensory deprived animals might be needed.

There is some evidence available that has indicated that neurons in striate cortex have auditory and tactile in addition to visual inputs. However, these results have been debated and gone largely without reliable reproduction by other investigators. Frank Morell (Morell, 1972) studied visual and acoustic responses of neurons in parastriate (18 and 19) areas in adult cats using microelectrode recording techniques. Seventy of 169 neurons recorded (41.4%) were responsive to visual and acoustic stimulation. Interestingly, none of these neurons demonstrated a frequency tuning curve analogous to those of the 'primary auditory cortex' to acoustic stimuli of 5–50 kHz. However, the responsiveness of 'visual cells' to acoustic stimuli depended on the location of the sound source in space. Fishman and Michael (Fishman and Michael, 1973) studied striate cortex (area 17) also using microelectrode recordings in unanesthetized cats, and similarly found that 38% of the recorded cells responded to both auditory and visual

stimuli. As in the study by Morell (1972), bimodal cells had coincident acoustic and visual receptive fields and were distributed in functionally segregated, anatomically distinct clusters. Several previous studies had yielded similar findings (Lomo and Mollica, 1962; Jung et al., 1963; Murata et al., 1965; Spinelli et al., 1968). Therefore, these findings argue that neurons in striate and peristriate cortex might be engaged in the spatial localization of stimuli regardless of sensory modality and might indeed be tuned to specific topography along orientation columns. The anatomical pathways by which acoustic or tactile information reaches striate cortex are unclear. Thalamo-cortical or cortico-cortical pathways can be hypothesized but neither has been demonstrated to date.

Metamodal brain

Based on the data presented, the visual cortex seems to be a metamodal structure that receives not only visual, but also auditory and tactile stimuli. These inputs can be unmasked and functionally demonstrated as they gain functional relevance during visual deafferentation. Throughout these changes the ‘visual cortex’ appears to subservise spatial discrimination tasks regardless of the sensory input processed. Based on this example of the visual cortex, we propose that the brain, in a revised version of the views of the early 19th Century, is made up of metamodal operators. These operators are local neural networks defined by a given computation that is applied regardless of the sensory input received. This does not mean that there are not preferred sensory modalities for specific computations (and hence operators). Indeed, this is the case and the reason that the cortex gives the illusion of being built around sensory modalities rather than operators. We shall propose a model by which such a cortical architecture built around operators, rather than sensory modalities might be generated. This proposal is based on Robert Jacobs’ ‘mixture of experts’ (ME) architecture (Jacobs, 1999).

Mixtures of experts architecture

The ME architecture implicitly contains two important notions. The first is that there are structure–

function correspondences in the brain. Because the structural properties of different brain regions differ (e.g. different patterns of neural connectivity), different brain regions are best at performing particular types of functions. The second notion is that brain regions compete for the ability to perform a set of tasks. This competition leads to functional specialization of brain regions but also in the progressive segregation of the best suited inputs. This competition is not an altogether fair fight. It is biased by the structure–function correspondences; each region tends to win the competition for those functions for which its structure makes it particularly well-suited.

ME architecture incorporates the two ideas of competition and structure–function correspondences in a model that consists of two types of networks: expert networks and a gating network. The system is designed to try to learn training patterns, which consist of an input along with a desired output. The expert networks compete with each other to learn training patterns, while the gating network mediates this competition. The output of the entire architecture, denoted y , is the linear combination of the experts’ outputs:

$$y_{i-1}^n = \sum g_i y_i$$

where y_i denotes the output of the i -th expert network and g_i is the gating network output corresponding to the i -th expert. The connection strengths of the expert and gating networks are adjusted simultaneously during training. Each expert network’s output is compared with the target output at each time step. The expert whose output most closely matches the target is called the winner; the others are losers. The winning expert wins information and thus learns a lot about the current training pattern; the losers receive little or no information, and thus learn little about the current training pattern. The gating network receives information about the relative performances of the experts on the current pattern. It adjusts the connection strengths so that when the current input (or similar input) recurs in the future the activation of its output unit corresponding to the winning expert will be larger and the activation of its remaining output units will be smaller. This learning process has a positive feedback effect that ensures that an expert system that won the competition for a particular learning pattern will be most likely to win

the same pattern in the future. This positive feedback loop also forces different expert networks to learn different tasks, since no expert network aside from the one that won before will ever be more likely to win in the future. Conversely, as an expert network receives and incorporates the information it receives from the gating network in order to become specialized for a particular task, it will become less likely to compete well on patterns from unrelated tasks.

