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Nature of crossmodal plasticity in the blind brain and interplay with sight restoration

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Nature of crossmodal plasticity in the blind brain and interplay with sight restoration

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Résumé

Ce travail de thèse s’est intéressé à la plasticité cérébrale associée à la privation/restauration visuelle. A travers deux études transversales utilisant l’imagerie par résonance magnétique fonctionnelle auprès d’un groupe de participants présentant une cécité congénitale ou précoce (ainsi qu’auprès d’un groupe contrôle de participants voyants), nous avons tenté de caractériser la manière dont le cortex occipital - typiquement dédié au traitement de l’information visuelle - se réorganise afin de traiter différents stimuli auditifs. Nous démontrons qu’en cas de cécité précoce, différentes régions du cortex occipital présentent une préférence fonctionnelle pour certains types de stimuli non-visuels, avec une spécialisation fonctionnelle qui respecte celle de régions typiquement impliquées dans le traitement d’informations similaires en vision. Ces découvertes constituent une avancée conceptuelle concernant le rôle joué par les contraintes intrinsèques d’une part, et par l’expérience d’autre part, dans l’émergence de réponses sensorielles et fonctionnelles du cortex occipital. D’une part, l’observation de réponses occipitales à la stimulation auditive chez le non-voyant précoce (réorganisation transmodale) rend compte de la capacité du cortex occipital à réorienter sa modalité sensorielle préférentielle en fonction de l’expérience. D’autre part, l’existence de modules cognitifs spécialisés dans le cortex occipital du non-voyant précoce, semblables à ceux du cerveau voyant, démontre les contraintes intrinsèques imposées à une telle plasticité. Dans une étude de cas longitudinale, nous avons également exploré comment les changements plastiques associés à la cécité interagissent avec une récupération visuelle partielle à l’âge adulte. Nous avons réalisé des mesures pré et post-opératoires auprès d’un patient ayant récupéré la vision, en combinant les techniques comportementales ainsi que de neuroimagerie fonctionnelle et structurelle afin d’investiguer conjointement l’évolution de la réorganisation transmodale et de la récupération des fonctions visuelles à travers le temps. Nous démontrons que les changements structurels et fonctionnels caractérisant le cortex occipital du non-voyant sont partiellement réversibles suite à une récupération visuelle à l’âge adulte. De manière générale, ces recherches témoignent de l’importante adaptabilité du cortex occipital aux prises avec des changements drastiques dans l’expérience visuelle.

Mots-clés: cécité, plasticité transmodale, système ventral-dorsal, restauration visuelle, imagerie par resonance magnétique fonctionnelle

Abstract

The present Ph.D. work was dedicated to the study of experience-dependent brain plasticity associated with visual deprivation/restoration. In two cross-sectional studies involving the use of functional magnetic resonance imaging in a group of participants with congenital or early blindness (and in a control group of sighted participants), we attempted to characterize the way the occipital cortex - typically devoted to vision – reorganizes itself in order to process different auditory stimuli. We demonstrate that in case of early visual deprivation, distinct regions of the occipital cortex display a functional preference for specific non-visual attributes, maintaining a functional specialization similar to the one that characterizes the sighted brain. Such studies have shed new light on the role played by intrinsic constraints on the one side, and experience on the other, in shaping the modality- and functional tuning of the occipital cortex. On the one hand, the observation of occipital responses to auditory stimulation (crossmodal plasticity) highlights the ability of the occipital cortex to reorient its preferential tuning towards the preserved sensory modalities as a function of experience. On the other hand, the observation of specialized cognitive modules in the occipital cortex, similar to those observed in the sighted, highlights the intrinsic constraints imposed to such plasticity. In a longitudinal single-case study, we further explored how the neuroplastic changes associated with blindness may interact with the newly reacquired visual inputs following partial visual restoration in adulthood. We performed both pre- and post-surgery measurements in a sight-recovery patient combining behavioral, neurostructural and neurofunctional methods in order to jointly investigate the evolution of crossmodal reorganization and visual recovery across time. We demonstrate that functional and structural changes evidenced in the visually-deprived occipital cortex can only partially reverse following sight restoration in adulthood. Altogether, our findings demonstrate the striking adaptability of the occipital cortex facing drastic changes in visual experience.

