Chapter 18
Large-Scale Brain Plasticity Following Blindness and the Use of Sensory Substitution Devices

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18.1 Introduction

Living with a sensory impairment is challenging and those who have lost the use of one sensory modality need to find ways to deal with numerous problems encountered in daily life. When vision is lost, this may include navigating through space, finding objects, recognizing people or surroundings, reading or even communicating without much access to nonverbal signs provided by others such as eye gaze or facial expressions. Nevertheless, the blind manage to function efficiently in their environment, often so to a surprisingly high degree. The same is true for the deaf. How is this level of functioning achieved? What sort of cognitive restructuring is needed to allow the blind to, for instance, develop spatial representations using only auditory or tactile information, recognize and navigate through familiar environments, or build a representation of a novel space? How is such restructuring implemented in the brain? Finally, how does the nervous system deal with an initially large silent cortical surface: does this area simply remain silent or does it become integrated with the rest of the brain in an atypical, but nevertheless functional manner?

Answering these questions is not just of great theoretical interest but also has important implications for improving current and developing new rehabilitation approaches for blindness, deafness, and other clinical situations such as stroke. This includes "classical" approaches such as educational programs that teach blind children how to recognize and efficiently exploit tactile or auditory cues for spatial processing or initiatives aimed at providing wider and earlier access to the most efficient rehabilitation techniques. However, understanding the links between the brain's ability to remodel itself and behavior as well as the factors which influence

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this linkage is crucial for developing novel rehabilitation techniques aimed not just at compensating, but also restoring parts of the lost sensory functions. These primarily include neuroprostheses which attempt to restore visual function to the impaired visual system of the blind and sensory substitution devices (SSDs) which use a human–machine interface to provide visual information to the blind via a non-visual modality. Since these techniques depend crucially on the possibility of teaching the blind brain new complex perceptual skills involved in vision, they can be developed more efficiently if enough is known about the plasticity of our neural system as well as the neural foundations of information processing, especially sensory processing within and across individual modalities. Efficient use of these techniques is based on implicit assumptions that we are able to exploit and channel the brain's ability to reorganize itself and to link or translate information from individual senses to multisensory and back to the unimodal (visual) percepts with the goal of restoring some features of the lost modality.

However, it is difficult to control something that one does not adequately understand. This may explain why restoration of truly functional sensory modalities using neuroprostheses is still not possible and why, despite significant recent progress, SSDs have yet to reach their full potential. Solving these problems depends not only on increasing our knowledge of the general principles of brain plasticity, but also acknowledging the impact of individual differences on sensory rehabilitation. Although many factors might be important in this respect, the onset of sensory loss is the most prominent source of individual variance. Thus, although surgically restoring sight at an early age might result in almost full sensory recovery, attempting the same in an adult who has never had visual experience poses enormous challenges because vision is, in many ways, a learned skill. Giving the occipital cortex access to visual signals will therefore not automatically guarantee the emergence of normal vision and, if done later in life, may even hamper a reorganized functional system by interfering with tactile, auditory, language, or memory processing that has been rerouted to this cortical surface.

Thus, sight restoration and sensory substitution offer a unique and highly successful key to understanding brain plasticity, perception, sensory integration, and the binding problem – the link between brain activity and conscious perception, as well as other fundamental issues in neuroscience, psychology, philosophy, and other disciplines. Clearly, developing new approaches and improving existing rehabilitation techniques aimed at compensating for sensory loss depends to a great extent on how well current knowledge about normal sensory processing and the brain's potential for change can be integrated and applied. This chapter will attempt to present and integrate some of this knowledge, mainly concentrating on blindness and rehabilitation techniques available for the blind. Before introducing these, we will explore the minds and brains of those who need such devices in more detail, depict their cognitive adjustments to sensory impairments, and describe different types of neuroplastic changes which support such cognitive restructuring. We will then look at the importance of individual, especially developmental, differences in experimental and practical rehabilitation settings. Following this, we will review the currently available rehabilitation techniques, primarily sensory substitution devices, and, to

a somewhat lesser degree, clinical ophthalmologic and neuroprosthetic approaches. These techniques are designed to exploit one of the brain's fundamental intrinsic properties – its plasticity. This property manifests itself not only following sensory loss but in all normal or pathological contexts. The brain constantly changes and yet, despite the fact that it can (especially in some circumstances) undergo extensive modifications in basic morphology, connectivity, physiology, or neurochemistry, manages to preserve stability and continuity. Some of these general features of neuroplasticity will be discussed in detail as they can help understand specific changes that occur in cases of sensory impairment.

18.2 The Plastic Brain

Plasticity in the brain, i.e., neuroplasticity, reflects the brain's ability to change its structure and function throughout the course of a lifetime. This intrinsic property of the nervous system is visible across different levels of brain functioning which include genetic, neuronal, and synaptic, as well as the level of brain networks and the nervous system as a whole. Consequently, plasticity is also manifested in the dynamics of emergent cognitive processes and overt behavior. Each one of these levels can incorporate different types of changes, such as structural changes in axon terminals, dendritic arborization, and spine density in neurons, as well as changes in glial cells in case of synaptic plasticity (Kolb, 1995). Although the importance of these types of plastic changes has been recognized for many years (Malenka and Bear, 2004), Merabet et al. (2008) have recently argued that the capacity for plastic modulation at the level of single neurons is likely to be somewhat limited due to the high complexity of individual neurons and other constrains in higher vertebrates. As a result, this level must be complemented by higher potential for change at the neural network level. This is thought to be mediated through an architecture of distributed neural networks composed of nodes that perform computations somewhat independently of the properties of their inputs, thus enabling their integration into different networks. In this way, neural networks can remain highly dynamic and adaptable to changing environmental demands without endangering the stability of individual nodes. Some of these nodes or brain regions may be more or less susceptible to change. For example, although plasticity has mainly been investigated in regions such as the hippocampus, which is even characterized by a certain degree of adult neurogenesis (Eriksson et al., 1998), substantial plastic changes can also occur in neocortical regions (Kolb, 1995). In particular, a much higher degree of plasticity has been reported in associative unimodal or multisensory regions than in the primary sensory cortices, which may partly be due to high sensitivity of higher level areas to crossmodal inputs (Fine, 2008). Although useful, this separation into different levels of plastic changes is somewhat artificial because individual levels of brain organization are not mutually independent, but directly or indirectly influenced by all other levels (Shaw and McEachern, 2000). In addition, other non-developmental factors such as the previous history of synapse's activity may also influence this

potential for future plasticity (Abraham and Bear, 1996). Finally, it needs to be emphasized that the potential for change is itself not static, as it varies dramatically throughout the course of life. This potential is at its highest in early childhood, whereas it is typically assumed that large-scale reorganization in adulthood primarily occurs in response to pathological states. However, the adult brain also changes in non-pathological states, and such use-induced plasticity may differ from lesion-induced change in terms of its extent and the underlying mechanisms (Dinse and Merzenich, 2000). Finally, although constantly changing, the brain needs to remain stable to a certain degree. Therefore, neuronal plasticity must be balanced by neuronal stability through homeostatic control within and between different levels of neural functioning (Shaw and McEachern, 2000).

18.2.1 Plasticity Across the Lifespan

It is generally believed that the nervous system is the most plastic during its development, both in the case of normal development and following brain injury. Although the brain is thought to retain the ability to change throughout life, especially in pathological cases, this assumption is mostly corroborated by experimental findings. The developing brain is a highly dynamic system which undergoes several distinct phases from cell formation to the rapid growth and subsequent elimination of unused synapses before finally entering into a more stable phase following puberty (Chechik et al., 1998). The functional assignment of individual brain regions that occurs during this time is crucially dependent on synaptic development which undergoes drastic changes that often take place in spurts. In the visual cortex, during the first year after birth, the number of synapses grows tremendously and is subsequently scaled down to the adult level around the age of 11 through extensive decreases in synaptic and spine density, dendritic length, or even the number of neurons (Kolb, 1995). This process is primarily determined by experience and neural activity: synapses which are used are strengthened while others are not either reinforced or actively eliminated. Synaptic development is highly dependent on competition between incoming inputs, the lack of which can result in a decreased level of synaptic revision and persistence of redundant connections in adulthood (De Volder et al., 1997). This process of synaptic pruning represents fairly continuous and extended tuning of neural circuits and can be contrasted with other types of changes which occur at very short timescales. During such periods of intensified development (i.e., critical or, more broadly, sensitive periods; Knudsen, 2004; Michel and Tyler, 2005), the system is the most sensitive to abnormal environmental inputs or injuries (Wiesel and Hubel, 1963). Thus, injuries affecting different stages of development, even when they occur at a roughly similar age, may trigger distinct patterns of compensatory neuroplastic changes and lead to different levels of recovery. Specifically, early studies of recovery after visual loss (Wiesel and Hubel, 1963, 1965) suggested that visual deprivation of even short duration, but occurring at an early developmental stage when vision

is particularly sensitive to receiving natural input, may irreversibly damage the ability to normally perceive visual input at older ages. Conversely, recent sparse evidence of visual recovery after early-onset blindness (Fine et al., 2003; Gregory and Wallace, 1963), which will be discussed in more length in the next sections addressing visual restoration, demonstrates that this may not necessarily apply in all cases.

The potential for neuroplasticity after puberty is considered to be either much lower than in childhood, or possible only in cases of pathological states and neural overstimulation (Shaw and McEachern, 2000). However, recovery following different types of pathological states occurring in adulthood (Brown, 2006; Chen et al., 2002), changes in neural count and compensatory increase in the number of synapses in aging (Kolb, 1995), and the profound changes revealed by functional neuroimaging following short periods of blindfolding (Amedi et al., 2006; Pascual-Leone et al., 2005; Pitskel et al., 2007) suggest otherwise. In reconciling these seemingly contradictory conclusions, it is useful to take into account the multi-faceted nature of plasticity which includes different forms of changes occurring at different timescales and at different levels of neural functioning. For example, synaptic changes occurring in aging develop over an extended period of time and in synergy with altered experiences and needs characteristic for the later periods in life. The robust, short-term plasticity witnessed in blindfolding may arise from the recruitment of already existing, but commonly unused, inhibited, or masked pathways which become available once the source or reason for such masking (e.g., availability of visual input in those who have been blindfolded) is removed. Therefore, some forms of adult plasticity do not reflect "plasticity de novo" which is characterized by the creation of new connectivity patterns (Burton, 2003). In contrast, in pathological states, injuries, or late sensory loss, both of these types of changes can co-occur and mutually interact. Rapid changes reflecting the unmasking of existing connections occurring in the first phase promote and enable subsequent slow, but more permanent structural changes (Amedi et al., 2005; Pascual-Leone et al., 2005). This suggests that potentially similar functional outcomes may be mediated by different neural mechanisms whose availability depends on the developmental stage within which they occur.

