4 Building the brain in the dark: Functional and specific crossmodal reorganization in the occipital cortex of blind individuals

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4.1 Introduction

The brain has long been considered as being hard-wired in a predetermined manner shaped by evolution. This view has been challenged in the past decades by increasing evidence documenting the impressive capacity of the brain to be modulated through learning and experience, even well into adulthood. Pioneering studies of Hubel and Wiesel on the development of ocular dominance columns have compellingly demonstrated that alterations in visual experience can influence the normal development of the visual cortex (Hubel and Wiesel, 1963; Hubel, Wiesel and LeVay, 1977).

One of the most striking demonstrations of experience-dependent plasticity comes from studies in congenitally blind individuals (CB) showing dramatic cortical reorganizations as a consequence of visual deprivation. Experiments have documented that cortical sensory maps in the remaining senses of CB can expand with experience. For instance, finger representation in the somatosensory cortex is increased in proficient Braille blind readers (Pascual-Leone et al., 1993; Sterr et al., 1999) and the tonotopic map in the auditory cortex is larger in visually deprived individuals (Elbert et al., 2002). Such cortical changes are thought to underlie enhanced reading abilities and auditory

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processing skills in the blind (Elbert et al., 2002; Sterr et al., 1998).

Aside from these examples of intramodal plasticity, massive crossmodal changes have been reported in the occipital cortex deprived of its natural visual inputs. In people born blind, occipital regions that would normally process visual stimuli are “hijacked” by the other senses as these regions become responsive to non-visual input (Bavelier and Neville, 2002; Pascual-Leone et al., 2005). Importantly, such crossmodal recruitment of the deafferented visual cortices is functionally relevant for non-visual processing. First, a few studies have demonstrated that occipital activity correlates with superior behavioral performances of blind individuals in nonvisual processing (Amedi et al., 2003; Gougoux et al., 2005). Secondly, local and reversible disruption of occipital activity using transcranial magnetic stimulation (TMS) alters performance in non-visual processing (Amedi et al., 2004; Cohen et al., 1997; Collignon et al., 2007). Finally, recent studies suggest that the crossmodal recruitment of occipital cortices in CB might follow organizational principles that maintain the functional specialization of the colonized brain regions (Collignon et al., 2009; Dormal and Collignon, 2011).

In addition to these functional changes, structural differences have also been documented in the blind relative to the sighted brain. Early visual deprivation causes atrophy in the optic tracts and radiations as well as massive gray and white matter volume reduction in early visual areas (Noppeney, 2007; Pan et al., 2007; Park et al., 2009; Ptito et al., 2008; Shu et al., 2009a, b). Although increased cortical thickness of occipital cortex has also been reported in the blind (Jiang et al., 2009), it is believed to reflect the reduced surface area of the primary and secondary visual cortices (Park et al., 2009). Interestingly, a recent research reported that cortical thickness of occipital areas in early blind individuals was directly related to their superior behavioral performance, relative to the one of sighted controls, in two tasks involving pitch and melody discrimination (Voss and Zatorre, 2011).

Determining the neural mechanisms underlying these plastic changes is crucial for understanding the role of sensory experience in shaping the functional architecture of the brain and, further, for applying the knowledge gathered by fundamental neuroscience to sensory rehabilitation (Merabet et al., 2005). Indeed, success in visual restoration and rehabilitation highly depends on our understanding of how blindness affects the brain. In the present chapter, we review existing evidence of crossmodal reorganization in blindness and consider how the onset of sensory deprivation is likely to lead to different outcomes fo different types of rehabilitative interventions.

4.2 Crossmodal reorganization in the occipital cortex of early blind

In a pioneering study using positron emission tomography (PET), Veraart and colleagues demonstrated that metabolic activity in occipital areas of early blind individuals at rest was as high as the one observed in sighted participants when performing a visual task (Veraart et al., 1990; Wanet-Defalque et al., 1988). Another study from the same group showed that this elevated metabolic activity was truly related to neural activity rather than to gliosis (De Volder et al., 1997). Since these preliminary evidences, a wealth of neuroimaging studies have highlighted occipital task-dependent activations in the early blind brain during tactile (Buchel, 1998; Burton et al., 2002; Pietrini et al., 2004; Sadato et al., 1996), auditory (Kujala et al., 1995; Leclerc et al., 2000; Roder et al., 1999; Weeks et al., 2000), memory (Amedi et al., 2003; Roder, Rosler and Neville, 2001) and language-related (Burton et al., 2002; Roder, Rosler and Neville, 2000) processing. Importantly, these neuroplastic changes are believed to be compensatory in nature because they appear to underlie superior nonvisual abilities often observed in blind individuals (Amedi et al., 2003; Gougoux et al., 2005). For example, Amedi and collaborators (2003) were the first to report a positive correlation between behavioral performance of early blind participants during a verbal memory task and activations in primary visual cortices: individuals with the highest immediate and long-term memory performance were the ones who activated these regions the most (Amedi et al., 2003).