Keywords: blindness, crossmodal plasticity, ventral-dorsal systems, sight-restoration, functional magnetic resonance imaging.

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Introduction

Article #1: "Investigating auditory motion processing in the occipito-temporal cortex of early blind and sighted individuals"

List of abbreviations

BOLD: blood oxygen level dependent

DTI: diffusion tensor imaging

EB: early blind

EEG: electro-encephalography

fMRI: functional magnetic resonance imaging

LB: late blind

ms: milliseconds

MVPA: multivariate pattern analyses

OD: right eye

OS: left eye

PET: positron emission tomography

s: seconds

SI: sighted

VBM: voxel-based morphometry

Introduction

Introduction

The study of neuroplasticity has increased rapidly over the last decades, opening up exciting new fields of research based on the remarkable ability of both the young and the adult brain to be shaped by experience. The visual (occipital) cortex in particular has been extensively studied as a model of neuronal development and plasticity. Since the pioneering work of Hubel and Wiesel conducted in the early 1960's, it is widely accepted that alterations in visual experience have the potential to modify the typical development of the occipital cortex (Hubel & Wiesel, 1970; Wiesel & Hubel, 1963; 1965).

Striking demonstrations of experience-dependent plasticity in humans also originate from the study of individuals who are born with or have later acquired non-reversible blindness from a peripheral origin. In these individuals, the visually-deprived brain encounters important reorganizations resulting from the combination of the absent visual input and of an increased reliance on inputs provided by the spared sensory modalities.

Findings from several studies have suggested that sensory representations within the cortices subtending the preserved non-visual modalities are significantly expanded in blind compared to sighted individuals. For instance, the tonotopic map is enlarged within the auditory cortex of blind individuals (Elbert et al., 2002) and so is the somatosensory representation of the reading fingers in blind proficient Braille readers (Pascual-Leone & Torres, 1993; Sterr, Müller, Elbert, Rockstroh, Pantev, & Taub, 1998a; 1998b). These use-dependent cortical reorganizations are thought to underlie changes in the perceptual auditory and tactile abilities of the blind (Elbert et al., 2002; Sterr, Müller, Elbert, Rockstroh, Pantev, & Taub, 1998a; 1998b). Aside from these examples of intra-modal plasticity within the auditory and the somatosensory cortices, the visually-deprived occipital cortex itself is the locus of massive cross-modal reorganizations. Indeed, this large portion of the brain that is typically devoted to visual processing, becomes highly responsive to non-visual stimulation in blind subjects (for reviews see Bavelier & Neville, 2002; Frasnelli, Collignon, Voss, & Lepore, 2011; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). In congenitally- and early blind individuals in particular, this cross-modal plasticity is considered to be functional by nature since it may correlate with superior non-visual performance (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005) and transcranial magnetic stimulation (TMS) delivered on the occipital cortex alters non-visual functions (Amedi, Floel, Knecht, Zohary, & Cohen, 2004; Cohen et al., 1997; Collignon, Lassonde, Lepore, Bastien, & Veraart, 2007; Kupers et al., 2007). In addition, increasing evidence suggests that despite the reorientation in modality-tuning, the occipital cortex of early-blind individuals maintains a division of computational labor somehow similar to the one that characterizes the sighted brain (for reviews see Dormal & Collignon, 2011; Reich, Maidenbaum, & Amedi, 2012). As such, early blindness represents a unique model to investigate the role of sensory experience in shaping the modality and functional tuning of the "visual" cortex.

Using functional magnetic resonance imaging (MRI), the empirical work presented in the present thesis first aimed at investigating how specific neural systems typically associated to the dorsal and the ventral "visual" pathways have evolved in case of early visual deprivation. These studies are presented in chapter 2 and chapter 3.

