



Review

The effects of visual deprivation on functional and structural organization of the human brain

Uta Noppeney*

Max-Planck-Institute for Biological Cybernetics, Spemannstr. 38, 72076 Tuebingen, Germany

Abstract

Early onset blindness allows one to investigate how the human brain adapts to sensory experience in infancy and early childhood. Over the past decade, lesion, functional and structural imaging studies have accumulated evidence that severe perturbations to visual experience alter the functional and structural organization of the human brain. Visual deprivation can induce plastic changes not only in the visual system, but also in the remaining intact sensory–motor system, secondary to altered experience using these spared modalities. In particular, occipital, usually visual, areas are reorganized and recruited by the remaining senses and higher cognitive tasks primarily through cortico-cortical connectivity. Importantly, these plastic changes vary as a function of timing and are most pronounced in early onset blindness. Thus, sensory experience shapes functional and structural brain organization during sensitive periods in neurodevelopment.

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Keywords: Functional reorganization; Crossmodal plasticity; Visual deprivation; Blindness; Neurodevelopment; Voxel-based morphometry; Functional imaging; Connectivity; Structural imaging; Experience-dependent plasticity

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1. Introduction

How do sensory experiences shape brain structure? Blindness provides a unique opportunity to investigate

the effects of visual experience on functional and structural organization of the human brain. Visual deprivation induces neuroplasticity due to lack of visual experience, compensatory use of the spared sensory modalities and altered multi-sensory integration (Rauschecker, 1995; Merabet et al., 2005; Pascual-Leone et al., 2005; Bavelier and Neville, 2002; Roder et al., 1999; Lessard et al., 1998).

*Tel.: +49 7071 601 603; fax: +49 7071 601 616.
E-mail address: uta.noppeney@tuebingen.mpg.de

As blind individuals rely primarily on touch and audition to interact effectively with their environment, one may expect superior skills in auditory and tactile tasks. Indeed, blind individuals exhibit lower tactile thresholds (Sterr et al., 1998), heightened tactile spatial resolution (Van Boven et al., 2000), superior pitch discrimination (Gougoux et al., 2004; Hamilton et al., 2004), auditory spatial (Lessard et al., 1998; Roder et al., 1999; Niemyer and Starlinger, 1981) and recognition skills (Roder et al., 2001). Previous studies have suggested that these behavioral compensations are mediated by changes in (i) polymodal association and (ii) primary cortices of the visual and spared modalities. In animal studies, visual deprivation results in cross-modal reorganization of extrastriate cortex (Hyvarinen et al., 1981; Heil et al., 1991), primary visual areas (Hubel and Wiesel, 1977; Price et al., 1994) and hypertrophy of auditory cortex (Ryugo et al., 1975; Gyllensten et al., 1966). However, the extent and specificity of these changes are variable and depend on several critical factors such as the cause (e.g. dark rearing, enucleation, prematurity) and the timing of visual deprivation. Investigating the effect of blindness onset on the human nervous system may thus allow us to define sensitive periods for the multiple aspects of human vision (Hubel and Wiesel, 1977; Maurer et al., 2005; Lewis and Maurer, 2005; Hensch, 2005) and provide insight into the complex interactions between neurodevelopment and environmental input.

In the following sections, we will review functional imaging, lesion and structural imaging studies that have provided evidence for functional and structural reorganization in blind individuals (n.b. only studies of blindness of peripheral origin are included). Briefly, these studies have demonstrated that the visual cortex becomes involved in non-visual sensory functions and higher cognitive tasks as a function of blindness onset: the functional reorganization is particularly pronounced in early onset blindness. We will conclude by discussing the neuronal mechanisms that may mediate plastic changes induced by severe perturbations of visual experience.

2. Functional reorganization in early and late blind subjects

2.1. Functional imaging

The development of hemo-dynamic functional imaging methods (i.e. functional magnetic resonance imaging/fMRI, positron emission tomography/PET) has enabled the non-invasive investigation of the neural systems underlying sensory–motor and higher cognitive functions in humans. To characterize functional reorganization induced by visual deprivation, functional imaging studies have compared activations between sighted and blind subjects in a variety of paradigms ranging from passive non-visual stimulation to higher perceptual and cognitive tasks. Activations have been reported in bilateral striate (also referred to as primary visual cortex or V1) and extrastriate regions for tactile discrimination relative to a

non-discrimination task (Sadato et al., 1996; Sadato et al., 1998) and in the right hemisphere (Brodmann Area 18/BA18) for location of sounds relative to rest (Weeks et al., 2000). Interestingly, passive tactile stimulation (Sadato et al., 1996, 1998) or simple motor tasks (e.g. finger tapping) (Gizewski et al., 2003) did not elicit activation in the occipital cortex suggesting that only complex higher level but not simple sensory–motor tasks engage occipital regions in the blind.