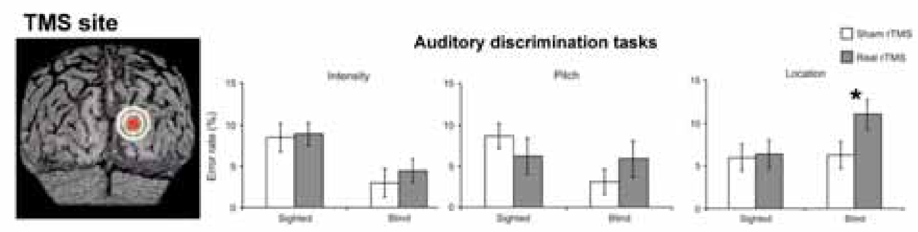
Experiments on “rewired” animals further confirm that areas normally dedicated to the processing of specific sensory inputs might revert to processing other sensory stimuli in a functional way. By making a series of brainstem lesions, experiments have demonstrated that it is possible to surgically re-route visual input toward primary somatosensory or auditory areas (Frost et al., 2000; Frost and Metin, 1985; Roe et al., 1990, 1992; Sur, Garraghty and Roe, 1988). Such observations account for the fact that the rewired regions share structural and functional similarities with cells recorded in the visual cortex of normally raised animals and further demonstrate that these changes mediate specific visually-guided behavior (Frost et al., 2000; von Melchner, Pallas and Sur, 2000). Hence, it appears that primary cortical areas can change their functional specificity depending on which inputs they receive.

4.3 Functional specificity in crossmodal reorganization

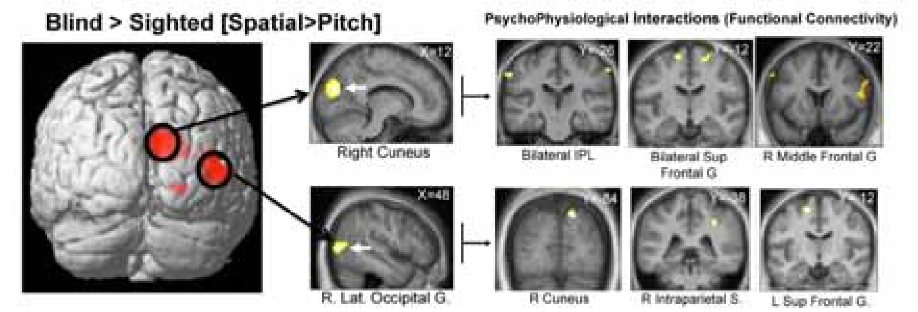
The occipital cortex of sighted individuals is divided into several functional areas, or “modules”, each of which is specialized in a particular aspect of vision. Recent studies on crossmodal reorganization in the blind suggest that the crossmodal recruitment of occipital cortices in blindness might follow organizational principles that maintain the functional specialization of the colonized brain regions (Collignon et al., 2009; Dormal and Collignon, 2011). For instance, a general principle of functional organization in the sighted brain is the existence of separate hierarchical pathways for object identification (the ventral “what” stream) and object localization in space (the dorsal “where” stream) in the visual and auditory cortices (Haxby et al., 1991; Rauschecker and Tian, 2000). Crucially, several neuroimaging studies carried out on early blind individuals bring evidence accounting for the maintenance of this hierarchical organization of the visual cortex for non-visual processing.

Dorsal functions and spatial hearing: On the one hand, different paradigms and neuroimaging techniques have consistently demonstrated dorsal occipital recruitment, mainly in the right hemisphere, for spatial hearing in the early blind. In a PET study, Weeks and collaborators (2000) reported that sound localization strongly activated association areas in the right dorsal occipital cortex of early blind individuals but not sighted controls (Weeks et al., 2000). Another PET study extended these findings demonstrating that a network of regions in the right dorsal extrastriate cortex was recruited in early blind individuals during monaural sound localization and, further, that activity in several foci of this network correlated with sound localization performance (Gougoux et al., 2005). More recently, Collignon and colleagues (2011) carried out an fMRI study on early blind and sighted individuals while participants were discriminating on pairs of sounds differing either in terms of location in space or in pitch. In this study, a staircase paradigm was used in order to equalize difficulty level across tasks and participants. The spatial localization task relative to the pitch discrimination task was shown to preferentially map onto specialized subregions of the right dorsal occipital stream in the early blind group but not in the sighted group (Figure 4.1b). More specifically, two regions corresponding to the right cuneus and the right middle occipital gyrus were mainly recruited, in the vicinity of regions that have previously been described in the sighted as the dorsal hV3, V3A and the hMT+/V5. Interestingly, these two regions have been extensively described as subserving visuospatial and motion processing in the sighted (Haxby et al., 1991; Sunaert et al., 1999). Collignon and collaborators (2011), using functional connectivity analyses demonstrated that these occipital regions are part of a larger parieto-frontal network including multisensory regions (i.e., the inferior parietal lobules, the intraparietal sulcus and the superior frontal gyrus) that are typically involved in spatial attention and awareness in the sighted brain (Szczepanski, Konen and Kastner, 2010). In other words, it appears that the dorsal occipital regions recruited by spatial hearing in the early blind are inherently part of the network involved in auditory localization (Collignon et al., 2011). Hence, crossmodal reorganization in the early blind brain might be constrained to regions characterized by the same functional specificity, accounting for the fact that these dorsal occipital regions are strongly connected to an extended brain network wired to serve a specific function. In the same vein, another study has documented the existence of massive functional connectivity between the hMT+/V5 area and prefrontal cortices in the early blind (Bedny et al., 2010). Further, diffusion tensor imaging indicates that limited changes occur in the occipito-parieto-frontal white matter tracts of early blind individuals relative to sighted controls (Shimony et al., 2006). Another recent study suggested that the specific recruitment of right dorsal occipital regions in early blind individuals might be present for processing both auditory and tactile inputs, and might correlate with performance (Renier et al., 2010). Moreover, the putative homolog of hMT+/V5 was also previously shown to respond to auditory (Bedny et al., 2010; Poirier et al., 2006) and haptic motion (Ricciardi et al., 2007) in early blind individuals. The functional relevance of dorsal occipital recruitment by sound localization in the early blind has been confirmed by studies using transcranial magnetic stimulation (TMS). When TMS is applied over the right dorsal extrastriate occipital cortex, performance in auditory spatial localization is selectively altered in the early blind but not in sighted controls, while pitch and intensity perception remains unaffected in either group (Figure 4.1a) (Collignon et al., 2007).