Among individuals deprived of visual experience early in life, the rare cases that recover vision after longstanding visual deprivation have the potential to answer the crucial question of how the long-deprived and reorganized "visual" cortex will cope with the newly acquired visual input. Indeed, crossmodal plasticity documented in blind individuals inevitably raises crucial challenges for visual recovery, as it may prevent the deprived and reorganized occipital cortex from performing its original function optimally (Merabet & Pascual-Leone, 2009).

We address this question in chapter 4, in the longitudinal case study of an early-onset visually impaired individual whose vision was partially restored in adulthood. In this study, we used fMRI in order to jointly investigate the evolution of crossmodal plasticity and visual recovery with the "visual" cortex.

Before the presentation of the 3 empirical studies, chapter 1 reviews existing evidence of crossmodal reorganization in blindness and considers the impact this phenomenon may have for the outcome of surgical interventions aimed at restoring visual input in the blind.

Chapter 1.

Crossmodal plasticity in the blind brain

Crossmodal plasticity in the blind brain

This chapter describes in detail existing evidence about the consequences of visual deprivation in humans, both at the behavioral and at the neural level. For the sake of clarity, we focus on findings reported in congenitally- and early blind individuals[1] in the first and second part of the chapter. We discuss the existence of sensitive periods for crossmodal reorganization in the third section of the chapter. The fourth section considers restoration and rehabilitation strategies and provides existing evidence suggesting that crossmodal plasticity may interfere with the recovery of visual functions.

1. Early evidence of crossmodal plasticity in the blind

The development of functional MRI (fMRI) and positron emission tomography (PET) has allowed the non-invasive investigation of the neural correlates of various sensory, motor and cognitive functions in humans, with a relatively high spatial resolution. In order to characterize functional reorganization in early-blind subjects, fMRI and PET studies have compared brain activations in blind and sighted participants either at rest or using a variety of paradigms ranging from passive stimulation to higher perceptual and cognitive tasks.

In two pioneer PET studies, Wanet-Defalque et al. (1988) and Veraart et al. (1990) investigated cerebral glucose metabolism in human subjects who became blind early in life. At rest, elevated metabolic activity was disclosed in occipital areas of early blind individuals. This activity was significantly higher than in blindfolded sighted individuals (Veraart et al., 1990; Wanet-Defalque et al., 1988) and was comparable to the one measured in sighted participants with opened eyes (Veraart et al., 1990). A follow-up study from the same group demonstrated that this elevated metabolic activity was indeed related to neural activity rather than to gliosis (De Volder et al., 1997). Following these seminal

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[1] Congenital blindness refers to individuals that were born blind and, as a result, never had any visual experience. Early blindness refers to cases of blindness that occurred during the first few years of life, generally before the age of 5, although there are exceptions (Cohen et al., 1999; Sadato, Okada, Honda, & Yonekura, 2002). Typically, early blind groups also include congenitally blind subjects. Late blindness generally refers to cases of blindness that occurred after puberty or in adulthood.

studies, increases in activation within occipital areas in early-blind individuals were primarily investigated in neuroimaging studies of Braille reading.

1.1. Braille reading

Using PET, Sadato and collaborators (1996) were among the first to document increases in activation in striate and extrastriate occipital areas of blind individuals during Braille reading compared to rest (Figure 1A) and to other non-Braille tactile discrimination tasks. In contrast, sighted control participants deactivated visual areas during tactile discrimination tasks (Sadato et al., 1996). Subsequent studies reported converging findings of task-related increases of activation in the occipito-temporal cortex of early blind individuals during Braille reading relative to rest (Gizewski, Gasser, de Greiff, Boehm, & Forsting, 2003; Sadato et al., 1996; 1998), relative to reading non-lexical Braille strings (Burton, Snyder, Conturo, Akbudak, Ollinger, et al., 2002a), relative to sweeping fingers over meaningless Braille strings (Amedi et al., 2003), relative to an auditory baseline (Büchel, Price, & Friston, 1998a) and relative to auditory words processing (i.e. controlling for implicit word processing) (Büchel, Price, Frackowiak, & Friston, 1998b). In these studies, the reported activations during Braille reading in blind individuals encompassed the striate and extrastriate occipital areas (but see Büchel, Price, Frackowiak, & Friston, 1998b). Unlike Braille and non-Braille tactile discrimination tasks (Sadato et al., 1996; 1998; 2002), simple sensori-motor tasks involving no discrimination such as passive tactile stimulation (Sadato et al., 1996; 1998) and finger tapping (Gizewski et al., 2003) did not elicit similar occipital activations suggesting that complex high-level tasks only engage occipital regions in the blind. Taken together, these studies compellingly demonstrated that blind individuals massively activate occipito-temporal areas during Braille reading[2].