Neuroplasticity in higher cognitive systems has been investigated initially through functional imaging studies of Braille reading. In blind subjects, Braille reading evoked responses in extrastriate and inconsistently primary visual areas relative to rest (Cohen et al., 1999; Melzer et al., 2001; Sadato et al., 2002), tactile non-discrimination tasks (Sadato et al., 1996, 1998), auditory processing (Buchel et al., 1998a,b) and reading non-lexical Braille strings (Burton et al., 2002a). While extrastriate activation has been observed consistently across all blind subjects, V1 activation for Braille reading depended on the onset age of blindness. Buchel et al. (1998a) reported V1 activation only for late blind subjects during a feature detection task and attributed it to visual imagery strategies that may have been employed by subjects with prior visual experience. In contrast, Sadato et al. (2002) observed V1 activation only for early blind subjects during a tactile Braille discrimination task (see also Cohen et al., 1999 for converging results). Hence, Sadato et al. (2002) argued for early sensitive periods during which visual deprivation can induce functional reorganization in striate cortices. These inconsistencies may result from differences in task, baseline, performance confounds, inter-subject variability and lack of sensitivity of group results when based on a limited number of subjects. Subsequent single subject analyses have demonstrated V1 activation consistently in all blind subjects during verb generation in response to auditory or tactile (Braille) words (Burton et al., 2002a, b), although striate activations tended to be more pronounced in early blind subjects. Collectively, the reviewed studies of Braille reading suggest that blind subjects recruit occipital areas during Braille reading, whereby the degree of functional reorganization, in particular the involvement of striate regions, depends on the neurodevelopmental stage during which blindness started (Burton et al., 2002a,b; Burton, 2003). However, as Braille reading invokes multiple perceptual and higher cognitive processes, these studies cannot specify the particular cognitive function that is sustained by the occipital cortex: is the occipital cortex involved in processing complex tactile stimuli, Braille orthography, lexical processing, phonology or semantics? To further elucidate the functional role of the occipital cortex in the blind, subsequent studies have therefore turned to memory and language paradigms.

Evidence for a functional role of occipital activations in language or higher cognitive processes was provided by studies of sound imagery (De Volder et al., 2001), auditory sentence processing (Roder et al., 2002), semantic retrieval

(Noppeney et al., 2003; Burton et al., 2003), verbal (Amedi et al., 2003) and episodic memory (Raz et al., 2005). A possible role of occipital cortex in semantic processing has been investigated by comparing semantic decisions to auditory feature detection (Noppeney et al., 2003) or phonological rhyming tasks (Burton et al., 2003). Consistently across studies, both early blind and sighted subjects activated a left-lateralized fronto-temporal system selectively for semantic decisions. In addition to this well-documented semantic retrieval/executive system (Vandenberghe et al., 1996; Petersen et al., 1989; Noppeney and Price, 2002; Roskies et al., 2001; Poldrack et al., 1999), early blind subjects activated extrastriate regions, which were coupling with frontal and temporal regions of the “core” semantic retrieval system (Noppeney et al., 2003). This over-expressed coupling is consistent with the abnormal pruning of synaptic connections during neurodevelopment (Huttenlocher et al., 1982; Huttenlocher, 1990; Batardiere et al., 2002; Burkhalter, 1993; Price et al., 1994). Normally, experience-dependent pruning leads to sparser connectivity, a more refined architecture and a greater degree of functional specification. In the absence of visual experience, however, an exuberant effective connectivity between key players of the semantic system and extra-striate cortex may be maintained. Thus, in early blind subjects, extra-striate regions could become incorporated into the semantic retrieval system via increased backwards connections from higher-order fronto-temporal brain areas.

Given that “experience-dependent” developmental mechanisms specify the functional anatomy of semantic retrieval, one may wonder whether plastic changes are more pronounced in parts of the semantic system that depend on visual experience. Visual deprivation might especially alter retrieval of semantic information related to color, form, action and motion that is learnt via visual experience, while sparing semantic information related to sounds that is acquired predominantly via the auditory sense. For instance, one might hypothesize that visual deprivation, which enforces action experience via somatosensory–motor associations rather than visual motion perception, reduces the action-selective response in a left posterior middle temporal (LPMT) area that is close to or even overlapping with visual motion area V5 (Chao et al., 1999, 2002; Chao and Martin, 2000; Martin et al., 1996; Noppeney et al., 2005b, 2006). Contrary to this conjecture, in both blind and sighted subjects, LPMT activation increased for semantic decisions on spoken words referring to actions relative to words referring to other features (Noppeney et al., 2003). This remarkable resilience of LPMT action-selectivity to early visual deprivation might be explained by multimodal response characteristics of LPMT, which may depend on its connections to motor areas.