Ventral visual pathway and object identification. Ventral visual pathway recruitment in the early blind brain during tasks involving the identification of an auditory or



(a) TMS study



(b) fMRI study

Figure 4.1. (a) The 3D brain representation displays the projection of the site of TMS application. This area corresponds to the right dorsal extrastriate occipital cortex (BA 18). The histograms denote the average error rate in early blind and sighted subjects after sham and real TMS targeting the dorsal occipital stream during auditory tasks involving discrimination of intensity, pitch and spatial location. The data show a significant increase of the error rate after real rTMS only in the early blind group and selectively for the sound location task. (b) The left part of the figure illustrates the activations obtained from the contrast testing which regions are specifically dedicated to the spatial processing of sounds in early blind subjects: [Blind $>$ Sighted] x [Spatial $>$ Pitch]. Functional data are overlaid (uncorrected < 0.001) over a 3D rendering of the brain and over sagittal sections of the mean structural image. The right part of the figure displays psychophysiological interaction results using the two main activity peaks as seed areas. Adapted with permission from Collignon et al. (2007, 2011).

a tactile input has been reported. For instance, several studies have shown that Braille reading is subserved by a large network of occipital regions in the early blind including an extended portion of the ventral visual pathway, with a predominance in the left, language-dominant, hemisphere (Buchel, Price and Friston, 1998; Sadato et al., 1998; Sadato et al., 1996). Recently, Reich and colleagues (2011) have shown that the visual word form area (VWFA), an area of the left occipito-temporal cortex specialized in visual reading in the sighted brain, is specifically recruited in early blind individuals when reading Braille words as compared to non-words. Evidence for occipital recruitment during Braille reading does not appear to be solely the result of life-long training with Braille in early blind individuals compared to sighted, because such activations are also found for non-Braille tactile discrimination tasks that do not require any training (Burton, McLaren and Sinclair, 2006; Sadato et al., 1998). For instance, using TEP, Sadato and colleagues (1998) demonstrated that early blind performing tactile discrimination tasks on angles, widths and characters strongly activated several ventral regions including the inferior occipital gyrus, the lingual gyrus and the fusiform gyrus, predominantly in the right hemisphere. Other language-related tasks such as language production (Amedi et al., 2003; Burton et al., 2002) and comprehension (Bedny et al., 2011) were demonstrated to recruit ventral regions of the left hemisphere in early blind but not-sighted controls. Pietrini and collaborators investigated brain responses for the tactile recognition of faces and man-made objects in blind subjects and demonstrated category-related patterns of response in more ventral cortical regions in the fusiform gyrus, indicating that visual experience is not necessary for category-related representations to develop in these cortices (Pietrini et al., 2004). In line with these results, a recent study demonstrated that the same regions of the ventral stream showing category preferences for nonliving stimuli and animals in sighted adults present the same category preferences in adults who are blind since birth (Mahon et al., 2009). Finally, voice perception, which is considered as the auditory counterpart of face perception for person recognition (Campanella and Belin, 2007), leads to activation of regions in the visually deprived ventral stream (Gougoux et al., 2009). TMS studies have confirmed the relevance of crossmodal reorganization in verb generation (Amedi et al., 2004) as well as Braille reading (Cohen et al., 1997) since application of TMS over the occipital cortex leads to altered performance in early blind participants but not-sighted participants. Even more convincing is the case study of a blind woman who was a proficient Braille reader before she developed Braille alexia following a bilateral occipital stroke (Hamilton et al., 2000).

In summary, whereas dorsal occipital regions with a right hemispheric dominance are activated during tasks involving spatial localization and motion, ventral occipital regions in the early blind seem to maintain a preferential coding for processing the identity of the input. This suggests that the dual-stream organization might be preserved in the rewired cortices of early blind individuals (Fig. 4.2). Beyond this general organization of the visual cortices, the similarity between the occipital regions activated by specific non-visual functions in the early blind and the ones associated to analogue functions in the visual modality in the sighted suggest that these areas may retain their functional coding ability despite visual deprivation. Hence, the nature of the organization of the visual cortex in early blind people appears to be constrained by the functional modularity that characterizes the same cortical structures in the sighted brain. Hence, it appears that the visual cortex is not a blank slate at birth but may rather be characterized by specific functional modules oriented to the accomplishment of a particular task. However, these modules may remain flexible with respect to the sensory input used to compute the process they are dedicated for, allowing their reorientation toward non-visual processing in case of early visual deprivation.