Neuroimaging evidence of crossmodal activations of the “visual” cortex in blind individuals during Braille reading does not prove that these areas are functionally relevant for non-visual processing. These activations may simply

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[2] Because our empirical contribution has employed fMRI in order to investigate crossmodal plasticity in blind individuals, we have focused on TEP and fMRI studies in this chapter. Aside from this work, a wealth of electrophysiological studies have consistently demonstrated that electrophysiological components display a more posterior distribution in blind compared to sighted subjects during a variety of tasks such as Braille reading (Uhl, Franzen, Lindinger, Lang, & Deecke, 1991; Uhl et al., 1994), detection of deviant sounds in frequency (Kujala et al., 1995), or intensity (Liotti, Ryder, & Woldorff, 1998), spatial localization of sounds (Leclerc, Saint-Amour, Lavoie, Lassonde, & Lepore, 2000; Röder et al., 1999) and more recently, voice identification (Föcker, Best, Hölig, & Röder, 2012).

reflect an epiphenomenon resulting from irrelevant neural activations. In order to demonstrate a causal role between a given brain region and a particular perceptual or cognitive function, researchers have turned to lesions that are either induced by a neurological condition or elicited experimentally via transcranial magnetic stimulation (TMS) ("virtual lesion") (Pascual-Leone, Walsh, & Rothwell, 2000). Clear evidence accounting for the necessary role of the occipital cortex in Braille reading comes from observations reported in a case study (Hamilton, Keenan, Catala, & Pascual-Leone, 2000). A woman had been blind since birth due to retinopathy of prematurity and was a proficient Braille reader. At the age of 62 years old, she suffered from a bilateral posterior artery stroke that lead to large bilateral occipital lesions (Figure 1B). Since then, she developed alexia for Braille while other more simple tactile discrimination abilities (e.g. tactile object recognition) remained unaffected. She described being able to *feel* Braille dots but could not *make sense* of this tactile perception. In the same vein, TMS studies have demonstrated that transient disruption of the medial occipital cortex induces a significant increase in error rates when early blind individuals read Braille letters (Cohen et al., 1997; Kupers et al., 2007) or embossed Roman letters (Cohen et al., 1997) whereas it has no effect on sighted control participants during the haptic identification of embossed Roman letters (Cohen et al., 1997) (Figure 1C). In contrast, TMS targeting the somatosensory cortex contralateral to the reading hand does not alter reading performance in the blind (Cohen et al., 1997; Kupers et al., 2007) whereas it alters performance in sighted control participants discriminating embossed Roman letters by touch (Cohen et al., 1997) (Figure 1C). These findings suggest that individuals with typical visual experience do not recruit the occipital cortex for tactile identification of Roman letters as early-blind individuals do for Braille reading and haptic identification of Roman letters (Cohen et al., 1997). In the latter study, Cohen and colleagues (1997) further reported that occipital stimulation using TMS occasionally elicited distorted somatosensory perceptions in early-blind subjects. This anecdotal report was more recently confirmed in a TMS study demonstrating that stimulation applied over the occipital cortex induces parasthesiae in the fingers of Braille blind readers in the absence of any tactile stimulation (Ptito, Fumal, de Noordhout, Schoenen, Gjedde, et al., 2008a). In contrast and replicating previous findings (Cowey & Walsh, 2000), the same experimental manipulation performed in individuals with typical visual experience induced phosphenes (Ptito, Fumal, de Noordhout, Schoenen, Gjedde, et al., 2008a).