In addition to semantic retrieval, occipital activations in blind individuals may play a role in verbal or episodic memory functions. Anecdotally, blind subjects have been

known for their superior memory skills. They served as living databases in ancient times (Amedi et al., 2003). Previous behavioral studies have shown that early blind subjects outperform sighted subjects in long-term verbal memory and digit span tasks. Two recent functional imaging studies were designed to identify the neural basis of these superior memory skills. In the first study (Amedi et al., 2003), blind and sighted subjects covertly recalled lists of well-studied words in the absence of any sensory input. Mirroring their superior memory skills, only blind but not sighted subjects showed increased striate and extrastriate activations during the verbal memory task. Furthermore, within the blind group, a strong correlation was found between the blind individual’s verbal memory skills and the magnitude of that individual’s V1 activation. In the second study (Raz et al., 2005), 1-year later, the same blind subjects performed a recognition task of a well- and a barely-practiced list of words presented in the first study. Again a correlation between V1 activation and performance measures was observed: Well-practiced lists of words and subjects with high recognition performance were associated with greater V1 activation. Collectively, these studies implicate extra striate and striate cortices in the early blind subjects in semantic and episodic memory functions. The correlation between performance measures and occipital activations suggests that the otherwise “unemployed” visual cortex may be re-utilized and mediate the superior memory skills of early blind individuals (Table 1).

2.2. Lesion or functional perturbation studies

It is important to appreciate that functional imaging can only establish correlations or statistical dependencies between cognitive functions and brain activations. It enables us to define a system of regions that are sufficient for a particular function in sighted or blind subjects. However, functional imaging cannot distinguish areas that are necessary for task performance from those that simply reflect processing that is implicitly invoked but not necessary for a particular task (Noppeney et al., 2004; Price and Friston, 2002). For instance, semantic retrieval may be sustained by the same “core” fronto-temporal system in both blind and sighted subjects with the occipital cortex only implicitly activated in the blind. In other words, the occipital activations in blind individuals may just be an epiphenomenon that is functionally irrelevant. To establish a causal link between the occipital activations and cognitive functions, researchers have employed lesion methods. Lesion studies are based on the fundamental rationale that a lesion-induced decline in a particular cognitive function demonstrates that the lesioned part was necessary or made an important contribution to this cognitive function. Lesions can either be permanently induced by ischemia, hypoxia, etc. or transiently (“virtual lesion”) by transcranial magnetic stimulation (TMS), electrical or pharmacological methods (Pascual-Leone et al., 2000).

Table 1
fMRI and PET studies of functional reorganization of the visual cortex in blind subjects

Study	Imaging modality	Subjects	Statistical comparison	Results and comments	Effect of OoB
Amedi et al. (2003)	fMRI	10 congenitally blind 7 sighted	Verb generation > auditory noise Verbal memory > rest (for b > s) Verbal memory vs. Braille reading (in b only)	V1 + extra-striate areas V1 activation correlates with verbal memory performance Functional specialization of V1 and LOC: V1 engaged in verbal memory, LOC in Braille	%
Arno et al. (2001)	PET	6 early blind (OoB < 6 y), 6 sighted	Listening to auditory coded visual pattern > rest (sensory substitution device) (for b > s)	Bilateral inferior occipital gyrus (BA18)	%
Buchel et al. (1998b)	PET	6 congenitally blind, 3 late blind (OoB > 18 y), 11 sighted	Reading Braille words > letter strings (in b) and Reading visual words > letter strings (in s)	Left posterior inferior temporal area (BA37)	%
Buchel et al. (1998a)	PET	6 congenitally blind, 3 late blind (OoB > 18 y)	Braille reading > listening to spoken words (for late > early blind)	V1 + right occipital cortex	Late > early
Burton et al. (2002a)	fMRI	9 early blind (OoB < 6 y), 7 late blind (OoB > 9 y)	Braille reading > non-Braille tactile control	V1 + extra-striate areas	Early > late
Burton et al. (2003)	fMRI	9 early blind (OoB < 5 y), 7 late blind (OoB > 7 y), 8 sighted	Semantic decision > rhyme task on spoken words (in b only)	V1 + extra-striate areas	Early > late
Burton et al. (2004)	fMRI	9 early blind (OoB < 6 y), 9 late blind (OoB > 6 y), 8 sighted	Tactile discrimination > rest	V1 + extra-striate areas	Early > late
Burton et al. (2006)	fMRI	9 early blind (OoB < 6 y), 9 late blind (OoB > 6 y), 10 sighted	Reading embossed capital letters > rest (for b > s)	V1 + extra-striate areas superior temporal cortex	Early > late, early > late
Burton and McLaren, 2006	fMRI	2 Braille naïve late blind (OoB > 18 y), 7 late blind (OoB > ? y)	Rhyme task on spoken words > rest or Semantic decision on spoken words > rest (in b only)	V1 + extra-striate areas even for Braille naïve blind	%
Cohen et al. (1999)	PET	4 congenitally blind, 4 early blind (OoB < 13 y), 4 late blind (OoB > 15)	Braille reading > rest	V1 + extra-striate areas	Early > late
De Volder (2001)	PET	6 early blind (OoB < 6 y), 6 sighted	Mental imagery to spoken words > listening to sounds (for b > s)	Extra-striate areas	%
Gizewski et al. (2003)	PET	9 congenitally blind, 3 early (?) blind	Braille + non-Braille tactile task > rest (for b > s) Sensory stimulation + finger tapping > rest (in b only)	Visual cortex No visual cortex activation	%
Melzer et al. (2001)	fMRI	5 congenitally blind, 5 blind (OoB: < 13 y)	Braille reading > rest	Single subject analysis in region of interest > 7 subjects in V1	%
Noppeney et al. (2003)	fMRI	11 early blind (OoB < 2 y), 12 sighted	Semantic decision on spoken words > auditory task on reversed words (for b > s)	Primarily extra-striate areas increased connectivity between extra-striate and frontal areas in blind	%