## 18.3 Plastic Changes Following Sensory Loss

Regardless of when it occurs, sensory loss drastically affects both cognitive functioning and the anatomy and physiology of the nervous system enabling those functions. Studying changes triggered by sensory impairment provides a unique opportunity for exploring not only the plasticity relevant for pathological states, but also the fundamental principles guiding the formation and functional organization of any nervous system. This is especially true for congenital blindness, deafness, and similar conditions which represent the most documented cases of plasticity, compensatory, and otherwise. Given their early-onset and the fact that they occur in an

undeveloped system, these conditions allow large-scale changes that promote full reorganization, which may result in a functional network remarkably different from the one seen in healthy individuals or individuals that sustain brain or peripheral injuries later in life. For example, blindness or deafness resulting from peripheral damage (i.e., dysfunctional retina/cochlea or the sensory tracts) does not injure the brain itself, but withholds parts of the brain from their natural input. However, despite the lack of visual and auditory input, the visual and auditory cortices of the blind and deaf do not simply degenerate but, to some extent, become integrated into other brain networks. Such functional reintegration is enabled through the changed structure, connectivity, and physiology of these areas in comparison to those typically encountered in the majority of the population. A similar reintegration, but to a different extent and partially mediated through different neurophysiological mechanisms, occurs in the case of late sensory loss. Before discussing the differences between these populations in more detail, we present some general findings which are relevant for all sensory impaired individuals. These include recent electrophysiological and neuroimaging studies investigating cognitive and neural processing following loss of sensory (primarily visual) function and the neurophysiological mechanisms underlying these changes.

Just like the sighted, in order to function independently and act efficiently in the world, the blind need to acquire information about their environment and represent it in a way that can constantly be updated and used in different reference frames and for different purposes. Unlike most others, to achieve these goals they rely on fewer sensory modalities and are therefore not privileged to the same qualitative and quantitative richness of information available to the sighted. These individuals need to somehow "compensate for lack of vision," a modality which commonly offers a wide range of information needed for everyday life and draws attention to relevant external events (Millar, 1981). Not having access to this information source, the blind need to identify useable cues from other modalities and/or develop alternative cognitive strategies, allowing them to build a representation of themselves and their environment that can be effectively exploited for (goal-directed) action. This process may, in turn, result in profound changes in higher-order cognitive or sensory functions outside the affected modality. For example, it has been shown that the blind, compared to the sighted, possess superior memory (D'Angiulli and Waraich, 2002; Hull and Mason, 1995; Pozar, 1982; Pring, 1988; Raz et al., 2007; Röder et al., 2001; Smits and Mommers, 1976; Tillman and Bashaw, 1968), as well as tactile, and auditory perceptual abilities: they are, for instance, able to better discriminate between small tactile dots or auditory spatial locations than the sighted and even better identify odors (Collignon et al., 2006; Doucet et al., 2005; Goldreich and Kanics, 2003, 2006; Grant et al., 2000; Hugdahl et al., 2004; Murphy and Cain, 1986; Röder et al., 1999; Smith et al., 2005; Wakefield et al., 2004). This superiority is not always identified (Lewald, 2002; Zwiers et al., 2001), suggesting that optimal development of some aspects of sensory processing in the unaffected modalities may depend on (or at least benefit from) concurrent visual input. Nevertheless, the majority of findings still indicate a compensation for the missing modality through hyper-development of other senses and higher cognitive

functions. Once achieved, this advantage could, as indicated by inferior performance of the partially blind (Lessard et al., 1998), even be compromised by the presence of visual information. Comparable to results in the blind, deaf individuals also show improved visual abilities on certain tasks (Bavelier et al., 2006). This clearly runs counter the assumption that sensory loss necessarily leads to general maladjustment and dysfunction in other cognitive domains which cannot develop without the supporting vision. Therefore, this, so-called general-loss hypothesis, can be abandoned to a large extent in favor of the alternative, compensatory view according to which sensory loss leads to the superior development of the remaining senses (Pascual-Leone et al., 2005).

The described changes in cognitive functioning in the blind are necessarily paralleled by changes in many features of neural processing reflecting both the altered computations underlying their unique cognitive functioning and the lack of visual input promoting an atypical organization of the occipital cortex. In the last decades, studies investigating neural processing of blind individuals, as well as more invasive animal experiments, have shown that sensory loss triggers robust modifications of functioning across entire brain networks. Results from electrophysiological studies indicate shorter latencies of event-related potentials (ERP) in auditory and somatosensory tasks in the blind in contrast to the sighted, suggesting more efficient processing in this population (Niemeyer and Starlinger, 1981; Röder et al., 2000). In addition, identified differences in topographies of ERP components in the sighted and the blind suggest a reorganization in the neural implementation of non-visual functions, so as to engage the occipital cortex of the blind (Kujala et al., 1992; Leclerc et al., 2000; Rösler et al., 1993; Uhl et al., 1991). Functional neuroimaging methods characterized by higher spatial resolution corroborate these findings by showing that the occipital cortex is not just neurally active (De Volder et al., 1997) but also functionally engaged in perception in other modalities, namely audition (Gougoux et al., 2005; Kujala et al., 2005) and tactile Braille reading (Büchel et al., 1998; Burton et al., 2002; Gizewski et al., 2003; Sadato et al., 1998, 1996). Even more dramatic are the changes in higher cognitive, verbal, and language functions (Amedi et al., 2004; Burton et al., 2003; Burton et al., 2002; Ofan and Zohary, 2007; Röder et al., 2002) and memory processing (Amedi et al., 2003; Raz et al., 2005). Studies in which processing within the occipital cortex was transiently disrupted using transcranial magnetic stimulation (TMS) confirm the necessity of the targeted occipital engagement in auditory (Collignon et al., 2006) and tactile processing including Braille reading (Cohen et al., 1997; Merabet et al., 2004) as well as linguistic functions (Amedi et al., 2004), suggesting that such processing reflects functionally relevant contributions to these tasks (see Fig. 18.1). Similarly, it has been shown that the auditory cortex of the congenitally deaf is activated by visual stimuli (Finney et al., 2001), particularly varieties of visual movement (Campbell and MacSweeney, 2004). It is important to realize that the involvement of unimodal brain regions in crossmodal perception is not only limited to individuals with sensory impairments but can, under certain circumstances, also be identified in the majority of the population (Amedi et al., 2006; Merabet et al., 2004; Zangaladze et al., 1999). This involvement is much more pronounced in the blind and deaf
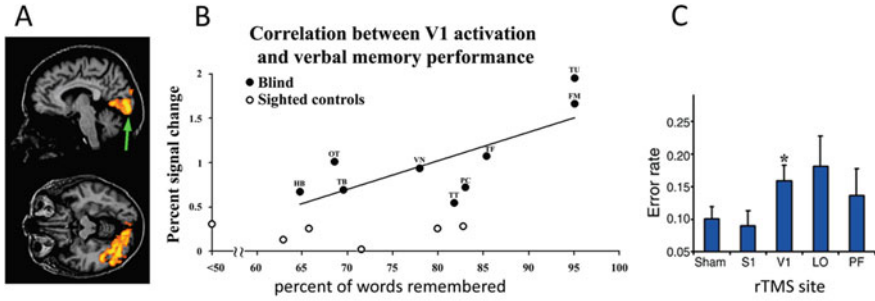
Fig. 18.1 An extreme example of brain plasticity in the primary visual cortex of the blind for verbal memory and language. (**a**) Verbal memory fMRI activation in the early "visual" cortex of the congenitally blind. The results of the congenitally blind group (only) showed robust activation in the visual cortex during a verbal memory task of abstract word retrieval which involved no sensory stimulation. The left lateralized activity was extended from V1 anteriorly to higher order "visual" areas. (**b**) The activation in V1 was correlated with the subjects' verbal memory abilities (*middle panel*). Subjects were tested on the percent of words they remembered 6 months after the scan (or online inside the scanner in an additional study). In general, blind subjects remembered more words and showed greater V1 activation than the sighted controls. Only blind subjects also showed a significant correlation of V1 activity and performance (A and B are modified from Amedi et al., 2003). (**c**) Verb-generation error rates in a blind group show that rTMS over left V1 increased error rates relative to sham and right S1 stimulation, signifying that V1 is functionally relevant to verbal memory task success; error bars, s.e.m. *$P<0.05$ (modified from Amedi et al., 2004)

because sensory areas deprived from their customary sensory input become functionally integrated into other circuits which leads to profound changes within the affected modality and the system as a whole. These include crossmodal, intramodal, multisensory (multimodal), and supramodal changes, namely those pertaining to the involvement of typically visual areas in processing tactile and auditory information in the blind (or typically auditory areas in processing visual information in the deaf), plastic changes occurring within the cortices of unaffected modalities, changes in multisensory regions and global, whole-brain changes involving more than unimodal and multimodal sensory networks, respectively. Although somewhat autonomous, these different types of changes are in reality strongly interdependent and cannot be separated on the level of either cognitive or neural processing.

Multisensory plasticity refers to the reorganization of multisensory areas following sensory loss which arises from the impairment of one modality and compensatory hyper-development of the remaining ones. This altered structure of sensory inputs leads to changes in multisensory areas, the development of which is shaped by the convergence of incoming inputs from unimodal systems (Wallace, 2004). For example, studies investigating the multisensory anterior ectosylvian (AES) cortex in congenitally blind cats indicate an expansion of auditory and somatosensory fields into the area usually housing visual neurons (Rauschecker and Korte, 1993)

as well as sharpened spatial filtering characteristics (Korte and Rauschecker, 1993) following blindness. These changes underlie the improved spatial abilities of these animals and may also be crucially important for the development of crossmodal plasticity.