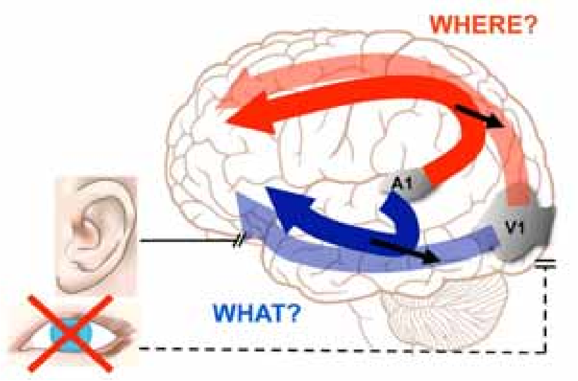


Figure 4.2. In auditory and visual cortices, information is thought to be processed along two distinct (but interacting) streams: a dorsal or "where" pathway involved in localization processes and a ventral or "what" pathway involved in identification processes. Recent data suggest that the dual-stream organization might be preserved in the rewired sensory cortices of early blind individuals.

4.4 Critical periods for crossmodal reorganization

The large majority of the studies showing massive crossmodal reorganization and superior behavioral performances in blind individuals have been carried out in persons who have been blind from birth or lost their sight early in life. Because the brain is known to be most receptive to change in response to experience encountered early in life, some studies have suggested the existence of a critical period beyond which visual deprivation is no longer susceptible to lead to massive neuroplastic changes in occipital cortices, and in V1 in particular (Cohen et al., 1999; Sadato et al., 2002). For example, Veraart and collaborators (1990) showed, using PET-scan, that glucose utilization in the occipital cortex of early blind is elevated and comparable to the one of sighted subjects with opened eyes. However, metabolic activity in late blind individuals is significantly lower and comparable to sighted subjects with eyes closed. On the other hand a number of studies have clearly demonstrated that the visually-deprived brain maintains a high capacity of plasticity late into adulthood, since crossmodal recruitment of visual cortex has also been documented in individuals who lost sight later in life, although to a lesser extent (Buchel et al., 1998; Burton et al., 2003).

A crucial and still unresolved question concerns the existence of a sensitive period in order for specific crossmodal organization to occur in case of visual deprivation. Indeed, the maintenance of functional specificity in the occipital regions deprived of their natural inputs might highly depend on the time of onset of visual deprivation. To date, two studies address this hypothesis (Bedny et al., 2010; Gougoux et al., 2009). Gougoux and colleagues (2009) characterized brain activations of early- and late-blind subjects while they passively listened to human voices or to a control condition consisting of various sounds of the environment. When comparing activity elicited by the voice condition relative to the control condition, early blind but not-late blind subjects show activation of the fusiform gyrus bilaterally and of the lingual/inferior occipital gyrus in the right hemisphere, close to regions that have classically been described as subserving face perception in the sighted brain (Kanwisher, McDermott and Chun, 1997). More recently, Bedny and colleagues (2010) demonstrated that the putative homolog of hMT+/V5 responded to auditory motion in congenitally blind participants compared to a group of sighted controls. Crucially, this region did not show this motion preference response in late blind participants or in an early blind subject who lost vision between 2 and 3 years of age. These observations suggest that visual deprivation needs to occur early in life in order for hMT+/V5 to develop specific crossmodal responses to motion. In the same vein, we compared brain activations of congenitally blind and late blind subjects when they processed either the pitch or the spatial attributes of sounds. We observed that the right dorsal stream (lateral occipito-temporal and cuneus) was preferentially activated for the spatial processing of sounds in CB but not in LB. This again suggests that vision has to be lost during an early sensitive period in order to transfer its functional specialization for space processing to a non-visual modality (Collignon et al., 2011b).

4.5 Putative mechanisms for crossmodal reorganization

The exact mechanisms mediating crossmodal reorganization and associated behavioral compensation in the blind remain largely elusive. We know from neuro-developmental studies in humans and primates that following a first period of exuberant proliferation of synapses, their number is gradually reduced (Bourgeois and Rakic, 1993, 1996; Huttenlocher and de Courten, 1987). Hence, the elimination of weaker, unused or redundant synapses is thought to mediate the specification of functional and modular neuronal networks (Changeux, Courrege and Danchin, 1973; Changeux and Danchin, 1976).

The human occipital cortex undergoes such changes in synaptic density during its normal development (Huttenlocher and de Courten, 1987). After a peak of proliferation ending approximately at the age of 8 months, about 40% of the synapses of the visual cortex are gradually removed to achieve a stable synaptic density in childhood, around the age of 11 years of age (Huttenlocher and de Courten, 1987). Indeed, experiments in kittens have demonstrated that projections from the auditory cortex to the occipital cortex are eliminated either through cell death or retraction of exuberant collaterals during the synaptic pruning phase (Dehay, Kennedy and Bullier, 1988; Innocenti, 1986; Innocenti, Berbel and Clarke, 1988; Innocenti and Clarke, 1984; Kennedy, Bullier and Dehay, 1989). Importantly, in kittens deprived of vision at birth, these extrinsic connections to the occipital cortex seem to remain (Berman, 1991; Yaka, Yinon and Wollberg, 1999). It is thus possible that in the absence of competitive visual inputs during the synaptic stabilization phase, a significant number of auditory connections to the occipital cortex persist due to their activity, explaining the massive functional intervention of this region for the processing of sounds in blind individuals. A recent study carried out in humans further supports this account, providing evidence that cortico-cortical connectivity between primary auditory and visual cortices is stronger in early blind individuals as compared to sighted controls (Klinge et al., 2010).