Table 1 (continued)

Study	Imaging modality	Subjects	Statistical comparison	Results and comments	Effect of OoB
Raz et al. (2005)	fMRI	9 congenitally blind	Word recognition > phonological task (in b only)	V1 + extra-striate areas, V1 predicted by memory performance within and across subjects	%
Roder et al. (2002)	fMRI	10 congenitally blind, and 11 sighted controls	Listening to speech > backward speech (for b > s)	Region of interest analysis: V1 + extra-striate areas	%
Sadato et al. (1996)	PET	8 blind (OoB < 10 y), 10 sighted	Braille reading > non-Braille tactile discrimination (for b > s)	V1 + extra-striate areas	%
Sadato et al. (1998)	PET	4 congenitally blind, 4 blind (OoB: < 12 y), 3 congenitally blind, 3 blind (OoB: < 5 y), 10 sighted	Braille reading > rest (for all b) Non-Braille tactile discrimination task > rest (for b > s)	V1 + extra-striate areas Primarily extra-striate areas	% %
Sadato et al. (2002)	fMRI	9 early blind (OoB < 16 y), 6 late blind (OoB > 16 y)	Braille tactile discrimination > rest (for all b)	Both groups: extra-striate areas, V1 primarily in early	Early > late
Weeks et al. (2000)	PET	9 congenitally blind, 9 sighted	Sound localization > rest (for b > s)	right dorsal and ventral occipital cortex (BA18)	
Wittenberg et al. (2004)	TMS/PET	5 early blind (OoB < 5 y), 5 late blind (OoB > 5 y), 10 sighted	rTMS > sham over somato-sensory cortex (S1) (for b > s)	Increased V1 activation increased functional connectivity between S1 and V1 in early blind	Early > late

b = blind, s = sighted; OoB = onset of blindness, LOC = Lateral occipital cortex, y = years.

Clear evidence for a necessary role of the occipital cortex in Braille reading in the early blind has been provided by a case report of a congenitally blind woman, who was a proficient Braille reader (Hamilton et al., 2000). Following a bilateral posterior artery stroke, she was severely impaired on Braille reading, while her tactile discrimination skills (for simple stimuli) were preserved. Similarly, application of repetitive TMS to the occipital cortex (Cohen et al., 1997) caused distorted tactile perceptions, a transient impairment of Braille reading and identification of Roman embossed letters in blind but not sighted subjects. A follow-up study (Cohen et al., 1999) investigated the effect of repetitive TMS as a function of blindness onset by comparing early (< 4 years) and late (> 14 years) blind subjects. While early and late blind subjects were both impaired on Braille reading after TMS over somato-sensory cortices, TMS over occipital cortex induced an increase in error rate only in early blind subjects. Thus, repetitive TMS studies suggest that cross-modal reorganization may interact with neurodevelopment and be limited to or particularly pronounced during early sensitive periods. However, subsequent repetitive TMS studies investigating the short-term effects of blindfolding in sighted subjects suggest additional fast plastic mechanisms such as unmasking or release from inhibition that are not limited to early sensitive periods but can be observed even after a short period of blindfolding (Pascual-

Leone et al., 2005). To further specify the particular functional contribution of the occipital cortex to Braille reading, researchers (Pascual-Leone et al., 2005) have employed single-pulse TMS that provides additional information about the timing of information processes (see reviews on mental chronometry, Pascual-Leone et al., 2000). A TMS pulse applied over parietal/somato-sensory cortex 20 ms after Braille stimulus presentation interfered with tactile stimulus detection in both early blind and sighted subjects. In contrast, TMS application over occipital cortex disrupted Braille symbol identification (but not detection) only in the blind subjects 50–80 ms after Braille stimulus presentation. These results suggest that in early blind subjects parietal activity associated with letter detection precedes occipital processes underlying letter identification. One may therefore hypothesize that tactile information reaches the occipital cortex through parieto-occipital i.e. cortico-cortical connections. Indeed, in a recent study combining PET and repetitive TMS, TMS over somato-sensory cortex evoked extra-striate activation in the early blind, but not in the late blind or sighted subjects (Wittenberg et al., 2004). As extra-striate activations were observed in the absence of any thalamic activation, the recruitment of occipital regions for cognitive tasks may be mediated through altered cortico-cortical connections rather than a sub-cortical loop.