Intramodal plasticity refers to changes occurring within one sensory modality as a consequence of altered, either increased or decreased, use of the respective sensory modality. For example, studies investigating the neural foundations of this phenomenon indicate a high degree of reorganization of sensory maps in different modalities following local peripheral damage, extensive training, or perceptual learning (Buonomano and Johnson, 2009; Kaas, 2000; Recanzone et al., 1992). This reorganization includes a coordinated shrinkage of maps representing the unused, and expansion of those representing the modality/limb experiencing increased use (Rauschecker, 2008), and is determined by the amount of stimulation and structure of the input pattern within which competition between the inputs plays an important role (Buonomano and Johnson, 2009). Another example of intramodal changes may include superior performance of the blind in auditory or tactile tasks. However, these changes can also be a reflection of *crossmodal plasticity* which refers to the reassignment of a particular sensory function to another sensory modality, for instance processing of auditory information to the visual cortex. Numerous invasive studies in animals have shown the vast potential for such reorganization, reflecting the fact that most aspects of structure and function of a given brain area are determined by its inputs, not topographic location. For example, it has been shown that typical auditory areas, after being exposed to visual input through thalamic fibers normally going to primary visual areas, can develop orientation-sensitive cells with the pattern of connectivity resembling the one typically found in the normally developed visual cortex (Sharma et al., 2000) and fulfill the visual functionality of the rewired projections (von Melchner et al., 2000). Similarly, tissue transplanted from the visual cortex into the somatosensory cortex acquires functional properties of its "host" and does not hold on to its genetic predisposition (Schlaggar and O'Leary, 1991). Thus, it can be hypothesized that the crossmodal plasticity observed in the blind is most probably subserved by altered connectivity patterns. It has generally been suggested that all levels of connectivity, including connections within local circuits, long-range cortico-cortical and subcortical connections, are altered in the blind (Bavelier and Neville, 2002). Corroborating this, recent evidence indicates that the visual tracts connecting the visual cortex with the eyes are degenerated in the blind (Noppeney et al., 2005; Pan et al., 2007; Shimony et al., 2006). A similar example of drastic reorganization of afferent nerves going from the eyes to the thalamus and cortex that resulted in changed retinotopic maps in the unaffected hemisphere (such as to represent the ipsilateral in addition to normally represented contralateral visual field), thus enabling almost normal vision in both hemifields, has also recently been reported in a young girl born with only one cerebral hemisphere (Muckli et al., 2009). Furthermore, studies in mammals show that congenital blindness (caused by early enucleation) causes a rewiring of tactile and auditory inputs to the visual cortex of mammals (Chabot et al., 2007; Izraeli et al., 2002; Karlen et al., 2006; Laemle et al., 2006; Piche et al., 2007) which

facilitate or enable the involvement of the visual cortex in tactile and auditory tasks. In addition, although it was previously assumed that there are no direct connections between sensory modalities, recent anatomical studies in primates indicate the existence of projections from the auditory to the visual cortex and multisensory feedback connections to primary visual areas (Falchier et al., 2002; Rockland and Ojima, 2003). According to the reverse hierarchy model (Amedi et al., 2003; Büchel, 2003), feedback connectivity may play a crucial role in crossmodal (and supramodal) plasticity. Specifically, connections stemming from temporal, parietal, and frontal lobes may, in the absence of visual input, be responsible for providing non-visual input to the occipital lobe, enabling its engagement in non-visual processing. This is particularly true for areas which are involved in multisensory processing even in the sighted, such as regions within the lateral occipital complex that are naturally active both during tactile and visual object recognition (Amedi et al., 2002; Amedi et al., 2001). Such areas retain some of their original sensory input after the loss of one modality which allows them to preserve their original functions (i.e., tactile shape recognition, including Braille reading). Confirming this notion, it has been shown that the area involved in (visual and auditory) motion processing in the sighted is involved in auditory (Poirieret al., 2006) as well as tactile (Ricciardi et al., 2007) motion processing in the blind. Similar conclusions can be drawn from findings showing the engagement of the ventral visual pathway typically involved in processing information related to the identification of objects and faces (Ungerleider and Mishkin, 1982) in auditorily mediated object recognition, but only if detailed shape information is provided and efficiently extracted (Amedi et al., 2007; Poirieret al., 2006). All of these results are congruent with the more general notion that crossmodal plasticity occurs in situations where the information originally processed within a certain area is similar to the input which is being rerouted into it (Grafman, 2000). This implies that each cortical area operates in a metamodal fashion (Pascual-Leone and Hamilton, 2001) and is specialized in a particular type of computation rather than tied to a specific input modality. However, this type of broad generalization is subject to caution because it is still not clear how such metamodal computations would develop, especially in the case of significantly altered inputs in development.

Supramodal plasticity refers to changes which encompass areas and brain functions that are typically considered non-sensory. Evidence for such plasticity has been revealed in studies showing the involvement of the occipital cortex in memory or language processing in the blind (Amedi et al., 2004; Amedi et al., 2003; Burton et al., 2003; Burton et al., 2002; Ofan and Zohary, 2007; Raz et al., 2005; Röder et al., 2000, 2002). This type of plasticity is comparable to crossmodal plasticity and is enabled by altered connectivity patterns between the visual cortex and other supramodal brain regions. For example, the blind show decreased functional connectivity of the occipital cortex and various other cortical sites, including the supplementary motor area (SMA), pre- and postcentral gyri, superior parietal lobule, the left superior and middle temporal gyri (Yu et al., 2008), which is paralleled with increased functional connectivity with frontal language regions (Liu et al., 2007). These changes in connectivity could account for the altered pattern of

inputs reaching the occipital cortex, which may in the end determine morphological and physiological features of this area and enable its functional reassignment to non-sensory tasks.

18.4 Developmental and Adult Plasticity Following Blindness

Age of sensory loss is an important factor which strongly influences the type and extent of subsequent cognitive and neural changes as well as the later potential for rehabilitation. Outcomes of late and early injuries are typically not comparable because the potential for neuroplastic reorganization differs qualitatively and quantitatively in the developing and the adult brain. In addition, the early experience of vision in individuals who become blind later in life significantly shapes their development and possibly limits potential for reorganization of both cognitive and neural functioning following sensory loss. Once they lose their visual function, the late blinded need to relearn and reorganize information processing in order to compensate for the lack of input. However, although visual information is no longer available to them, these individuals can still rely on some visual strategies, e.g., visual imagery (Büchel et al., 1998) which may then be mediated by the visual cortex. The degree to which these individuals use visual strategies and the nature of cortical reorganization following sensory loss is primarily determined by the amount of their prior visual experience, the developmental stage at which sight loss occurred and subsequent experiences. In contrast, in the congenitally blind it is almost impossible to talk about the reorganization of the "visual cortex" because their occipital brain regions have never had experience with visual information and could therefore become integrated into other brain networks in a more flexible way. This flexibility is, of course, limited by the functional needs of the whole system, the idiosyncratic nature and connectivity of the occipital cortex, its potential for coordination with other brain regions as well as the general potential for plasticity in the brain. However, although the mechanisms underlying such integration are still unknown, they are surely less fixed in the congenitally blind than in individuals whose cognition and brain have been shaped by the experience of vision.

Confirmation of the importance of the age at sensory loss for future cognitive and brain reorganization comes from studies comparing performance on non-visual tasks across different populations of the blind. Some of these have suggested that processing advantages and large-scale cortical reorganization are often limited to the congenitally and early blind, with the performance of late blinded resembling more that of the sighted (Fine, 2008). Similarly, Cohen et al. (1999) suggested that the critical period of susceptibility for significant crossmodal plasticity ends at puberty. However, other studies have demonstrated significant reorganization in the occipital cortex of the late blind (Büchel et al., 1998; Burton et al., 2002; Voss et al., 2004). Similarly, it has been shown that cortical maps can be modified to a high degree (Kaas, 1991) even in adulthood. Although these findings suggest that

significant potential for plastic changes following sensory loss exists throughout the lifespan, this does not imply that these are also identical in their extent or the underlying neurophysiological mechanisms. On the contrary, they probably reflect the use of different cognitive strategies (Büchel et al., 1998) or changes in different levels/stages of neural processing (Fieger et al., 2006). For example, the brains of different subpopulations of the blind are probably differentially susceptible not just to intramodal, but also to crossmodal and multisensory plasticity. Those who had experience with vision were able to develop fully functioning multisensory systems (Wallace, 2004) which can have a significant role in shaping the cortices of the later impaired modality through feedback connections. In contrast, congenital lack of one sensory system alters the computations underlying multisensory integration and the development of multisensory brain regions, implying that there may be substantial differences across congenitally, early and late blinded individuals. In addition, different functional systems may be differently impaired by sensory loss occurring during certain phases of development. For example, Neville and Bevelier (2000) suggested that systems dedicated to dynamically shifting relations between locations, objects, and events, e.g., the dorsal visual pathway or regions subserving grammatical processing, develop earlier and are differently sensitive to developmental deficits in comparison to, e.g., the areas within the ventral visual stream which are still being modified during early adolescence (Golarai et al., 2007).

Although the early blind may in adulthood show better performance on nonvisual tasks, the development of such superior abilities is gradual and often challenging. For example, it has been shown that blind children have difficulties with some tasks, especially those requiring reference to external cues and directions, as they rely mostly on self-reference and movement sequences (Millar, 1981). Recognition of potentially useful information from other modalities can sometimes be more easily accomplished if concurrent visual input is available during learning. In this case, the existence of redundant or overlapping information stemming from more than one modality can guide attention, enhance learning of amodal stimulus features (Lickliter and Bahrick, 2004), and thus facilitate the recognition of helpful auditory or somatosensory features. However, even without the visual cues, one may still learn to recognize these features (Collignon et al., 2009) using different information, for example, those derived from self-motion. If this learning is successful, spatial representations which are generated on the basis of haptic and auditory input in the blind can be considered as equivalent to those of the sighted which are based on visual input (Röder and Rösler, 1998).

In conclusion, although sensory loss triggers plastic changes in all individuals, the age at which it occurs influences the type, extent, and mechanisms supporting these changes as well as the functional outcomes they enable. However, even equivalent functional outcomes do not necessarily imply that they are supported by the same underlying mechanisms. For example, profound changes identified in recently blinded or even sighted, e.g., the engagement of the posterior occipital lobe in tactile discrimination after being blindfolded for only a week (Merabet et al., 2008), may result from "unmasking" of existing connections between the visual and other cortices, which are dormant (inhibited) in normal conditions. Although such

unmasking may then promote more stable changes including alterations in connectivity patterns, this might require extended periods of sensory deprivation or even the onset of blindness to be set at the critical or sensitive period in early childhood. This again indicates how different populations of the blind cannot be considered or treated as equivalent. Consequently, the variability in developmental and adult plasticity following blindness necessarily needs to be taken into account when studying the blind as it may also have important consequences for the rehabilitation of these individuals.

18.5 Rehabilitation in the Case of Blindness and Severe Visual Impairment

Sensory loss and blindness in particular decrease the quality of life and impose severe challenges for efficient functioning on millions of individuals. Blindness hinders independent navigation in space in familiar and especially unfamiliar places, reading, and even recognizing people and communicating with them efficiently, using nonverbal communication via hand gesturing or facial expressions such as gaze direction or smiling. An anecdotal indication for this are discussions in forums for the blind, commenting how many years of life would they trade in exchange for regaining vision (though it is important to note that some blind answer that they are happy as they are and do not wish to bother themselves with such questions). Numerous approaches and potential solutions aimed at overcoming these difficulties have been put forward (with various levels of success), offering hope and help to those suffering from sensory (both visual and auditory) impairment. In the blind, these include reading and mobility aids, more advanced sensory substitution devices (SSDs), as well as invasive sensory restoration and neuroprosthetic approaches. In this part of the chapter we present some of these techniques. The main focus is on sensory substitution devices which are gaining increasing popularity thanks to their non-invasiveness, low cost, and high potential for providing systematic rehabilitation solutions for any type of blindness. In addition, we will briefly discuss the potential for medically enabled sensory restoration which, although holding great potential, still needs to overcome many technical and other challenges before it can be truly useful for most of the blind.