Does ME architecture actually work, and can networks configured with ME architecture learn to make the kinds of distinctions that functionally distinct brain modules seem to be able to make? Naturally, the only way to find out would be to attempt to train these networks on tasks that mimic the kinds of processes we believe occur in brains. Jacobs and Kosslyn (1994) speculated that different subsystems in the brain are responsible for making categorical and coordinate visual judgements. In other words, they hypothesized that different neural agencies (or ‘operators’ in our terminology) using different kinds of information are responsible for classifying a stimulus (e.g. object A is a building) versus identifying a stimulus as a particular exemplar (e.g. object A is the Leaning Tower of Pisa). They hypothesized that systems that make categorical judgements would be more efficient if they monitored visual neurons with small non-overlapping receptive fields (and thus with low-resolution representation of visual objects), whereas systems that make coordinate visual judgements should be more efficient if they monitor neurons with large, overlapping receptive fields (high-resolution representation). Jacobs and Kosslyn used computer simulations to support this theoretical structure–function relationship, demonstrating that neural networks with small receptive learn category tasks more quickly, while networks with large receptive fields learn coordinate tasks more quickly. They then trained competing networks using small or large receptive field sizes and ME architecture and found that networks with small receptive fields tended to win the competition for category tasks while networks with large receptive fields won the competition for coordinate tasks. This set of simulations demonstrates that structure–function relationships and competition between networks can lead to functional specialization of processing, and suggests that ME architecture is a plausible and

computationally efficient model for achieving this specialization.

For the purposes of applying ME architecture to biological systems, it is important to note that there is no need to determine which neural structure corresponds to the gating network. This is because the ME architecture is computationally and thus functionally equivalent to another architecture that does not contain gating networks, but instead contains inhibitory connections between expert networks that suppress each other’s output. The strengths of the inhibitory connections depend on the value of the current input pattern, such that, depending on the task at hand, different expert networks would be more or less capable of winning the competition for that task. At the end of training, the expert that won the competition in the context of the current input, or closely related inputs, strongly suppresses the outputs of other experts. Experts that are the losers in the competition for a particular task suppress the outputs of other experts weakly or not at all.

Given what is currently known about how ME architecture works, it is not difficult to theorize how particular regions of the cortex might have acquired functional specificity using a network that approximates this architecture. One must first assume that there exist initial differences between competing neural modules. The occipital cortex, for example, might obtain the domain of visual processing because it is best suited for computations that may benefit from the information best supplied by vision. The data transformations at which the occipital cortex may initially excel might not be vision, *per se*. Instead, the occipital cortex may initially be a region of the brain with structural and functional qualities that enable it to excel at tasks which require high-acuity processing of spatial information. If this were the case, one would anticipate that the occipital cortical regions would constitute the expert network that would win the competition for vision, a sensory modality that provides tremendous amounts of distance and spatial information (as compared, for example, with sound or touch). As the occipital cortex continues to win the competition between expert networks for the input of vision, it is able to perform its task (spatial decoding) more and more accurately and hence adapts to become better and better at it, reinforcing visual input while increasingly suppress-

ing inputs from other sensory modalities. Eventually, the occipital cortex may become so specialized for vision that it seems as though it is a ‘visual’ cortex, designed for the specific task of further subdividing and processing visual information. As evidenced in the studies of Sur and colleagues discussed earlier (Sur et al., 1990; Merzenich, 2000), the input to a brain region is a powerful bias that helps to determine the nature of the processing that the module ultimately performs. If ME architecture bears any resemblance to the development of functional brain modules, it may not be the visual cortex that determines what the act of seeing will be like. Rather, it is the task of seeing that instructs the functional modules of the developing brain regarding what vision will be like, and how it must be processed.

If the development of functional specificity of cortical modules is the result of competition between expert networks that have distinct structural and functional properties, it becomes possible to suggest a mechanism by which apparent ‘crossmodal neuroplasticity’ might occur. In the case of early blind subjects, for example, the brain loses a major source of sensory input, which normally constitutes a complex task, or set of tasks, that is normally ‘won’ by occipital networks. Without training from visual input, occipital cortical areas may not become specific for the particular functions involved in seeing. Furthermore, since occipital cortical networks may be initially structurally and functionally predisposed to excel at tasks that require high-acuity and high-fidelity processing of spatial information, they may begin to win the competition for other tasks that make these kinds of processing demands. Tactile discrimination or auditory localization may represent just such kinds of tasks. As a result, the occipital cortex may begin to subserve the functions of touch and hearing, which it would not have been able to do nearly as well if the demanding and specific needs of visual processing still had to met.