Table 2
TMS studies of functional reorganization of the visual cortex in blind subjects

Study	Imaging modality	Subjects	Experimental task & statistical comparison	Results & Comments	Effect of OoB
Amedi et al. (2004)	rTMS	9 early blind (OoB < 3 y)	Verb generation to spoken words rTMS > sham applied over V1 rTMS applied over V1 > S1 (for b > s)	Primarily semantic errors for TMS over occipital cortex in b	%
Cohen et al. (1997)	TMS	6 congenitally blind, 4 early blind (OoB < 10 y)	Reading Braille and embossed Roman letters TMS applied over mid-occipital (and other positions)	TMS over occipital cortex induced errors only in b	%
Cohen et al. (1999)	rTMS	3 congenitally blind 2 early blind (OoB < 4 y) 5 late blind (OoB > 15)	Braille reading TMS applied over mid-occipital	TMS over occipital cortex induced errors in congenitally and early b	Early > late

b = blind, s = sighted; OoB = onset of blindness.

The functional perturbation studies reported so far suggest that the occipital cortex plays a necessary role in complex tactile recognition processes such as Braille reading. Are the activations observed during higher cognitive and language tasks then purely epiphenomenal? One TMS study (Amedi et al., 2004) suggests that the occipital cortex may also make an important functional contribution to higher cognitive and more specifically semantic processing. When applying TMS over the occipital pole, Amedi et al. (2004) showed reduced accuracy on a verb-generation task in blind subjects but not in sighted controls. Furthermore, the reduction in accuracy could be attributed primarily to semantic rather than phonological or articulatory errors suggesting a necessary role of the occipital pole in higher-level semantic processing (Table 2).

2.3. Summary of functional imaging and lesion studies

Over the past decade, functional imaging and lesion studies have accumulated evidence that the unemployed “visual” cortex is functionally reorganized and plays a prominent role in non-visual tasks in early blind subjects. Interestingly, the visual cortex is not involved in simple non-visual processing but in complex tactile and a range of higher cognitive functions such as Braille reading, imagery, semantic and episodic memory tasks. The question therefore emerges whether the occipital cortex sustains one particular cognitive function that is commonly involved in all tasks or whether regions within the occipital cortex become functionally specialized for different cognitive processes. Comparing Braille reading and verbal memory tasks, a recent functional imaging study (Amedi et al., 2003) has suggested a topographical specialization within occipital cortex. While posterior regions were more active for verbal memory tasks, anterior regions showed increased

activation for Braille reading. This pattern of results may be interpreted as a “reversed hierarchical organization” of the occipital cortex in the early blind with more posterior regions being involved in more abstract processing.

Furthermore it is clear that occipital cortex can adjust itself to severe perturbations of visual experience (such as blindness or even transient blindfolding) throughout lifetime, the functional imaging and lesion studies investigating the effect of blindness onset suggest that plastic changes may be more pronounced in early blind subjects. Some mechanisms underlying neuroplasticity may thus depend on the stage of brain maturation.

3. Structural reorganization

According to traditional views, the adult human brain adapts to changes in the environment through functional reorganization rather than structural plastic changes. Novel observer-independent morphometric techniques that enable quantitative analysis of subtle changes in gray/white matter volume (Ashburner and Friston, 2000, 2003), cortical thickness (Fjell et al., 2006) or gyrification indices (Luders et al., 2006) have called this view into question and suggest that even the macro- or mesoscopic structure of the human brain dynamically adapts to environmental demands. Training-induced changes in regional gray or white matter volumes have been shown for musicians (Gaser and Schlaug, 2003), jugglers (Draganski et al., 2004), bilinguals (Mechelli et al., 2004) and students during exam periods (Draganski et al., 2006). For instance, a recent longitudinal study (Draganski et al., 2004) has demonstrated bilateral increases in gray matter volumes of motion areas MT/V5 following a 3-month juggling training period and subsequent reductions after the end of training.

Early onset blindness provides additional insights into experience-dependent plasticity, as it allows one to