Taken together, these early findings were interpreted as suggesting that, when deprived of visual input early in life, the occipital cortex reorganizes in order to perform tactile processing in a functionally-relevant manner, notably in order to support Braille reading. However, other studies at the time revealed task-dependent occipital responses in early blind subjects during various tasks other than tactile processing, such as during the spatial localization of sounds compared to rest (Weeks et al., 2000) or during mental imagery of shape triggered by sounds of objects compared to a control auditory condition (De Volder et al., 2001). Other studies, described in the next section, provided evidence suggesting that task-dependent increases of activation in occipital areas during Braille reading in the blind might underlie linguistic processes *per se*.

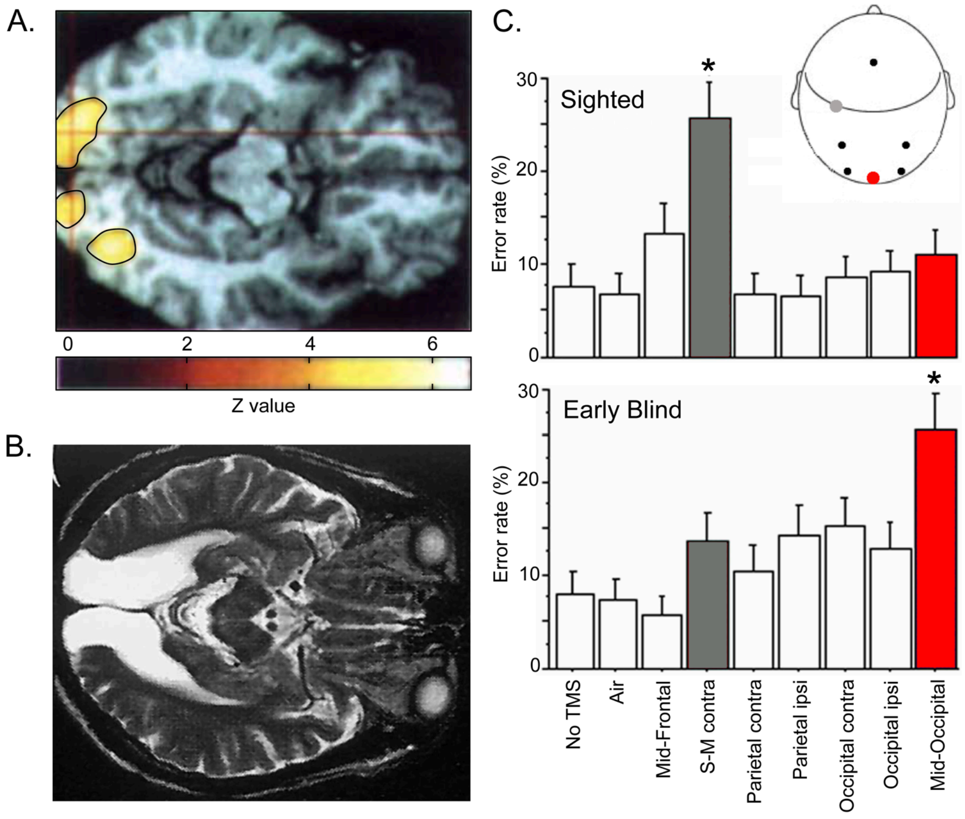

***Figure 1. Occipital cortex participation in Braille reading in the early blind brain**. (A) Activation map for Braille reading compared to rest in a group of early blind participants. Color bar represents Z values. (B) Anatomical MRI image of the patient described by Hamilton et al. (2000) denoting large bilateral occipital lesions resulting from a cerebrovascular accident. (C) TMS applied over the mid-occipital cortex (red) alters performance of early blind participants reading Braille. In contrast, this has no effect on*

the performance of sighted control participants performing a tactile discrimination task on embossed Roman letters. Opposite findings are observed when applying TMS over the somatosensory cortex contralateral to the reading hand (gray). Adapted from Sadato et al. (1996) (A), Hamilton et al. (2000) (B) and Cohen et al. (1997) (C).