18.5.1 Sensory Substitution Devices

Sensory substitution refers to the transformation of the characteristics of one sensory modality into the stimuli of another modality. For example, it is possible to replace vision with touch or audition, audition or vestibular senses with touch. In the case of blindness, SSDs represent a non-invasive rehabilitation approach within which visual information is captured by an external device such as a video camera and communicated to the blind via a human–machine interface in the form of

auditory or tactile input. Pioneering work which paved the way to modern SSD was done by Louis Braille (1809–1852) who developed Braille writing, substituting visually read letters by a raised dot code. However, Braille can only work for materials transformed offline from printed visual letters to Braille dots and cannot be used for online reading of regular letters. Recently other reading substitutions have been developed for online reading, e.g., Optacon (print-to-tactual-image device devised for reading embossed letters (Goldish and Taylor, 1974) or various versions of dedicated text-to-speech engines (from the Kurzweil reading machine (Kleiner and Kurzweil, 1977) to current speech software). In addition to these reading aids, a great deal of effort has been invested in developing devices aimed at improving the mobility of the blind. The long cane used to mechanically probe for obstacles represents the simplest, most commonly used device. In recent years its more advanced counterparts, e.g., electronic travel aids designed to be used along with the long cane which extend the distance for environmental preview and thus increase the speed and efficiency of travel provided by the cane, have become available. Such devices, such as the Sonic Pathfinder (Heyes, 1984) or Sonicguide (Kay and Kay, 1983), typically scan the environment acoustically (ultrasonically) or optically (laser light) and transmit spatial information regarding obstacles and objects in the surroundings via vibrotactile or auditory signals.

In contrast to these devices which are typically designed for a limited purpose and successful in substituting for only certain functional aspects of vision, more sophisticated techniques that replace vision through tactile or auditory information have been developed over the last few decades (see Fig. 18.2). The first targeted modality for substituting vision was touch, due to the simplicity and ease of transforming visual into tactile signals which are both characterized by 2-D spatial representations. Pioneering work in this field was done in the 1970s by Paul Bach-y-Rita who devised a tactile display which mapped images from a video camera to a vibrotactile device worn on the subject's back. This device (Bach-y-Rita, 2004; Bach-y-Rita and Kercel, 2003; Bach-Y-Rita et al., 1969), dubbed the tactile vision substitution system (TVSS), provided tactile transformation of black-and-white images at a resolution of 20×20 pixels, and enabled the blind to perform sufficiently well in some visual tasks. However, it was extremely large and non-mobile which motivated the development of smaller mobile tactile devices placed on the tongue and forehead (for a review, see Bach-y-Rita, 2004) that are characterized by better spatial somatosensory resolution. One of these, the Tongue display unit (TDU; Bach-y-Rita et al., 1998), an electrotactile device comprised of a 12×12 matrix of stimulators (measuring approximately 3 cm^2) placed on the subject's tongue, provides blind individuals an initial "visual" acuity (tested by the Snellen E chart) comparable to 20/860, which significantly improves following training. Other studies investigating this device suggest that at least a subgroup of early-onset blind may particularly benefit from its use (Chebat et al., 2007).

Audition emerged as the second candidate to substitute for vision. The development of auditory-based devices was triggered by certain limitations of tactile SSDs, namely their price and the fact that they are inherently limited by the spatial resolution of touch. The first auditory SSD device was The vOICe system (Meijer, 1992),

Fig. 18.2 The general concept of sensory substitution (SSD) and a typical visual-to-auditory and visual-to-tactile setup. SSDs typically include a visual capturing device (for example camera glasses), a computational device transforming the visual input into either a tactile or an auditory display using a simple known transformation algorithm, and an output device, transmitting this information to the user. The right side illustrates an example of an auditory SSD (such as The vOICe; Meijer, 1992) transmitting the sensory-transformed information using headphones, and on the left side is an example of a tactile device which may transmit the tactile information via an electrode array targeting the tongue (such as the TDU, Bach-y-Rita et al., 1998) or another skin surface, in this case presented on the neck (copyright of image, by Amir Amedi)

which currently uses a default resolution of 176×64 sampling points. This device is mobile and inexpensive, and it consists of a video camera which provides the visual input, a small computer running the conversion program, and stereo headphones that provide the resulting sound patterns to the user. Given the fact that 87% of the world's visually impaired live in developing countries (WHO, 2009, fact sheet 282), the importance of providing not just high-resolution, but also cheap and accessible solutions for these individuals cannot be underestimated. Visual-to-auditory SSDs fulfill all of these criteria to some extent. On the other hand, these devices possess great challenges both to developers and to the brains of blind individuals trying to use them because the conversion algorithms of these devices are much less intuitive when compared to visual-to-tactile SSDs. For example, in The vOICe, the visual-to-auditory SSD (see Fig. 18.3), the conversion program transforms the visual into auditory information ("soundscapes") based on three simple rules: the vertical axis (i.e., elevation of the object) is represented by frequency, horizontal axis by time and stereo panning, while brightness of the image is encoded by loudness. Although these conversion rules appear relatively simple, it is not trivial to understand even simple shapes without explicit and quite extensive training. Similar but not identical
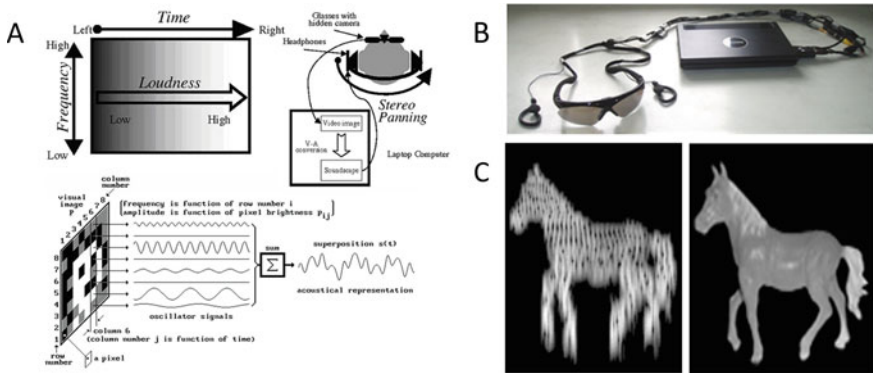
Fig. 18.3 An example of a visual-to-auditory SSD (The vOICe algorithm). (**a**) Schematic summary of the algorithm employed for the visuo-auditory conversion and the components of the system (adapted from Meijer, 1992). The functional basis of the visuo-auditory transformation employed lies in spectrographic sound synthesis from any input image, which is then further perceptually enhanced through stereo panning and other techniques. Time and stereo panning constitute the horizontal axis in the sound representation of an image, tone frequency makes up the vertical axis, and loudness corresponds to pixel brightness. Visual information in the sound representations of complicated gray-scale images is preserved up to a resolution of about 60×60 pixels for a 1 s sound scan and a 5 kHz audio bandwidth. Further technical details can be obtained at http://www.seeingwithsound.com/ where it is also possible to demo the algorithm and get a sense of the generated soundscapes (adapted from Amedi et al., 2007; original algorithm presented in Meijer, 1992). (**b**) An applied setup of The vOICe SSD includes camera glasses, a netbook, and earphones (image courtesy of Peter Meijer). (**c**) Example spectrogram of a one-second sound generated by The vOICe. On the right is the original picture transformed by The vOICe, on the left is the spectrogram of the sound generated from the picture (modified and adapted from Amedi et al., 2007, copyright of Peter Meijer, with permission)

transformations are implemented in two more recently developed auditory SSDs, the Prosthesis Substituting Vision with Audition (PSVA; Capelle et al., 1998), and SmartSight (Cronly-Dillon et al., 1999, 2000). PSVA uses different tones to provide horizontal location directly, whereas SmartSight presents the vertical location information in terms of musical notes. PSVA can break down the "visual sound" into components of vertically and horizontally oriented edges. Additionally, PSVA applies a magnification to the center of the image to simulate the better resolution (magnification factor) of the human fovea.

Although differing to a higher degree, both auditory and tactile SSDs can potentially be very useful for the blind. Recent tests show that blind and/or blindfolded sighted individuals can, especially after training or prolonged use of the device (Poirier et al., 2006), learn to interpret the transmitted information and use it in simple visual discrimination and recognition (Arno et al., 1999, 2001; Sampaio et al., 2001) as well as more complex tasks in which they need to acquire knowledge of spatial locations of objects (Auvray et al., 2007; Proulx et al., 2008) or construct mental images of more complex environments (Cronly-Dillon et al., 2000).

While recent studies demonstrate the behavioral range of SSDs, they also focus on the way blind and sighted brains process such sensory-transformed information. Observing the outcomes of sensory restoration and substitution is not only practically relevant but also offers a unique opportunity for addressing numerous theoretical questions about perception, the nature of qualia and brain plasticity. Functional properties of multisensory regions can easily be studied using SSD as a methodology of choice, as SSDs are naturally processed in a multimodal or transmodal manner. For example, several recent studies used SSDs to test the metamodal processing theory (Pascual-Leone and Hamilton, 2001), which states that each brain region implements a particular type of computation regardless of the modality of its input. These studies showed that object shape information drives the activation of the lateral–occipital complex in the visual cortex, regardless whether it is transmitted in the visual, tactile, or auditory modality (Amedi et al., 2007; Poirier et al., 2006) in sighted as well as blind individuals (see Fig. 18.4). Interestingly, applying TMS to this region can disrupt shape identification using an auditory SSD (Merabet et al., 2008). In the same way, studies conducted using PSVA in the sighted show that auditorily mediated face perception can activate the visual fusiform face area (Plaza et al., 2009), while depth perception activates the occipito-parietal and occipito-temporal regions (Renier et al., 2005). The early visual cortex may to some extent be a multimodal operator for
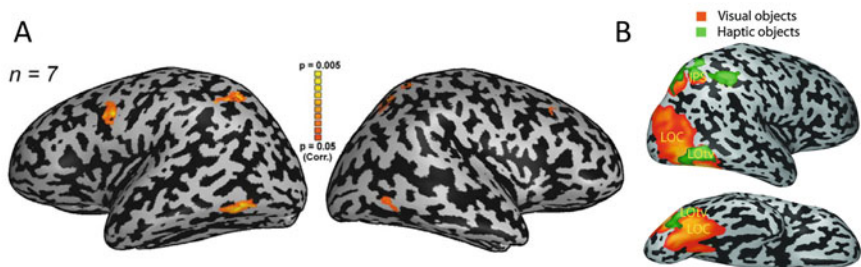
Fig. 18.4 SSDs can be a powerful tool in studying brain plasticity, perception, and multisensory integration. (**a**) A conjunction analysis for shape perception across modalities and experimental conditions in a group of seven expert users of The vOICe SSD (five sighted, one late blind, and one congenitally blind). A conjunction analysis testing for common areas of activation between object recognition using the soundscapes (i.e., using the vOICe SSD to extract the shape information) and touch, but not by typical sounds made by objects (which do not convey shape information) or corresponding sensory controls. The contrast random effect GLM model, corrected for multiple comparisons, showed bilateral LO activation with weaker responses in the right hemisphere, signifying that the LOC region is a multimodal operator for shape (modified and adapted from Amedi et al., 2007). (**b**) Object-related regions in the visual and haptic modalities shown on an inflated right hemisphere (*top*: lateral view; *bottom*: ventral view). Visual object selectivity is relative to scrambled visual images; haptic object selectivity is relative to haptic textures. Visuo-haptic object selectivity in the lateral–occipital complex (LOC) is found within the lateral occipito-temporal sulcus (delineating LOtv), similar to the location of the multisensory object-related area shown in A (modified and adapted from Amedi et al., 2001; and from Lacey et al., 2009)

sensory spatial mapping, as stimulating it in highly trained blind TDU users appears to result in spatially organized tactile sensations on the tongue (Kupers et al., 2006).