investigate the effect of sensory–motor experience on brain structure during neurodevelopment. Anecdotally, atrophy of chiasm, optic nerve, optic radiation and enlargement of the calcarine fissure has been described in blind subjects based on visual inspection of MRI structural images (Breitenseher et al., 1998) and post mortem analysis (Beatty et al., 1982). A recent MRI study (Noppeney et al., 2005a) used voxel-based morphometry to characterize, quantify and statistically evaluate changes in gray and white matter volumes within the entire brain at mesoscopic and macroscopic levels. Relative to sighted controls, visual deprivation induced both gray and white matter changes within the visual, somato-sensory and motor systems (see also Emmorey et al., 2003; Penhune et al., 2003 for related findings in early deaf subjects). The reduced gray matter volume in primary and secondary visual areas (BA 17/18) may reflect changes in synaptic density, dendritic spine numbers or axonal arborizations that have been described previously in morphological studies of visually deprived animals (Globus and Scheibel, 1966). The gray matter loss was accompanied by atrophy of the optic chiasm and the optic radiation extending into the corpus callosum highlighting the importance of early binocular input for the development of callosal connections (Innocenti et al., 1985). The changes in white matter were further characterized through diffusion tensor imaging and tractography (Shimony et al., 2006) that measure apparent diffusion coefficient (i.e. total molecular motion averaged over all directions) and fractional anisotropy (i.e. degree to which diffusion is directional) to evaluate white matter integrity at the micro-structural level and neuronal connectivity. Consistent with post-mortem and voxel-based morphometry studies, blind subjects exhibited decreased anisotropy and enhanced diffusivity in areas juxtaposed to V1/V2, the geniculo-calcarine tract and the posterior corpus callosum. Similarly, diffusion tensor tractography, a computational procedure to reconstruct major fiber bundles, revealed attenuated or absent geniculo-calcarine tracts, but preserved cortico-cortical connections to the frontal and temporal cortices in early blind subjects.

In contrast to the atrophy of the afferent white matter tracts in the visual system, blind subjects showed an

increase in the size of white matter tracts associated with primary somatosensory and motor cortices possibly due to experience-dependent compensatory plasticity (Noppeney et al., 2005a). In the absence of visual experience, blind subjects engage more frequently in tactile exploration of objects and later Braille reading (see also Pascual-Leone et al., 1993). Recent studies have identified molecular mechanisms mediating myelination in response to neuronal activity (Stevens et al., 2002). Hence, the enhanced motor activity in blind subjects may increase the number, diameter and in particular myelination of relevant axons.

So far, studies investigating structural changes after visual deprivation have focused on early blind subjects precluding a full characterization of the emergence and time course of experience-dependent structural plasticity. Nevertheless, post-mortem studies show that axon diameter and myelin sheaths grow markedly in the first 2 years of life (Yakovlev and Lecours, 1967). An effect of blindness onset may thus be apparent even in the first years of life. Indeed, a voxel-based morphometry analysis (Noppeney et al., 2005a) demonstrated robust effects of blindness onset on white matter density even though all blind participants lost eyesight before the age of two: Earlier onset decreased white matter density in the optic tracts bilaterally and, at a lower significance threshold, increased white matter density in the tracts associated with primary somatosensory and motor cortices. Hence, at least some mechanisms of experience-dependent structural plasticity may interact with stages of neurodevelopment and be effective only in early sensitive periods (Table 3).

4. Neural mechanisms of cross-modal plasticity

While it is clear that the occipital cortex undergoes remarkable plastic changes following visual deprivation, the underlying neural mechanisms remain to be determined. At the systems level, two classes of neural mechanisms have been proposed involving either subcortical or cortico-cortical circuitries (see Bavelier and Neville, 2002 for extended review and Figs. 1 and 2): (1) crossmodal rewiring experiments in animals have revealed *subcortical* mechanisms whereby sensory input accesses a thalamic

Table 3
VBM and DTI-tractography studies of structural reorganization in the visual system of blind subjects

Study	Imaging modality	Subjects	Results & Comments	Effect of OoB
Noppeney et al. (2005a)	MRI	11 early blind (OoB < 2y) 46 sighted	Gray matter: reduced volume primarily in BA17/18 White matter: atrophy of optic chiasm and optic radiation	Effect of blindness onset
Shimony et al. (2006)	MRI DTI	5 congenitally blind	Gray matter: reduced volume in V1/V2 White matter: tractography revealed atrophy of geniculo-cortical tracts	%

b = blind, s = sighted; OoB = onset of blindness.