In light of the aforementioned model of modular specificity and the hypothesis of plasticity across sensory modalities that emerges from it, it seems that referring to the kinds of cortical changes seen in blind Braille readers and other subjects as cross-modal plasticity is something of a misnomer. Function-specific brain modules do not appear to have preordained roles that simply get ‘switched’ when

the kinds of input received are radically altered. Rather, if cortical modules compete with each other to perform particular processing tasks, they should be thought of as being ‘metamodal’ brain centers that perform particular computational operations without specific reference to type of sensory input. It is these processes, and hence the cortical modules performing them, that are subsequently exploited and shaped by the demands of the sensory modalities that require them. Thus the many studies that demonstrate processing of sensory information outside of the classically recognized cortical boundaries for that modality may not be examples of the brain being redundant or ‘getting its wires crossed,’ but instead may represent the workings of an efficient metamodal brain, which uses inputs to those cortical regions (operators) that seem best suited to execute their computations successfully.

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References

- Büchel, C., Price, C., Frackowiak, R.S.J. and Friston, K. (1998) Different activation patterns in visual cortex of late and congenitally blind subjects. *Brain*, 121: 409–419.
- Clarke, E. and Jacyna, L.S. (1987) *Nineteenth-Century Origins of Neuroscientific Concepts*. University of California Press, Berkeley, CA.
- Cohen, L.G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Dambrosia, J., Honda, M., Sadato, N., Gerloff, C., Catala, M.D. and Hallett, M. (1997) Functional relevance of cross-modal plasticity in blind humans. *Nature*, 389: 180–183.
- Cohen, L.G., Weeks, R.A., Sadato, N., Celnik, P., Ishii, K. and Hallett, M. (1999) Period of susceptibility for cross-modal plasticity in the blind. *Ann. Neurol.*, 45: 451–460.
- Degenaar, M. (1996) *Molyneux’s Problem: Three Centuries of Discussion on the Perception of Forms*. Kluwer Academic, Dordrecht.
- Descartes, R. (1976/1662) *Treatise on Man*. Harvard University Press, Cambridge.