In order to further understand such mechanisms, we used TMS to disclose the time-course of the spatial processing of sounds in the dorso-lateral "where" stream of blind and sighted individuals (Collignon et al., 2008, 2009). To address this issue, we induced a virtual lesion at different delays on either the right intra-parietal sulcus (rIPS) or the right dorsal extrastriate occipital cortex (rOC) of blind and sighted subjects performing a sound lateralization task. We observed that TMS applied over rIPS 100-150 ms after sound onset disrupted the spatial processing of sounds in sighted subjects but surprisingly had no influence on the task performance in blind individuals at any timing. In contrast, TMS applied over rOC 50 ms after sound onset, disrupted the spatial processing of sounds in blind and in sighted participants. These studies suggest an early contribution of rOC in the spatial processing of sounds in the blind but also, to some extent, in sighted participants. Further, it points to lesser involvement of rIPS in this ability in blind participants. Given the very short latency of the disruptive effect of TMS applied over rOC on auditory spatial processing and considering the absence of rIPS contribution to this function in the blind, we suggested that sounds may reach the occipital cortex of blind subjects via direct "feedforward" afferences arising from the auditory cortex (Falchier et al., 2002).

Aside changes in cortico-cortical connections from auditory to visual cortex, some have suggested that reorganization of subcortical pathways might drive auditory information in the visual cortex of the blind. Indeed, neuronal tracing studies in blind animals have revealed that the inferior colliculus, an auditory relay, may project to thalamic structures normally occupied by the visual system (i.e., the lateral geniculate nucleus) (Chabot et al., 2008; Doron and Wollberg, 1994; Izraeli et al., 2002; Piche et al., 2007). Hence, coexisting cortical and subcortical connectivity changes might explain how auditory inputs reach the visually deprived occipital cortex in the early blind brain (Karlen, Kahn and Krubitzer, 2006).

While the maintenance of normally transient intermodal connections may underlie, at least in part, the plastic changes observed in cases of early loss of sight, this hypothesis can not account for the cerebral reorganization observed in cases of late blindness since visual deprivation arises in a brain already wired for visual processing. Differences in the mechanisms mediating crossmodal plasticity in early and late blind subjects might explain the different patterns of occipital recruitment observed between these populations. Whereas crossmodal recruitment of occipital regions in early blindness is thought to occur because of the persistence of normally transient connections between auditory and visual centers, these extrinsic inputs would not escape the normal developmental synaptic pruning in late blindness, due to the presence of stabilizing visual input. In line with such an assumption, an elegant study combining PET scan and TMS was carried out in order to probe the connection between primary somatosensory cortex (S1) and early visual cortex (V1) in early blind, late blind and sighted subjects (Wittenberg et al., 2004). This study demonstrated that the application of TMS over S1 induced significant activation of V1 only in the early blind group, consistent with the hypothesis of reinforced cortico-cortical connections between primary visual and somatosensory cortices in early- but not in late blind subjects.

However, the observation that crossmodal reorganization occurs even in individuals that have become blind later in life is supported by animal anatomical studies showing the existence of direct connections between auditory and visual cortical regions in adult sighted monkeys (Cappe and Barone, 2005; Clavagnier, Falchier and Kennedy, 2004; Falchier et al., 2002; Rockland and Ojima, 2003). Indeed, such findings suggest that some exuberant intermodal connections might not be pruned in early infancy, even if their functional purpose remains elusive. The cross-modal plasticity in the case of late blindness may in fact rely on the strengthening of connections that are already present within the occipital visual areas of the sighted brain. This idea receives further support from studies using short-term visual deprivation through blindfolding of normally sighted subjects. In these studies, changes in occipital activity occur within a few hours or days of blindfolding and are thus unlikely to be due to the development of new connections (Pascual-Leone et al., 2005; Pascual-Leone and Hamilton, 2001; Lazzouni et al, 2012).

In summary, while early visual deprivation might lead to the maintenance of intermodal connections between cortical areas that are normally pruned in infancy, preventing the strengthening of typical visual cortical networks, late sensory deprivation would not preclude these extrinsic connections to encounter the normal developmental synaptic pruning due to the presence of stabilizing visual input. Hence, crossmodal plasticity observed in late deprivation may reflect the strengthening of existing intermodal connections present in sighted subjects. This may be determined by mechanisms of Hebbian competition, where a synapse's efficiency strengthens if it participates in driving a postsynaptic cell (Hebb, 1949), as may be the case for intermodal connections in late blind individuals.