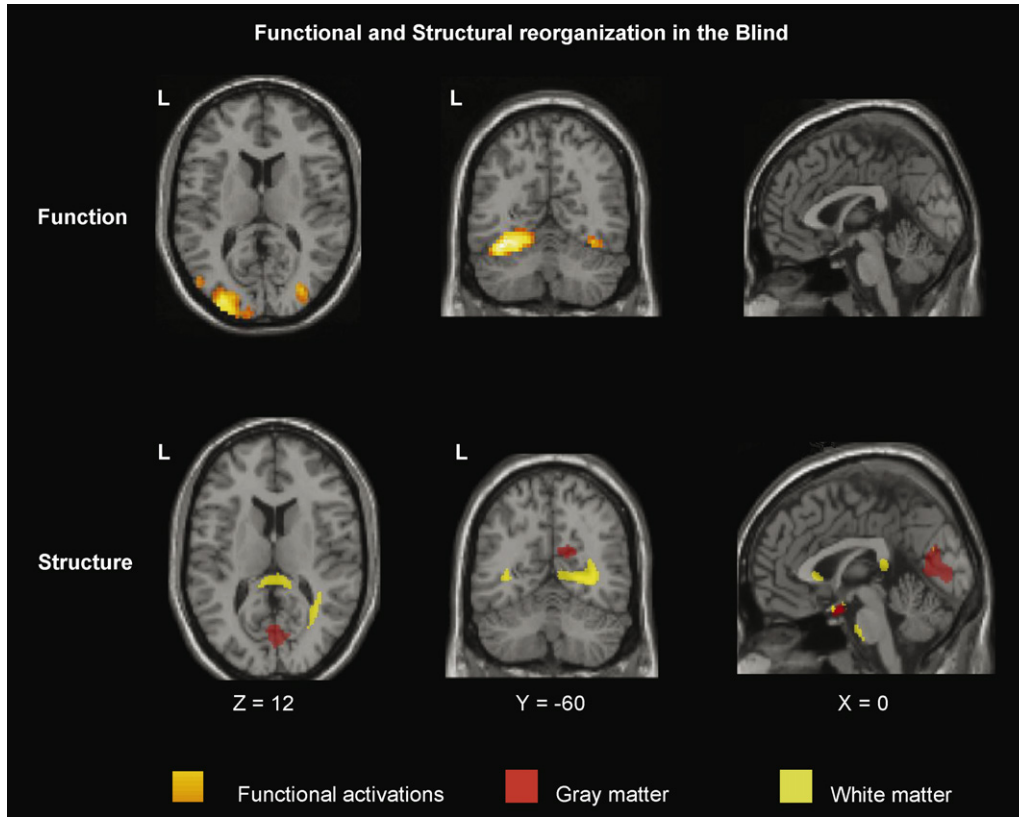


Fig. 1. Bottom: Increases in semantic activations for blind relative to sighted presented on coronal, axial and sagittal slices of a canonical structural image (adapted from Noppeney et al., 2003). Height threshold: $p < 0.001$ uncorrected. Voxel extent threshold > 0 voxels for illustrational purposes. Bottom: Decreases in Gray and white matter volume for blind relative to sighted presented on coronal, axial and sagittal slices of a canonical structural image (adapted from Noppeney et al., 2005a). Height threshold: $p < 0.001$ uncorrected. Voxel extent threshold > 100 voxels for illustrational purposes. Red = Gray matter. Yellow = White matter.

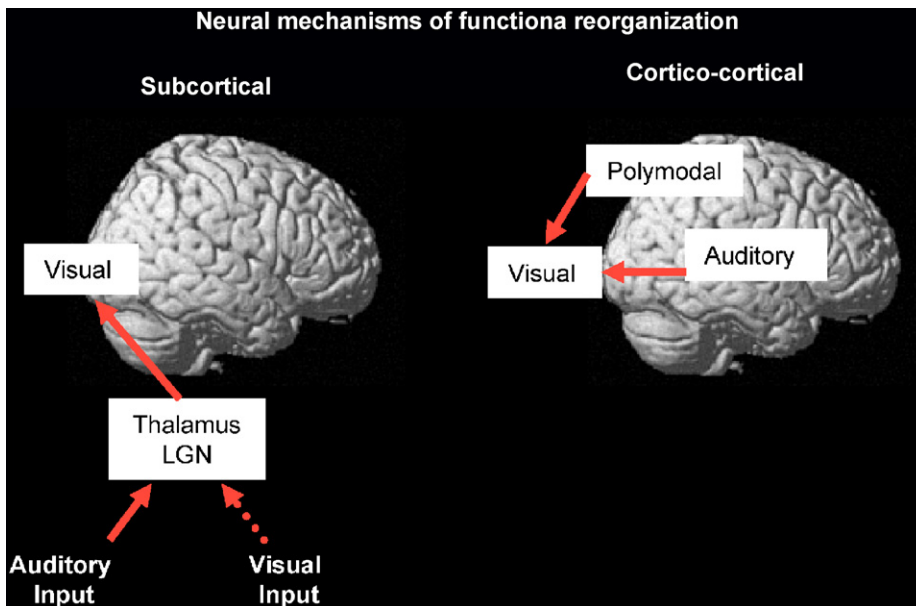


Fig. 2. Subcortical and cortico-cortical mechanisms of functional reorganization in the blind. Subcortical mechanism (left): Non-visual (e.g. auditory) input may access thalamic structures that have been de-afferented from visual input. Cortico-cortical mechanism (right): In the absence of visual input, projections from higher order multi-sensory integration areas and sensory areas from other modalities may be enhanced. (Adapted from Bavelier and Neville, 2002). LGN = Lateral Geniculate Nucleus.