- Fishman, M.C. and Michael, C.R. (1973) Integration of auditory information in the cat's visual cortex. *Vision Res.*, 13: 1415–1419.
- Gall, F.J. and Spurzheim, J.C. (1835) *On the Function of the Brain and Each of its Parts: with Observations on the Possibility of Determining the Instincts, Propensities and Talents, or the Moral and Intellectual Dispositions of Men and Animals, by the Configuration of the Brain and Head*. Marsh, Capen, and Lyon, Boston.
- Gregory, R.L. and Wallace, J. (1963) *Recovery From Early Blindness: A Case Study*, Heffer and Sons.
- Gross, C.G. (1998) In: C.G. Gross (Ed.), *Brain, Vision, Memory: Tales in the History of Neuroscience*. MIT Press, Cambridge, MA.
- Hamilton, R.H. and Pascual-Leone, A. (1998) Cortical plasticity associated with Braille learning. *Trends Cogn. Sci.*, 2: 168–174.
- Hamilton, R., Keenan, J.P., Catala, M.D. and Pascual-Leone, A. (2000) Alexia for Braille following bilateral occipital stroke in an early blind woman. *NeuroReport*, 11: 237–240.
- Howard, I.P. and Templeton, W.B. (1966) *Human Spatial Orientation*, Wiley, London.
- Jacobs, R.A. and Kosslyn, S.M. (1994) Encoding shape and spatial relations: the role of receptive field size in coordinating complementary representations. *Cogn. Sci.*, 18: 361–386.
- Jacobs, R. (1999) Computational studies of the development of functionally specialized neural modules. *Trends Cogn. Sci.*, 3: 31–38.
- James, W. (1890) *The Principles of Psychology*. Henry Holt, New York.
- Jung, R., Kornhuber, H.H. and Da Fonseca, J.S. (1963) Multi-sensory convergence on cortical neurons: neuronal effects of visual, acoustic and vestibular stimuli in the superior convolutions of the cat's cortex. In: G. Moruzzi, A. Fessard and H.H. Jasper (Eds.), *Progress in Brain Research*. Elsevier, Amsterdam, pp. 207–240.
- Kauffman, T., Hamilton, R., Warde, A., Keenan, J.P. and Pascual-Leone, A. (2000) The role of visual cortex in tactile Braille reading: the early blind, the sighted, and the blindfolded. *Ann. Neurol.*, in press.
- Kiriakopoulos, E., Baker, J., Hamilton, R. and Pascual-Leone, A. (1999) Relationship between tactile spatial acuity and brain activation on brain functional magnetic resonance imaging. *Neurology*, 52(Suppl. 2): A307.
- Kosslyn, S.M. (1994) *Image and the Brain: The Resolution of the Imagery Debate*. MIT Press, Cambridge.
- Kujala, T., Alho, K. and Näätänen, R. (2000) Cross-modal reorganization of human cortical functions. *Trends Neurosci.*, 23: 115–120.
- Lomo, T. and Mollica, A. (1962) Activity of single units in the primary optic cortex in the unanesthetized rabbit during visual, acoustic, olfactory and painful stimulation. *Arch. Ital. Biol.*, 100: 86–120.
- Maguire, D.P., Stickgold, R., Warde, A., Kiriakopoulos, E. and Pascual-Leone, A. (1999) Appearance of Charles Bonnet syndrome (CBS) following prolonged blindfolding and Braille training. *Soc. Neurosci. Abstr.*, 25: 1315.
- Melchner, L.v., Pallas, S.L. and Sur, M. (2000) Visual behaviour mediated by retinal projections directed to the auditory pathway. *Nature*, 404: 871–876.
- Merzenich, M. (2000) Seeing in the sound zone. *Nature*, 404: 820–821.
- Morell, F. (1972) Visual system's view of acoustic space. *Nature*, 238: 44–46.
- Morgan, M.J. (1977) *Molyneux's Question: Vision, Touch and the Philosophy of Perception*. Cambridge University Press, Cambridge.
- Müller, J.M. (1965/1838) On the specific energies of nerves. In: R. Herrnstein and E. Boring (Eds.), *Sourcebook of the History of Psychology*. Harvard University Press, Cambridge, MA.
- Murata, K., Cramer, H. and Bach-y-Rita, P. (1965) Neuronal convergence of noxious, acoustic and visual stimuli in the visual cortex of the cat. *J. Neurophysiol.*, 28: 1223–1240.
- Pascual-Leone, A. and Torres, F. (1993) Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. *Brain*, 116: 39–52.
- Pascual-Leone, A., Cammarota, A., Wassermann, E.M., Brasil-Neto, J.P., Cohen, L.G. and Hallett, M. (1993) Modulation of motor cortical outputs to the reading hand of Braille readers. *Ann. Neurol.*, 34: 33–37.
- Pascual-Leone, A., Wassermann, E.M., Sadato, N. and Hallett, M. (1995) The role of reading activity on the modulation of motor cortical outputs to the reading hand in Braille readers. *Ann. Neurol.*, 38: 910–915.
- Pascual-Leone, A., Tarazona, F. and Catala, M.D. (1996) Modulation of motor cortical output maps associated with the acquisition of the Braille reading skill. *Neuroimage*, 3: S554.
- Rauschecker, J.P. (1995) Compensatory plasticity and sensory substitution in the cerebral cortex. *Trends Neurosci.*, 18: 36–43.
- Roe, A.W., Pallas, S.L., Hahm, J.-O. and Sur, M. (1990) A map of visual world induced in primary auditory cortex. *Science*, 250: 818–820.
- Sadato, N., Pascual-Leone, A., Grafman, J., Ibañez, V., Deiber, M.-P., Dold, G. and Hallett, M. (1996) Activation of the primary visual cortex by Braille reading in blind subjects. *Nature*, 380: 526–528.
- Sadato, N., Pascual-Leone, A., Grafman, J., Deiber, M.-P., Ibañez, V. and Hallett, M. (1998) Neural networks for Braille reading by the blind. *Brain*, 121: 1213–1229.
- Schlaug, G., Halpern, A.R., Press, D.Z., Baker, J., Edelman, R.R. and Pascual-Leone, A. (1999) Changes in cortical auditory processing after blindfolding. *Soc. Neurosci. Abstr.*, 25: 1628.
- Schlaug, G., Chen, C., Press, D.Z., Warde, A., Chen, Q. and Pascual-Leone, A. (2001) Hearing with the mind's eye. *Hum. Brain Mapping*, in press.
- Sharma, J., Angelucci, A. and Sur, M. (2000) Induction of visual orientation modules in auditory cortex. *Nature*, 404: 841–847.
- Spinelli, D.W., Starr, A. and Barrett, T.W. (1968) Auditory specificity in unit recordings from cat's visual cortex. *Exp. Neurol.*, 22: 75–84.
- Stein, B.E. and Meredith, M.A. (1993) *The Merging of the Senses*. MIT Press, Cambridge, MA.
- Sur, M., Pallas, S.L. and Roe, A.W. (1990) Cross-modal plastic-

- ity in cortical development: differentiation and specification of sensory neocortex. *Trends Neurosci.*, 13: 227–233.
- Van Boven, R., Hamilton, R., Kaufman, T., Keenan, J.P. and Pascual-Leone, A. (2000) Tactile spatial resolution in blind Braille readers. *Neurology*, in press.
- Von Senden, M. (1932) *Space and Sight: The Perception of Space and Shape in the Congenitally Blind Before and After Operation*. J.A. Barth.

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