Studying the use of SSDs in a longitudinal fashion also provides a good opportunity to monitor in real time how newly acquired information is learned and investigate the accompanying cognitive and neural changes. For example, several studies have looked into differential activation before and after learning how to use a specific SSD. One study showed that after short training, and only in the early-onset blind individuals (but not in sighted), shape discrimination using the TDU SSD generated activation of the occipital cortex (Ptito et al., 2005), suggesting that the occipital lobe of the blind may, even in adulthood, be more prone to plasticity or to crossmodal processing when compared to that of the sighted. Crossmodal activation of the visual cortex of sighted subjects was also demonstrated, following training on the PSVA SSD (Poirier et al., 2007). Although these behavioral and imaging finding benefits have been shown for both early-onset (Arno et al., 2001) and late-onset blind (Cronly-Dillon et al., 1999) and sighted individuals (Poirier et al., 2007), it has recently been suggested that the recruitment of occipital areas during the use of SSDs could be mediated by different mechanisms in different populations. Specifically, while the early blind might exhibit real bottom-up activation of occipital cortex for tactile or auditory perception, in the late blind and sighted this activation might reflect top-down visual imagery mechanisms (Poirier et al., 2007). However, recent evidence of multisensory integration for object recognition, as shown by using a novel crossmodal adaptation paradigm (Tal and Amedi, 2009), suggests that the sighted can share some bottom-up mechanisms of tactile and visual integration in visual cortex. Regardless, the possible behavioral potential of such SSDs may vary between the groups, as the late-onset blind can better associate the crossmodal input to the properties of vision as they knew it (for example, they have better knowledge of the 2-D representation of visual pictures, which is useful in most current 2-D SSDs), while the early blind lack such understanding of the visual world, but may have more highly developed crossmodal networks and plasticity. This difference in utilizing visual rehabilitation between the two blind groups may be even more valid in the case of sensory restoration, which will be discussed in the next section.

Importantly, this differentiation between early- and late-onset blind in SSD use also highlights the importance of introducing such devices as early as possible in development, while the brain is still in its plasticity prime. Similar to the improved outcomes of cochlear implantation in early childhood (Harrison et al., 2005), it may be of particular interest to teach young blind children to utilize such devices. Several early attempts to teach blind infants to use the Sonicguide (Kay and Kay, 1983) showed some promise, as younger subjects showed a more rapid sensitivity to the spatial information provided by the device (Aitken and Bower, 1982, 1983), although with highly variable results (for a discussion see, Warren, 1994). However, to our knowledge, only a few preliminary later attempts (Segond et al., 2007) have been made to adapt the use of SSDs to children.

Overall, although there is still a lot of work to be done in this area, initial experiences with SSDs have shown more than promising results. These devices truly offer new hope for the sensorily impaired in a somewhat non-intuitive, but "brain-friendly" manner, as they use its normal resources and functioning modalities for transmitting previously unavailable information. In order to fully appreciate their value, it might be useful to imagine how exciting it would be (not to mention valuable to many commercial and military applications) to have infrared vision or hear ultrasound frequencies. Interestingly, using one of the future, second-generation SSDs this might just become possible: just like visual information can be transmitted and used by the blind through their functioning auditory or tactile modality, so could infrared or ultrasound frequencies be seen or heard by anyone using functioning vision or audition, making such "super-human" abilities more widely available. Furthermore, observing the outcomes of sensory restoration and substitution is of more than just practical relevance, as it also offers a unique opportunity to address and potentially answer numerous theoretical questions about the fundamental principles of brain organization, neuroplasticity, unimodal sensory processing, and multisensory integration.

18.5.2 Sensory Restoration Approaches

Restoration of sensory input to the visually impaired represents an alternative to sensory substitution devices. Such devices are currently at the forefront of medical, technological, and scientific advances. Conventional sight restoration includes surgical removal of cataracts and treatment of or surgical solutions to vision loss caused by glaucoma. Although highly practical and demonstrating remarkable results (Ostrovsky et al., 2006; Sinha, 2003), these solutions were originally only useful for specific causes and stages of vision loss. Sight restoration in blindness due to other etiologies, such as congenital or late-onset degeneration (for example age-related macular degeneration) of the retina or optic tract, is only nowadays being addressed. The development of such visual prostheses was motivated by early studies in which visual percepts (phosphenes, visual light dots or patterns) were successfully generated by electrical stimulation of the visual cortex (Penfield and Rasmussen, 1950). Although few researchers at the time thought that actual clinical techniques could be developed (Haddock and Berlin, 1950; Newman et al., 1987), in recent years the field of visual prostheses has developed extensively. Today, different approaches are under investigation or are being tested in clinical trials in which visual information is recorded by external (or implanted) devices and transmitted to the sensory tract or secondary processing cells in the retina, ganglion cells, thalamus, or the visual cortex, thereby replacing the healthy receptors of the sensory organs (for several recent reviews of current technologies and remaining challenges see, Dagnelie, 2008; Dowling, 2008; Merabet et al., 2005; Rizzo et al., 2007; Weiland et al., 2005).

There are four main types of approaches in sensory restoration, targeting the retina, optic nerve, lateral geniculate nucleus (LGN), and the visual cortex. The retinal approach is designed to stimulate secondary neurons in the inner retina by an electrode array placed on the inner retinal surface or inserted under the retina (for a description of the different groups and devices developed in recent years see, Dowling, 2008). Such an approach is mainly useful in cases of retinitis pigmentosa and age-related macular degeneration (ARMD) which cause selective degeneration of the photoreceptor layer of the outer retina. In this case the information sent to the visual cortex can still be transmitted over minimally damaged retinal ganglion cells. Optic nerve approaches (Brelen et al., 2005; Veraart et al., 2003) use two forms of stimulation, namely the simultaneous activation of many optic nerve fibers through cuff electrodes and more focused stimulation of small groups of fibers with penetrating microelectrodes. The thalamic prostheses (Pezaris and Reid, 2005, 2009) attempt to stimulate a later station in the visual pathways, i.e., the LGN, but this is currently only under preliminary methodological research in primates. The cortical approach (Fernandez et al., 2002) places electrodes over the central visual field projection in primary visual cortex. Typically this is accomplished using surface (or penetrating) electrodes that may provide relatively good stability of tissue stimulation, but are hard to position in the optimal location based on the known retinotopic mapping of V1. However, this approach can be applied in most cases of blindness, including those (such as glaucoma and diabetic retinopathy, but apart from cortical blindness) which affect the retina and may not benefit from a retinal prosthesis. Devices based on these approaches have so far shown some promising results, as experienced blind users can, to some extent, utilize visual phosphenes generated by some of these devices in order to create meaningful visual percepts and succeed in detecting motion (Weiland and Humayun, 2008) or identifying very simple patterns, shapes, and even letters (Brelen et al., 2005; Dobelle, 2000; Weiland and Humayun, 2008). However, there are still several major issues currently preventing these approaches from becoming true clinical solutions. First of all, their invasive nature makes them prone to risks related to surgical procedures in the brain, such as inflammation, hemorrhage, increased patient morbidity and mortality, and focal seizures induced by direct cortical stimulation. Moreover, retinal prostheses, which currently appear more promising as future solutions for blindness, are not applicable to all populations of the blind, as they require the existence of residual functional retinal ganglion cells. Additionally, these techniques are expensive and have severe technical limitations, such as the relatively low resolution, narrow field of view, and complicated image processing algorithms which compensate for the visual processing taking place in the retina itself. Functionally, these devices typically do not take advantage of eye movements (an exception to this is the system developed by Palanker et al. (2005)) and require large and slow head movements to scan entire visual patterns (Brelen et al., 2005; Chen et al., 2007; Veraart et al., 2003). Therefore, visual prostheses (which are currently not yet available except in preliminary clinical trials) do not provide sight that resembles natural vision and a key milestone in this field has yet to be reached in order to allow generating truly useful and functional vision, at affordable costs. If, however,

visual prostheses research succeeds to overcome these difficulties, these approaches could provide a real visual experience and not just the "visual" information provided by SSDs.

As previously mentioned, attempts aimed at restoring audition in the deaf via an artificial receptor, i.e., artificial cochlea (Spelman, 2006), are currently more widely available and show much better rehabilitation outcomes. However, even when surgical restoration procedures in vision or audition become available for commercial use, only the first step in establishing full perceptual abilities in the newly restored modality will be accomplished. Learning how to interpret the new sensory input delivered to the patient's brain will require further behavioral rehabilitation which may allow gradual restoration of the sensory function in question. For example, cochlear implants work because patients learn to associate meanings between sounds and their sources by generating new associations. This is accompanied and enabled by corresponding plasticity in the auditory cortex (Lee et al., 2001). Two case studies of surgical sight restoration after long-term visual deprivation (Fine et al., 2003; Gregory and Wallace, 1963) suggest that in the case of vision as well, restoration of the lost sensory input may not suffice. In both cases the patients showed profound difficulties in recognizing objects, even after a long period of sight and visual training. Thus, visual perception in this case is impaired, even when vision reaches the brain physiologically via a functional retina. In addition to the surgical procedure, specific additional rehabilitation strategies are needed to modulate brain processing and make it capable of extracting relevant and functionally meaningful information from neuroprosthetic inputs. Furthermore, although the behavioral outcomes of cochlear implant patients are encouraging, it is illusory to expect that they can easily generalize to different subpopulations of sensorily impaired. On the contrary, great interindividual variability is to be expected in adapting to the implant (e.g., in cochlear implant patients, speech recognition performance ranges from very poor to near perfect). This is particularly true with regard to the variability in blindness onset, as was discussed for rehabilitation using SSDs. Late-onset blind may particularly benefit from reacquiring visual information, as their visual cortex has developed in a way which would allow it to process such information. Therefore, following sensory loss their visual cortex needs to reorganize to a smaller degree in contrast to the early-onset or congenitally blind who would require greater reorganization and therefore face more difficulties with adapting to visual information. Furthermore, sensory implantation (and, although in a different manner, SSDs) is prone to influence the brain as a system, not just one modality. For example, it was shown that visual information can disrupt the processing of auditory information in newly transplanted cochlear implant patients, most probably due to crossmodal visual processing in the auditory cortex (Champoux et al., 2009). Such interference may occur following visual restoration in all tasks which are functionally dependent on the occipital lobe of the blind (particularly tasks which can be disrupted by occipital TMS, as described in previous sections). At least some of these problems could be minimized, if not solved, through extensive cognitive and behavioral training. In addition, it is possible to speculate that the integration of SSDs and prostheses may also be helpful in this

respect, as these provide fairly distinct advantages. Specifically, while prostheses may allow entry of visual signals to the brain, training how to process and interpret this information could be facilitated through some initial training with SSDs which can be very useful in teaching the brain how to interpret the input from the new modality. It is possible to assume that the brains of individuals who have undergone training with SSDs are already sensitive to the structure and able to extract the meaning out of visual signals which could be very beneficial when they first encounter the visual signals delivered through the surgically restored sensory system.