4.6 Outcomes of visual restoration and rehabilitation

Understanding the plastic changes occurring along the visual pathway of the early- and the late-blind is of primary importance given current advances in the field of sensory rehabilitation technologies, whether they are invasive or non-invasive (Merabet et al., 2005; Veraart et al., 2004).

Whereas non-invasive interventions may take advantage of increased neural resources in the processing of the remaining senses resulting from crossmodal plasticity, invasive techniques rely on the integrity of the deprived visual system (Figure 4.3). In the latter case, massive crossmodal reorganization following visual deprivation might prevent the reorganized cortex to perform its original function efficiently, especially in those who have lost sight early in life (Merabet, et al., 2005; Veraart, et al., 2004).

The most striking example certainly comes from historical cases of sight-recovery individuals following early-onset blindness. These rare cases have demonstrated that early visual deprivation permanently and deeply affects visual functions (Fine et al., 2003; Gregory, 2003; Levin et al., 2010). One of the most famous report concerns SB, a patient studied by Richard Gregory in the 1960s (Gregory and Wallace, 1963). SB lost his sight at 10 months of age and received a corneal graft after fifty years as a blind person. Despite the fact that his retina was functional, SB experienced extreme difficulties interpreting what he saw. Among these difficulties, depth perception was highly problematic. For instance, SB was completely insensitive to visual illusions that are typically observed in sighted individuals, accounting for his deficits in perspective and depth perception. SB was only able to recognize certain objects in the environment

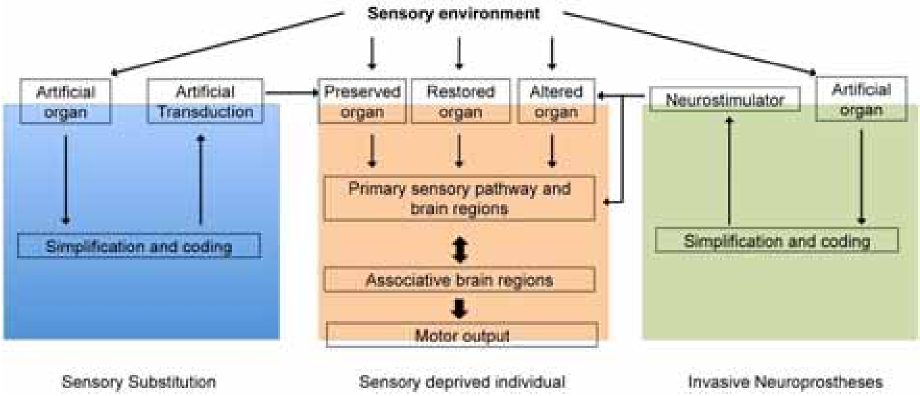


Figure 4.3. Model of rehabilitation procedures for sensory deprived individuals. The middle section represents a sensory deprived person for whom environmental information can be transmitted to the brain by means of a remaining modality after sensory substitution (left panel), surgical restoration of the defective organ, or by the use of an implanted neuroprosthesis stimulating the deficient sensory system (right panel). With sensory substitution, the environmental inputs usually gathered by the defective sense are simplified and coded in order to be manipulated in a preserved remaining modality. With neuroprostheses, the lacking sensory information is simplified and coded into electrical impulses to stimulate the fully or partly preserved portion of the deficient sense.

provided they were moving or they were already familiar to him by touch. Further, he was unable to recognize familiar persons by their face and would do so by their voice. Sometimes situations that he managed very well while he was blind appeared suddenly problematic because of the presence of concurrent and confusing visual information. As a consequence, SB continued to highly rely on audition and touch in order to efficiently interact with his environment. As he went from being a successful blind individual to an unsuccessful sighted one, he became clinically depressed shortly after his surgery (Gregory and Wallace, 1963). Another similar and fascinating case was recently documented in the literature (Fine et al., 2003). MM, a man who was blind since the age of 3 years old, received a stemcell transplant in his right eye at the age of 46. MM also encountered important visual difficulties after his surgery. Although he could recognize colors and simple shapes, he had a hard time perceiving complex forms, including faces, and was insensitive to depth cues. For example, like SB, MM perceived Neckers cubes as being completely flat. Again, his visual difficulties were thought to be of central rather than peripheral origin. Visual deficits were accounted by neuroimaging evidence showing extensive cortical reorganization following partial visual restoration. For example, MM demonstrated a massive reduction of activation to faces and objects in the fusiform and lingual gyri bilaterally (Fine et al., 2003). Seven years after the intervention, MM still had poor spatial resolution and limited visual abilities that prevented him from efficiently relying on his vision in his day-to-day activities (Levin et al., 2010; Saenz et al., 2008). In contrast to the marked difficulties encountered by SB and MM, motion perception abilities appeared to be relatively preserved. fMRI measures in MM documented robust and specific activations for visual motion stimuli in area MT+/V5. This was interpreted as a consequence that motion processing develops earlier and faster compared to form processing and might therefore have been more established and robust, allowing its preservation despite many years of visual deprivation (Fine et al., 2003; Saenz et al., 2008). It thus appears that specific visual functions are differently affected by visual deprivation and visual restoration. In accordance with this, studies of adults treated early in life for congenital bilateral cataracts after varying periods of visual deprivation have documented the existence of different developmental periods for specific aspects of vision (Bavelier and Neville, 2002; Lewis and Maurer, 2005). For instance, the loss of sight before the first 6 months of age leads to permanent deficits in sensitivity to global motion and holistic face processing whereas the loss of sight after 6 months of age preserves the global perception of motion even if the period of blindness is extended as it is the case for SB and MM (Fine et al., 2003; Gregory and Wallace, 1963) but still can dramatically impair face perception abilities.