structure that has been de-afferented from its normal input of a different modality. For instance, re-routing retinal axons into the auditory thalamus induces auditory cortex to be driven by spatial and temporal patterns of activity due to vision (Sur et al., 1990; Roe et al., 1990). Conversely, the occipital cortex may adopt auditory functional properties when activated by auditory input via the lateral geniculate nucleus. For instance, in the blind mole rat, a subterranean rodent with a reduced peripheral visual system, the remnant thalamo-cortical visual pathway seems to be taken over by auditory input mediated by projections from the inferior colliculus (Bronchti et al., 1989, 2002). Thus, rewiring and de-afferentation experiments have highlighted the role of thalamo-cortical input in the development and functional specification of sensory cortices. (2) Alternatively, crossmodal reorganization may be mediated by *cortico-cortical* connectivity. Here, the properties of sensory cortex are modulated by its structural and functional connectivity with higher polymodal association and sensory areas from other modalities. The importance of top-down modulation through backward connections from higher polymodal association areas on primary, presumptive unimodal, visual areas has long been appreciated (Macaluso and Driver, 2005). Recently, tracer studies in primates (Falchier et al., 2002; Rockland and Ojima, 2003) have revealed direct anatomical connections between early auditory and primary visual areas. Both classes of cortico-cortical connections could convey auditory or tactile input to visual areas and thus modulate processing of visual information. Under normal circumstances, feed-back from higher polymodal association areas may mediate effects of crossmodal attention (Macaluso and Driver, 2005). Direct connections with other sensory areas may explain the audio-visual integration effects in early auditory or visual cortices in anaesthetized monkeys and humans (Kayser et al., 2005; Foxe et al., 2000; Calvert et al., 1999; Schroeder and Foxe, 2002; Fu et al., 2003) and the early audio-visual incongruity effects that have been observed in EEG (Molholm et al., 2004).

While subcortical and cortico-cortical mechanisms may contribute to functional reorganization following visual deprivation in humans, the reviewed evidence from current structural and functional imaging studies emphasizes the role of cortico-cortical mechanisms: First, voxel-based morphometry (Noppeney et al., 2005a), diffusion tensor imaging and tractography (Shimony et al., 2006) have revealed atrophy of the geniculo-cortical tracts in the absence of any novel afferent thalamo-cortical tracts. This pattern of structural changes suggests that visual cortex functionality in blindness is primarily mediated by cortico-cortical as opposed to thalamo-cortical connections. Second, a cortico-cortical mechanism may also explain the reported double dissociation between structural and functional plasticity within visual cortex. While gray matter loss is observed primarily in lower visual areas (BA17/18), functional responses to non-visual stimuli are reported predominantly for higher-level visual association areas

(Buchel et al., 1998b; Weeks et al., 2000; Burton, 2003; Noppeney et al., 2003), and less so for primary visual cortex (see Figs. 1 and 2). Visual association cortex may preserve its structural integrity by being incorporated into other functional systems via cross-modal cortico-cortical connectivity. The primary visual cortex may enjoy only limited crossmodal plasticity via cortico-cortical connectivity and therefore be more susceptible to disuse atrophy. Third, increased cortico-cortical connectivity as a mechanism for crossmodal plasticity has been suggested by two studies combining fMRI, TMS and effective connectivity analysis techniques. In a semantic paradigm, increased effective connectivity or coupling between prefrontal and extra-striate regions was observed in the blind relative to sighted control subjects (Noppeney et al., 2003). Similarly, a combined TMS and fMRI study indicated increased connectivity directly between somato-sensory and visual areas in blind subjects (Wittenberg et al., 2004). Furthermore, the timing of the TMS effects on behavioral performance over somato-sensory and visual cortices indicates that tactile information is first processed in parietal cortices and later in occipital cortices. Collectively, the reviewed evidence suggests that visual deprivation alters the balance between geniculo-cortical and cortico-cortical input to visual areas. These shifts in connectivity may emerge with different time courses: rapid transient plasticity may rely on unmasking of pre-existing connectivity and account for non-visual occipital responses in sighted (Zangaladze et al., 1999) and blindfolded subjects (Pascual-Leone et al., 2005). If the absence of visual input persists, in particular during early neurodevelopment, the predominance of cortico-cortical input to occipital cortex may induce structural changes leading to a stabilization of cortico-cortical and an attenuation or atrophy of thalamo-cortical connectivity.

5. Conclusions

In this paper, we have reviewed evidence from TMS, functional and structural imaging indicating remarkable dynamic changes of the human brain in response to visual deprivation. Functional imaging studies have demonstrated that brain regions usually responsive to visual input are involved in processing information from other senses and higher cognitive tasks. TMS and lesion studies demonstrate that occipital activations in the blind are not purely epiphenomenal but functionally relevant for task performance. The recruitment of visual areas for non-visual tasks is most likely mediated through increased cortico-cortical connectivity. Importantly, these plastic changes vary as a function of timing. Rapid plastic changes in blindfolded subjects may be mediated by unmasking of pre-existing connections. Sustained severe perturbations of visual experience may induce functional and structural plastic changes that are most pronounced in early onset blindness. Thus, sensory experience shapes functional and

structural brain organization during sensitive periods in neurodevelopment.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Max Planck Society.

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