18.6 Concluding Remarks

The main goal of this chapter was to illustrate the effects of sensory loss, including changes in cognitive functioning as well as the radical reorganization of the neural architecture supporting these functions, which varies greatly with regard to the timing of sensory loss in development. Many, but not all, of these changes are beneficial and allow the impaired individual to optimally use the available resources to efficiently function in his/her surroundings. Sensory loss triggers robust remodeling of the whole brain which occurs on all spatial and temporal scales. These different types of changes are supported by different neurophysiological mechanisms which are not equally available at different stages of development. Understanding each of these changes, the factors which influence them, as well as how they relate to each other represents a major challenge for future research. Accomplishing this goal is of great practical importance for hundreds of millions of sensorily impaired (e.g., 314 million of individuals are visually impaired worldwide; WHO report 2009, fact sheet 282), as it will allow further development of rehabilitation techniques. This will, however, be a difficult challenge, as we still need to learn a great deal about how to let the brain adapt following sensory restoration using the same mechanisms which allowed its original adaptation to the lost sensory input. In many ways plasticity can be viewed as a "double-edged sword" which occasionally leads to functionally beneficial, and occasionally to maladaptive outcomes. Mastering such phenomena will not be easy. In fact, it may never be possible if interindividual and intergroup differences characterized by different initial cognitive and neural systems as well as a general potential for change are ignored. Even when the most technological issues have been resolved, introducing visual inputs into the brain via a functional prosthetic retina will not automatically result in normal visual perception. This skill will need to be trained and such learning will be greatly facilitated by the use of inputs from other modalities and multisensory regions which may serve as "teaching signals" for the impaired modality. Observing the outcomes of sensory restoration and substitution is thus not just practically relevant but also offers a unique opportunity to address and potentially answer numerous fundamental theoretical questions about perception, multisensory integration, as well as discover the principles underlying brain reorganization and neuroplasticity.

References

Abraham WC, Bear MF (1996) Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci 19(4):126–130

Aitken S, Bower TG (1982) Intersensory substitution in the blind. J Exp Child Psychol 33(2):309–323

Aitken S, Bower TG (1983) Developmental aspects of sensory substitution. Int J Neurosci 19(1–4):13–19

Amedi A, Camprodon J, Merabet L, Bermpohl F, Haligan E, Bass-Pitskel N et al (2006) Highly transient activation of primary visual cortex (V1) for tactile object recognition in sighted following 5 days of blindfolding. Paper presented at 7th annual meeting of the international multisensory research forum, Universtify of Dublin

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG (2004) Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci 7(11):1266–1270

Amedi A, Jacobson G, Hendler T, Malach R, Zohary E (2002) Convergence of visual and tactile shape processing in the human lateral occipital complex. Cereb Cortex 12(11):1202–1212

Amedi A, Malach R, Hendler T, Peled S, Zohary E (2001) Visuo-haptic object-related activation in the ventral visual pathway. Nat Neurosci 4(3):324–330

Amedi A, Merabet LB, Bermpohl F, Pascual-Leone A (2005) The occipital cortex in the blind. Lessons about plasticity and vision. Curr Dir Psychol Sci 14(6):306–311

Amedi A, Raz N, Pianka P, Malach R, Zohary E (2003) Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci 6(7):758–766

Amedi A, Stern WM, Camprodon JA, Bermpohl F, Merabet L, Rotman S et al (2007) Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. Nat Neurosci 10(6):687–689

Arno P, Capelle C, Wanet-Defalque MC, Catalan-Ahumada M, Veraart C (1999) Auditory coding of visual patterns for the blind. Perception 28(8):1013–1029

Arno P, De Volder AG, Vanlierde A, Wanet-Defalque MC, Streel E, Robert A et al (2001) Occipital activation by pattern recognition in the early blind using auditory substitution for vision. Neuroimage 13(4):632–645

Auvray M, Hanneton S, O'Regan JK (2007) Learning to perceive with a visuo-auditory substitution system: localisation and object recognition with 'The vOICe'. Perception 36:416–430

Bach-y-Rita P (2004) Tactile sensory substitution studies. Ann N Y Acad Sci 1013:83–91

Bach-Y-Rita P, Collins CC, Saunders FA, White B, Scadden L (1969) vision substitution by tactile image projection. Nature 221(5184):963–964

Bach-y-Rita P, Kaczmarek KA, Tyler ME, Garcia-Lara J (1998) Form perception with a 49-point electrotactile stimulus array on the tongue: a technical note. J Rehabil Res Dev 35(4):427–430

Bach-y-Rita P, Kercel SW (2003) Sensory substitution and the human-machine interface. Trends Cogn Sci 7(12):541–546

Bavelier D, Dye MW, Hauser PC (2006) Do deaf individuals see better? Trends Cogn Sci 10(11):512–518

Bavelier D, Neville HJ (2002) Cross-modal plasticity: where and how? Nat Rev Neurosci 3(6):443–452

Brelen ME, Duret F, Gerard B, Delbeke J, Veraart C (2005) Creating a meaningful visual perception in blind volunteers by optic nerve stimulation. J Neural Eng 2(1):S22–S28

Brown JA (2006) Recovery of motor function after stroke. Prog Brain Res 157:223–228

Büchel C (2003) Cortical hierarchy turned on its head. Nat Neurosci 6(7):657–658

Büchel C, Price C, Frackowiak RS, Friston K (1998) Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 121(Pt 3):409–419

Buonomano DV, Johnson HA (2009) Cortical plasticity and learning: mechanisms and models. In: Squire LR (ed) Encyclopedia of neuroscience. Academic Press, London

Burton H (2003) Visual cortex activity in early and late blind people. J Neurosci 23(10):4005–4011

Burton H, Diamond JB, McDermott KB (2003) Dissociating cortical regions activated by semantic and phonological tasks: a FMRI study in blind and sighted people. J Neurophysiol 90(3):1965–1982. Epub 2003 Jun 1964

Burton H, Snyder AZ, Conturo TE, Akbudak E, Ollinger JM, Raichle ME (2002) Adaptive changes in early and late blind: a fMRI study of Braille reading. J Neurophysiol 87(1):589–607

Burton H, Snyder AZ, Diamond JB, Raichle ME (2002) Adaptive changes in early and late blind: a FMRI study of verb generation to heard nouns. J Neurophysiol 88(6):3359–3371

Campbell R, MacSweeney M (2004) Neuroimaging studies of cross-modal plasticity and language processing in deaf people. In: Calvert G, Spence C, Stein BE (eds) The handbook of multisensory processes). MIT Press, Cambridge, MA, pp. 773–785

Capelle C, Trullemans C, Arno P, Veraart C (1998) A real-time experimental prototype for enhancement of vision rehabilitation using auditory substitution. IEEE Trans Biomed Eng 45(10):1279–1293

Chabot N, Robert S, Tremblay R, Miceli D, Boire D, Bronchti G (2007) Audition differently activates the visual system in neonatally enucleated mice compared with anophthalmic mutants. Eur J Neurosci 26(8):2334–2348

Champoux F, Lepore F, Gagne JP, Theoret H (2009) Visual stimuli can impair auditory processing in cochlear implant users. Neuropsychologia 47(1):17–22

Chebat DR, Rainville C, Kupers R, Ptito M (2007) Tactile-'visual' acuity of the tongue in early blind individuals. Neuroreport 18(18):1901–1904

Chechik G, Meilijson I, Ruppin E (1998) Neuronal regulation: a mechanism for efficient synaptic pruning during brain maturation. Neuroscience Letters, S9-S9

Chen R, Cohen LG, Hallett M (2002) Nervous system reorganization following injury. Neuroscience 111(4):761–773

Chen SC, Hallum LE, Suaning GJ, Lovell NH (2007) A quantitative analysis of head movement behaviour during visual acuity assessment under prosthetic vision simulation. J Neural Eng 4(1):S108

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J et al (1997) Functional relevance of cross-modal plasticity in blind humans. Nature 389(6647):180–183

Cohen LG, Weeks RA, Sadato N, Celnik P, Ishii K, Hallett M (1999) Period of susceptibility for cross-modal plasticity in the blind. Ann Neurol 45(4):451–460

Collignon, O, Lassonde M, Lepore F, Bastien D, Veraart C (2007) Functional cerebral reorganization for auditory spatial processing and auditory substitution of vision in early blind subjects. Cereb Cortex 17(2):457–465

Collignon O, Renier L, Bruyer R, Tranduy D, Veraart C (2006) Improved selective and divided spatial attention in early blind subjects. Brain Res 1075(1):175–182

Collignon O, Voss P, Lassonde M, Lepore F (2009) Cross-modal plasticity for the spatial processing of sounds in visually deprived subjects. Exp Brain Res 192(3):343–358

Cronly-Dillon J, Persaud K, Gregory RP (1999) The perception of visual images encoded in musical form: a study in cross-modality information transfer. Proc Biol Sci 266(1436):2427–2433

Cronly-Dillon J, Persaud KC, Blore R (2000) Blind subjects construct conscious mental images of visual scenes encoded in musical form. Proc Biol Sci 267(1458):2231–2238

D'Angiulli A, Waraich P (2002) Enhanced tactile encoding and memory recognition in congenital blindness. Int J Rehabil Res 25(2):143–145

Dagnelie G (2008) Psychophysical evaluation for visual prosthesis. Annu Rev Biomed Eng 10:339–368

De Volder AG, Bol A, Blin J, Robert A, Arno P, Grandin C et al (1997) Brain energy metabolism in early blind subjects: neural activity in the visual cortex. Brain Res 750(1–2):235–244