Interestingly, the visual motion responses observed in MT+/V5 in MM coexisted with important crossmodal responses to auditory motion (Saenz et al., 2008) similar to the ones reported in the early blind brain (Bedny et al., 2010; Poirier et al., 2005). However, it was not ascertained if the presence of such crossmodal auditory motion responses competed with or improved visual motion perception following visual restoration. This question is of major importance because one of the challenges for MM is to use the strong nonvisual skills he developed as a proficient blind subject (sensory compensation in the remaining senses) in conjunction with his rudimentary vision in order to improve his visual abilities. In this sense, understanding how visual and nonvisual responses interact in sight-recovery patients is important for optimizing patients' use of their restored vision (Saenz et al., 2008). In the same vein, preserved visual skills are likely to be used as tools in order to favor visual improvement and learning in the visually impaired abilities. Ostrovky and colleagues (2006) reported the case of three congenitally blind subjects treated for bilateral cataract after years of blindness. As observed in SB and MM, these patients presented strong deficits in form perception. They perceived objects as distinct and separate patches of colors and had a hard time putting them together as a whole. However, performances in form and object recognition were greatly improved by the introduction of motion cues. Further, their ability to recognize static images of objects was higher for images of objects that typically move (e.g., a face or a bird as opposed to a flower or a telephone). Hence, it was suggested that motion information in an object might favor binding of the constituent parts together into a unique representation, allowing these patients to recognize such objects even when they were still. Despite the fact that the human brain appears to retain an impressive capacity for visual learning well into late childhood (Ostrovsky, Andalman and Sinha, 2006; Ostrovsky et al., 2006, 2009), an important point raised by these studies in sight-restored patients is that early intervention is often a good predictor of visual abilities in adults. In the particular case of congenital blindness, sight restoration in adults may be less spectacular than intuitively expected, probably because of the structural (deterioration of visual tracks) and functional (crossmodal plasticity) changes that are encountered by the deprived visual cortices of these individuals (Bavelier and Neville, 2002; Noppeney, 2007).

4.6.1 Neuroprostheses

In addition to classical surgical interventions that have restored vision in the blind, recent advances have led to the development of other invasive and sophisticated interventions, referred to as neuroprostheses. Visual neuroprostheses rely on the basic principle that stimulation of visual structures in the sighted brain produces the perception of patterned spots of light called phosphenes (Merabet et al., 2005; Zrenner, 2002). Such implants connect a digital camera to a signal processor that converts visual information into patterned electrical signals. Several approaches are currently under investigation and involve the stimulation of different structures along the visual pathway at the subretinal (Pardue et al., 2006; Zrenner et al., 1999), epiretinal (Humayun et al., 2003; Rizzo et al., 2003), optic nerve (Veraart et al., 1998, 2003) or cortical level (Schiller and Tehovnik, 2008; Schmidt et al., 1996; Tehovnik et al., 2005). Aside from the major issues of electrical safety and biocompatibility of the material (Veraart et al., 2004), knowledge about the selectivity and diffusivity of the stimulation is an essential problem in evaluating the behavioral effects of the stimulated area itself. As a result, researchers are currently trying to combine microstimulation of neural tissue with fMRI in order to provide the unique opportunity to visualize the networks underlying electrostimulation-induced perceptions (Logothetis et al., 2010). Visual prostheses have the limitation that they do not take advantage of the natural reorganization of the visual cortex of the blind since such invasive approaches stimulate the deprived sensory system directly. As such, it is generally assumed that a fully mature visual system and prior visual experience is a prerequisite in order for stimulation to efficiently produce the perception of phosphenes and in order for the patient to be able to interpret the induced visual percept in a meaningful way. For example, one study demonstrated that the perception of phosphenes elicited by the application of TMS over the occipital area is dramatically reduced in subjects with an early onset of visual deprivation, especially in those who lost vision early in life (Gothe et al., 2002). Indeed, the structural (deterioration of visual tracks) and functional (crossmodal plasticity) changes associated to early visual deprivation might hamper the reacquisition of the original visual function of a given structure via the prosthetic implant.

Hence, there are reasons to believe that neuroprostheses might be better suited for late-blind individuals since far less reported alterations (Jiang et al., 2009; Park et al., 2009) and less crossmodal recruitment of occipital regions by non-visual stimuli (Burton et al., 2003; Cohen et al., 1999; Voss et al., 2008) have been observed in subjects who developed late-onset blindness. Moreover, studies of sustained blindfolding in sighted subjects suggest that the crossmodal recruitment of occipital cortex associated to visual deprivation later in life may be fast to reverse following the reintroduction of vision (Merabet et al., 2008; Pascual-Leone et al., 2005). Late-blind individuals might thus be candidates of choice for visual prosthetic implantation, especially because blindness acquired later in life may favor less the development of the compensatory mechanisms observed in the early blind. Further, because of more limited enhancement of abilities in the remaining senses, the late blind may encounter greater difficulty in coping with their handicap (Wan et al., 2010).