Dinse HR, Merzenich MM (2000) Adaptation of inputs in the somatosensory system. In: Fahle M, Poggio T (eds) Perceptual learning. MIT Press, Cambridge, MA, pp 19–42

Dobelle WH (2000) Artificial vision for the blind by connecting a television camera to the visual cortex. ASAIO J 46(1):3–9

Doucet ME, Guillemot JP, Lassonde M, Gagne JP, Leclerc C, Lepore F (2005) Blind subjects process auditory spectral cues more efficiently than sighted individuals. Exp Brain Res 160(2):194–202

Dowling, J (2008) Current and future prospects for optoelectronic retinal prostheses. Nature-Eye 23:1999–2005

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA et al (1998) Neurogenesis in the adult human hippocampus. Nat Med 4(11):1313–1317

Falchier A, Clavagnier S, Barone P, Kennedy H (2002) Anatomical evidence of multimodal integration in primate striate cortex. J Neurosci 22(13):5749–5759

Fernandez E, Ahnelt P, Rabischong P, Botella C, & Garcia-de Quiros F (2002) Towards a cortical visual neuroprosthesis for the blind. IFMBE Proc 3(2):1690–1691

Fieger A, Röder B, Teder-Salejarvi W, Hillyard SA, Neville HJ (2006) Auditory spatial tuning in late-onset blindness in humans. J Cogn Neurosci 18(2):149–157

Fine, I (2008) The behavioral and neurophysiological effects of sensory deprivation. In: Rieser JJ, Ashmead DH, Ebner FF, Corn AL (eds) Blindness and brain plasticity in navigation and object perception. Taylor & Francis, New York, pp. 127–155

Fine I, Wade AR, Brewer AA, May MG, Goodman DF, Boynton GM et al (2003) Long-term deprivation affects visual perception and cortex. Nat Neurosci 6(9):915–916

Finney EM, Fine I, Dobkins KR (2001) Visual stimuli activate auditory cortex in the deaf. Nat Neurosci 4(12):1171–1173

Gizewski ER, Gasser T, de Greiff A, Boehm A, Forsting M (2003) Cross-modal plasticity for sensory and motor activation patterns in blind subjects. Neuroimage 19(3):968–975

Golarai G, Ghahremani DG, Whitfield-Gabrieli S, Reiss A, Eberhardt JL, Gabrieli JD et al. (2007) Differential development of high-level visual cortex correlates with category-specific recognition memory. Nat Neurosci 10(4):512–522

Goldish LH, Taylor HE (1974) The optacon: a valuable device for blind persons. New Outlook Blind 68(2):49–56

Goldreich D, Kanics IM (2003) Tactile acuity is enhanced in blindness. J Neurosci 23(8): 3439–3445

Goldreich D, Kanics IM (2006) Performance of blind and sighted humans on a tactile grating detection task. Percept Psychophys 68(8):1363–1371

Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F (2005) A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. PLoS Biol 3(2):e27

Grafman J (2000) Conceptualizing functional neuroplasticity. J Commun Disord 33(4):345–355; quiz 355–346

Grant AC, Thiagarajah MC, Sathian K (2000) Tactile perception in blind Braille readers: a psychophysical study of acuity and hyper acuity using gratings and dot patterns. Percept Psychophys 62(2):301–312

Gregory RL, Wallace JG (1963) Recovery from early blindness: a case study. Reproduced in 2001 from Exp Psychol Soc Mon. 2. Heffers, Cambridge

Haddock JN, Berlin L (1950) Transsynaptic degeneration in the visual system; report of a case. Arch Neurol Psychiat 64(1):66–73

Harrison RV, Gordon KA, Mount RJ (2005) Is there a critical period for cochlear implantation in congenitally deaf children? Analyses of hearing and speech perception performance after implantation. Dev Psychobiol 46(3):252–261

Heyes AD (1984) The sonic pathfinder: a new electronic travel aid. J Vis Impair Blindness 78(5):200–202

Hugdahl K, Ek M, Takio F, Rintee T, Tuomainen J, Haarala C et al. (2004) Blind individuals show enhanced perceptual and attentional sensitivity for identification of speech sounds. Brain Res Cogn Brain Res 19(1):28–32

Hull T, Mason H (1995) Performance of blind-children on digit-span tests. J Vis Impair Blindness 89(2):166–169

Izraeli R, Koay G, Lamish M, Heicklen-Klein AJ, Heffner HE, Heffner RS et al. (2002) Cross-modal neuroplasticity in neonatally enucleated hamsters: structure, electrophysiology and behaviour. Eur J Neurosci 15(4):693–712

Kaas JH (1991) Plasticity of sensory and motor maps in adult mammals. Annu Rev Neurosci 14 137–167

Kaas JH (2000) The reorganization of somatosensory and motor cortex after peripheral nerve or spinal cord injury in primates. Prog Brain Res 128:173–179

Karlen SJ, Kahn DM, Krubitzer L (2006) Early blindness results in abnormal corticocortical and thalamocortical connections. Neuroscience 142(3):843–858

Kay L, Kay N (1983) An ultrasonic spatial sensor's role as a developmental aid for blind children. Trans Ophthalmol Soc N Z 35:38–42

Kleiner A, Kurzweil RC (1977) A description of the Kurzweil reading machine and a status report on its testing and dissemination. Bull Prosthet Res 10(27):72–81

Knudsen EI (2004) Sensitive periods in the development of the brain and behavior. J Cogn Neurosci 16(8):1412–1425

Kolb B (1995) Brain plasticity and behavior. Lawrence Erlbaum Associates, Inc., Mahwah, NJ

Korte M, Rauschecker JP (1993) Auditory spatial tuning of cortical neurons is sharpened in cats with early blindness. J Neurophysiol 70(4):1717–1721

Kujala T, Alho K, Paavilainen P, Summala H, Naatanen R (1992) Neural plasticity in processing of sound location by the early blind: an event-related potential study. Electroencephalogr Clin Neurophysiol 84(5):469–472

Kujala T, Palva MJ, Salonen O, Alku P, Huotilainen M, Jarvinen A et al. (2005) The role of blind humans' visual cortex in auditory change detection. Neurosci Lett 379(2):127–131

Kupers R, Fumal A, de Noordhout AM, Gjedde A, Schoenen J, Ptito M (2006) Transcranial magnetic stimulation of the visual cortex induces somatotopically organized qualia in blind subjects. Proc Natl Acad Sci U S A 103(35):13256–13260

Lacey S, Tal N, Amedi A, Sathian K (2009) A putative model of multisensory object representation. Brain Topogr 21(3–4):269–274

Laemle LK, Strominger NL, Carpenter DO (2006) Cross-modal innervation of primary visual cortex by auditory fibers in congenitally anophthalmic mice. Neurosci Lett 396(2):108–112

Leclerc C, Saint-Amour D, Lavoie ME, Lassonde M, Lepore F (2000) Brain functional reorganization in early blind humans revealed by auditory event-related potentials. Neuroreport 11(3):545–550

Lee DS, Lee JS, Oh SH, Kim SK, Kim JW, Chung JK et al. (2001) Cross-modal plasticity and cochlear implants. Nature 409(6817):149–150

Lessard N, Pare M, Lepore F, Lassonde M (1998) Early-blind human subjects localize sound sources better than sighted subjects. Nature 395(6699):278–280

Lewald J (2002) Vertical sound localization in blind humans. Neuropsychologia 40(12):1868–1872

Lickliter R, Bahrick LE (2004) Perceptual development and the origins of multisensory responsiveness. In: Calvert G, Spence C, Stein BE (eds) The handbook of multisensory processes. MIT Press, Cambridge, MA, pp 643–654

Liu Y, Yu C, Liang M, Li J, Tian L, Zhou Y et al. (2007) Whole brain functional connectivity in the early blind. Brain 130(Pt 8):2085–2096

Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44(1):5–21

Meijer PB (1992) An experimental system for auditory image representations. IEEE Trans Biomed Eng 39(2):112–121

Merabet L, Thut G, Murray B, Andrews J, Hsiao S, Pascual-Leone A (2004) Feeling by sight or seeing by touch? Neuron 42(1):173–179

Merabet LB, Battelli L, Obretenova S, Maguire S, Meijer P, Pascual-Leone A (2009) Functional recruitment of visual cortex for sound encoded object identification in the blind. Neuroreport 20(2):132–138

Merabet LB, Hamilton R, Schlaug G, Swisher JD, Kiriakopoulos ET, Pitskel NB et al. (2008) Rapid and reversible recruitment of early visual cortex for touch. PLoS ONE 3(8):e3046

Merabet LB, Maguire D, Warde A, Alterescu K, Stickgold R, Pascual-Leone A (2004) Visual hallucinations during prolonged blindfolding in sighted subjects. J Neuroophthalmol 24(2):109–113

Merabet LB, Pitskel NB, Amedi A, Pascual-Leone A (2008) The plastic human brain in blind individuals: the cause of disability and the opportunity for rehabilitation. In: Rieser JJ, Ashmead DH, Ebner FF, Corn AL (eds) Blindness and brain plasticity in navigation and object perception. Taylor & Francis, New York, pp 23–42

Merabet LB, Rizzo JF, Amedi A, Somers DC, Pascual-Leone A (2005) What blindness can tell us about seeing again: merging neuroplasticity and neuroprostheses. Nat Rev Neurosci 6(1):71–77

Michel GF, Tyler AN (2005) Critical period: a history of the transition from questions of when, to what, to how. Dev Psychobiol 46(3):156–162

Millar S (1981) Cross-modal and intersensory perception and the blind. In: Walk RD, Pick HLJ (eds) Intersensory perception and sensory integration. Plenum Press, New York, pp 281–314

Muckli L, Naumer MJ, Singer W (2009) Bilateral visual field maps in a patient with only one hemisphere. Proc Natl Acad Sci U S A 106(31):13034–13039

Murphy C, Cain WS (1986) Odor identification: the blind are better. Physiol Behav 37(1):177–180

Neville HJ, Bavelier D (2000) Specificity of developmental neuroplasticity in humans: evidence from sensory deprivation and altered language experience. In Shaw CA, McEachern JC (eds) Toward a theory of neuroplasticity. New York: Taylor & Francis, pp. 261–275

Newman NM, Stevens RA, Heckenlively JR (1987) Nerve fibre layer loss in diseases of the outer retinal layer. Br J Ophthalmol 71(1):21–26

Niemeyer W, Starlinger I (1981) Do the blind hear better? Investigations on auditory processing in congenital or early acquired blindness. II. Central functions. Audiology 20(6):510–515

Noppeney U, Friston KJ, Ashburner J, Frackowiak R, Price CJ (2005) Early visual deprivation induces structural plasticity in gray and white matter. Curr Biol 15(13):R488–R490

Ofan RH, Zohary E (2007) Visual Cortex Activation in Bilingual Blind Individuals during Use of Native and Second Language. Cereb Cortex 17(6):1249–1259