4.6.2 Sensory substitution devices

On the other hand, non-invasive techniques of rehabilitation that take advantage of the preserved non-visual abilities in the blind might be expected to be more effective in early-blind individuals rather than in late-blind subjects. Indeed, crossmodal reorganization in blindness and associated superior behavioral performances in the remaining senses have served as a basis for the development of sensory substitution devices. The concept of sensory substitution refers to the use of one sensory modality to supply information normally gathered from another sense (Bach-y-Rita et al., 1969). The use of the longcane as an extension of the body (Serino et al., 2007), the development of fine tactile discrimination abilities to read Braille dots (Van Boven et al., 2000; Wong, Gnanakumaran and Goldreich, 2011), and the use of sounds reverberation to locate obstacles and discriminate object size (Dufour, Despres and Candas, 2005; Rice, 1967; Rice and Feinstein, 1965; Strelow and Brabyn, 1982, Thaler et al., 2011) are excellent examples of abilities that are mastered by blind individuals due to a combination of extensive training programs and neuroplastic mechanisms. For instance, Braille reading skills are the consequence of intensive practice and, as stated previously, are strongly related to occipital function in the early blind (Buchel, 1998; Burton et al., 2002; Cohen et al., 1997; Kupers et al., 2007; Sadato et al., 1996, 1998; Ptito et al., 2008).

Aside from these classical rehabilitative programs, researchers have also considered providing blind people with more sophisticated tools designed to facilitate the sensory-motor interactions with the environment in order to reduce the impact of visual deprivation. Bach-y-Rita was the first to design sensory substitution devices for the blind by using the preserved sense of touch to supply information usually gathered from vision (Bach-y-Rita et al., 1969). Since this seminal work, and partly due to subsequent technological improvements, several laboratories have developed and tested new sensory substitution prosthesis (Bach-y-Rita et al., 1998; Capelle et al., 1998; Cronly-Dillon et al., 1999; Kaczmarek et al., 1985; Meijer, 1992; Ptito et al., 2008). All these systems are designed to make use of the residual intact senses, audition and touch, to provide blind people with a sample of the visual world coded via another preserved modality through specific algorithms that are learned by practice (Collignon et al., 2009, 2011). These systems have proven their efficacy for the recognition of quite complex two-dimensional shapes (Arno et al., 1999, 2001), the localisation of objects (Proulx et al., 2008; Renier et al., 2010) or the navigation in a "virtual" environment (Segond et al., 2005). Further, the use of such devices was found to massively recruit the occipital cortex of blind individuals (Amedi et al., 2007; De Volder et al., 1999; Kupers et al., 2010; Merabet et al., 2009; Poirier et al., 2007; Ptito et al., 2008). For example, Amedi and colleagues (2007) reported activation of a sub-region of the lateral-occipital complex (LOtv) normally responsive to visual and tactile object-related processing when blind subjects extracted shape information from visual-to-auditory sensory substitution soundscapes. In our group, we investigated neuroplastic changes in early blind related to the use of a similar prosthesis, the PSVA (prosthesis for substitution of vision by audition) (Capelle et al., 1998). Early-blind participants engaged in a pattern recognition task using the PSVA were found to be more accurate and to recruit occipital cortex more strongly relative to sighted controls (Arno et al., 2001). Further, such occipital recruitment was demonstrated to be functionally relevant since TMS interfered with the use of the PSVA when applied over the right dorsal extrastriate cortex of blind participants, consistent with the spatial cognitive components associated to the use of the prosthesis (Collignon et al., 2007). By contrast, TMS targeting the same cortical area had no effect on performance in sighted subjects.

Hence, sensory substitution devices are interesting non-invasive techniques mainly because their working principles follow the natural tendency of the brain to reorganize itself in favor of the remaining sensory modalities. Unfortunately, these human-machine interfaces are still confined to the field of fundamental rather than applied research, because they have poor ergonomic quality. Firstly, the visual information gathered by the camera is generally too complex to be entirely translated in the substitutive modality without creating a "noisy" percept. Inevitably, such devices in every day life, as opposed to simple laboratory experiments, put excessive sensory and cognitive load on the individual. As a consequence, these devices occupy and tend to saturate a sensory channel (either audition or touch) on which blind individuals highly rely in their daily-life activities. For example, modern tactile devices have mainly used the tongue to transform the visual percept into tactile information. This body part has been preferred because its sensitivity, spatial acuity, and discrimination abilities are superior relative to other parts of the body (Bach-y-Rita et al., 1998). However, the use of the tongue implies aesthetic and hygienic problems, which certainly interferes with the willingness of the blind community to introduce the system as a standard aid. Finally, in order to become a real option for the blind in guiding their navigation, such systems should be complementary and thus provide new information to existing aids like the guide dog and the white cane.

In summary, more consideration is needed in the design of more ergonometric sensory substitution systems for visual rehabilitation purposes. Importantly however, sensory substitution greatly benefits from the crossmodal changes that occur in the brain of blind individuals. As such, they constitute a promising solution, especially for early-blind individuals for whom surgical intervention is not possible and who are thought to benefit from more extended plastic changes and associated superior non-visual abilities.

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