Ostrovsky Y, Andalman A, Sinha P (2006) Vision following extended congenital blindness. Psychol Sci 17(12):1009–1014

Palanker D, Vankov A, Huie P, Baccus S (2005) Design of a high-resolution optoelectronic retinal prosthesis. J Neural Eng 2(1):S105–S120

Pan WJ, Wu G, Li CX, Lin F, Sun J, Lei H (2007) Progressive atrophy in the optic pathway and visual cortex of early blind Chinese adults: a voxel-based morphometry magnetic resonance imaging study. Neuroimage 37(1):212–220

Pascual-Leone A, Amedi A, Fregni F, Merabet LB (2005) The plastic human brain cortex. Annu Rev Neurosci 28:377–401

Pascual-Leone A, Hamilton R (2001) The metamodal organization of the brain. Prog Brain Res 134:427–445

Penfield W, Rasmussen T (1950) The cerebral cortex of man: a clinical study of localization of function. Macmillan, New York

Pezaris JS, Reid RC (2005) Microstimulation in LGN produces focal visual percepts: proof of concept for a visual prosthesis. J Vis 5(8):367

Pezaris JS, Reid RC (2009) Simulations of electrode placement for a thalamic visual prosthesis. IEEE Trans Biomed Eng 56(1):172–178

Piche M, Chabot N, Bronchti G, Miceli D, Lepore F, Guillemot JP (2007) Auditory responses in the visual cortex of neonatally enucleated rats. Neuroscience 145(3):1144–1156

Pitskel NB, Merabet LB, Ramos-Estebanez C, Kauffman T, Pascual-Leone A (2007) Time-dependent changes in cortical excitability after prolonged visual deprivation. Neuroreport 18(16):1703–1707

Plaza P, Cuevas I, Collignon O, Grandin C, De Volder AG, Renier L (2009) Perceiving faces using auditory substitution of vision activates the fusiform face area. Paper presented at the Belgian Society for Fundamental and Clinical Physiology and Pharmacology, Spring Meeting, 2009

Poirier C, De Volder A, Tranduy D, Scheiber C (2007) Pattern recognition using a device substituting audition for vision in blindfolded sighted subjects. Neuropsychologia 45(5):1108–1121

Poirier C, De Volder AG, Scheiber C (2007) What neuroimaging tells us about sensory substitution. Neurosci Biobehav Rev 31(7):1064–1070

Poirier C, Richard MA, Duy DT, Veraart C (2006) Assessment of sensory substitution prosthesis potentialities in minimalist conditions of learning. Appl Cogn Psychol 20(4): 447–460

Poirier CC, Collignon O, Scheiber C, Renier L, Vanlierde A, Tranduy D et al. (2006) Auditory motion perception activates visual motion areas in early blind subjects. Neuroimage 31(1): 279–285

Poirier CC, De Volder AG, Tranduy D, Scheiber C (2006) Neural changes in the ventral and dorsal visual streams during pattern recognition learning. Neurobiol Learn Mem 85(1):36–43

Pozar L (1982) Effect of long-term sensory deprivation on recall of verbal material. Studia Psychologica 24(3–4):311

Pring L (1988) The 'reverse-generation' effect: a comparison of memory performance between blind and sighted children. Br J Psychol 79 (Pt 3):387–400

Proulx MJ, Stoerig P, Ludowig E, Knoll I (2008) Seeing 'where' through the ears: effects of learning-by-doing and long-term sensory deprivation on localization based on image-to-sound substitution. PLoS ONE 3(3):e1840

Ptito M, Moesgaard SM, Gjedde A, Kupers R (2005) Cross-modal plasticity revealed by electrotactile stimulation of the tongue in the congenitally blind. Brain 128(Pt 3):606–614

Rauschecker JP (2008) Plasticity of cortical maps in visual deprivation. In: Rieser JJ, Ashmead DH, Ebner FF, Corn AL (eds) Blindness and brain plasticity in navigation and object perception. Taylor & Francis, New York, 43–66

Rauschecker JP, Korte M (1993) Auditory compensation for early blindness in cat cerebral cortex. J Neurosci 13(10):4538–4548

Raz N, Amedi A, Zohary E (2005) V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb Cortex 15(9):1459–1468

Raz N, Striem E, Pundak G, Orlov T, Zohary E (2007) Superior serial memory in the blind: a case of cognitive compensatory adjustment. Curr Biol 17(13):1129–1133

Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, Dinse HR (1992) Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency-discrimination task. J Neurophysiol 67(5):1031–1056

Renier L, Collignon O, Poirier C, Tranduy D, Vanlierde A, Bol A et al. (2005) Cross-modal activation of visual cortex during depth perception using auditory substitution of vision. Neuroimage 26(2):573–580

Ricciardi E, Vanello N, Sani L, Gentili C, Scilingo EP, Landini L et al. (2007) The effect of visual experience on the development of functional architecture in hMT+. Cereb Cortex 17(12): 2933–2939

Rizzo JF 3rd, Snebold L, Keeney M (2007) Development of a visual prosthesis: a review of the field and an overview of the Boston retinal implant project. In: Tombran-Tink J, Barnstable CJ, Rizzo JF 3rd (eds) Visual prosthesis and ophthalmic devices. Humana Press, Totowa, NJ, pp. 71–93

Rockland KS, Ojima H (2003) Multisensory convergence in calcarine visual areas in macaque monkey. Int J Psychophysiol 50(1–2):19–26

Röder B, Rösler F (1998) Visual input does not facilitate the scanning of spatial images. J Ment Imag 22(3 and 4):127–144

Röder B, Rösler F, Neville HJ (2000) Event-related potentials during auditory language processing in congenitally blind and sighted people. Neuropsychologia 38(11):1482–1502

Röder B, Rösler F, Neville HJ (2001) Auditory memory in congenitally blind adults: a behavioral-electrophysiological investigation. Brain Res Cogn Brain Res 11(2):289–303

Röder B, Stock O, Bien S, Neville H, Rösler F (2002) Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci 16(5):930–936

Röder B, Teder-Salejarvi W, Sterr A, Rösler F, Hillyard SA, Neville HJ (1999) Improved auditory spatial tuning in blind humans. Nature 400(6740):162–166

Rösler F, Röder B, Heil M, Hennighausen E (1993) Topographic differences of slow event-related brain potentials in blind and sighted adult human subjects during haptic mental rotation. Brain Res Cogn Brain Res 1(3):145–159

Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M (1998) Neural networks for Braille reading by the blind. Brain 121(Pt 7):1213–1229

Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G et al. (1996) Activation of the primary visual cortex by Braille reading in blind subjects. Nature 380(6574):526–528

Sampaio E, Maris S, Bach-y-Rita P (2001) Brain plasticity: 'visual' acuity of blind persons via the tongue. Brain Res 908(2):204–207

Schlaggar BL, O'Leary DD (1991) Potential of visual cortex to develop an array of functional units unique to somatosensory cortex. Science 252(5012):1556–1560

Segond H, Weiss D, Sampaio E (2007) A proposed tactile vision-substitution system for infants who are blind tested on sighted infants. J Vis Impair Blindness 101(1):32–43

Sharma J, Angelucci A, Sur M (2000) Induction of visual orientation modules in auditory cortex. Nature 404(6780):841–847

Shaw CA, McEachern JC (2000) Transversing levels of organization: a theory of neuronal stability and plasticity. In: Shaw CA, McEachern JC (eds) Toward a theory of neuroplasticity. Taylor & Francis, New York, pp 427–448

Shimony JS, Burton H, Epstein AA, McLaren DG, Sun SW, Snyder AZ (2006) Diffusion tensor imaging reveals white matter reorganization in early blind humans. Cereb Cortex 16(11):1653–1661

Sinha (2003) Face classification following long-term visual deprivation. J Vis 3(9):104

Smith M, Franz EA, Joy SM, Whitehead K (2005) Superior performance of blind compared with sighted individuals on bimanual estimations of object size. Psychol Sci 16(1):11–14

Smits B, Mommers MJ C. (1976) differences between blind and sighted children on wisc verbal subtests. New Outlook Blind 70(6):240–246

Spelman FA (2006) Cochlear electrode arrays: past, present and future. Audiol Neurootol 11(2):77–85

Tal N, Amedi A (2009) Multisensory visual-tactile object related network in humans: insights gained using a novel crossmodal adaptation approach. Exp Brain Res 198(2–3):165–182

Tillman MH, Bashaw WL (1968) Multivariate analysis of the WISC scales for blind and sighted children. Psychol Rep 23(2):523–526

Uhl F, Franzen P, Lindinger G, Lang W, Deecke L (1991) On the functionality of the visually deprived occipital cortex in early blind persons. Neurosci Lett 124(2):256–259

Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Ingle DJ, M. Goodalec A, Mansfield RJW (eds) Analysis of visual behavior. MIT Press, Boston, pp 549–586

Veraart C, Wanet-Defalque MC, Gerard B, Vanlierde A, Delbeke J (2003) Pattern recognition with the optic nerve visual prosthesis. Artif Organs 27(11):996–1004

von Melchner L, Pallas SL, Sur M (2000) Visual behaviour mediated by retinal projections directed to the auditory pathway. Nature 404(6780):871–876

Voss P, Lassonde M, Gougoux F, Fortin M, Guillemot JP, Lepore F (2004) Early- and late-onset blind individuals show supra-normal auditory abilities in far-space. Curr Biol 14(19):1734–1738

Wakefield CE, Homewood J, Taylor AJ (2004) Cognitive compensations for blindness in children: an investigation using odour naming. Perception 33(4):429–442

Wallace MT (2004) The development of multisensory integration. In: Calvert G, Spence C, Stein BE (eds) The handbook of multisensory processes. MIT Press, Cambridge, MA, pp 625–642

Warren DH (1994) Blindness and children: an individual differences approach. Cambridge University Press, New York, NY

Weiland JD, Humayun MS (2008) Visual prosthesis. Proc IEEE 96(7):1076–1084

Weiland JD, Liu W, Humayun MS (2005) Retinal prosthesis. Annu Rev Biomed Eng 7:361–401

WHO (2009) Visual impairment and blindness: World Health Organization, Fact Sheet 282

Wiesel TN, Hubel DH (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 26:1003–1017

Wiesel TN, Hubel DH (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 28(6):1029–1040

Yu C, Liu Y, Li J, Zhou Y, Wang K, Tian L et al. (2008) Altered functional connectivity of primary visual cortex in early blindness. Hum Brain Mapp 29(5):533–543

Zangaladze A, Epstein CM, Grafton ST, Sathian K (1999) Involvement of visual cortex in tactile discrimination of orientation. Nature 401(6753):587–590

Zwiers MP, Van Opstal AJ, Cruysberg JR (2001) A spatial hearing deficit in early-blind humans. J Neurosci 21(9):RC142:141–145