1.2. Language and verbal memory

Röder and colleagues (2002) demonstrated that auditory speech processing elicited activations of striate and extrastriate occipital regions in congenitally blind subjects but not in sighted control subjects. Interestingly, activity level in occipital areas increased as a function of syntactic difficulty and semantic demands in congenitally blind participants, suggesting that these responses were related to linguistic/conceptual processing rather than to basic auditory operations (Röder, Stock, Bien, Neville, & Rösler, 2002). Focusing on semantic retrieval, other studies demonstrated increases in task-related occipital activations when early blind subjects performed semantic decisions on heard nouns (Noppeney, Friston, & Price, 2003) or covertly generated semantically related verbs to heard nouns (Amedi et al., 2003; Burton, Snyder, Diamond, & Raichle, 2002b) compared to control conditions matched for low-level characteristics. In the same vein, Burton and colleagues (2003) investigated this issue using lists of verbally presented words and observed preferential occipital activations in early-blind subjects during the covert generation of semantically-related words relative to the covert generation of phonologically-related words (Burton, Diamond, & McDermott, 2003) (Figure 2A). These occipital activations were not observed in sighted control subjects (Figure 2A). Importantly, the functional relevance of occipital cortex involvement in verb generation was accounted by Amedi and colleagues (2004) in a TMS study. These authors reported that transient disruption of the left primary visual cortex (V1) increased the error rate during a verb generation task in early blind but not sighted subjects (Amedi et al., 2004) (Figure 2B). A similar trend was also observed when TMS was applied over the left lateral occipital complex (LO). In contrast, TMS applied over a control site in the somatosensory cortex (S1) did not affect performance in either group (Figure 2B). Interestingly, among the errors elicited by the application of TMS over the occipital cortex of the blind, the authors noted a larger proportion of semantic errors compared to phonological and morphosyntatic errors, suggesting that TMS interfered more specifically with semantic verbal processing.

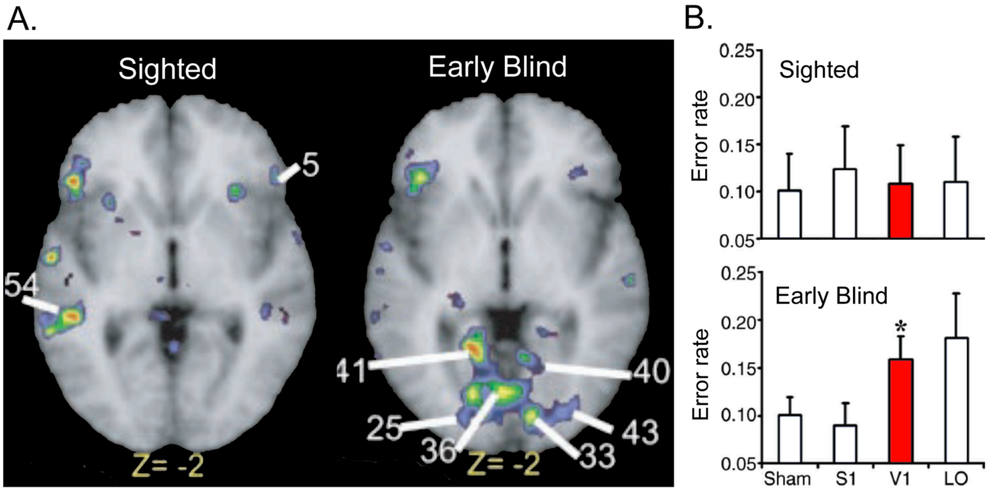

Figure 2. Occipital recruitment during linguistic tasks in the early blind brain. *(A) Differential activations observed in a group of sighted and early blind subjects during a covert verb generation task implying the generation of semantically-related vs. phonologically-related verbs in response to heard nouns. Large occipital activations are observed in early blind but not in sighted subjects. (B) TMS applied over the occipital pole (V1) alters behavioral performance in a similar verb generation task in early blind but not sighted subjects. A similar trend is observed when TMS is applied over the left lateral occipital complex (LO). In contrast, TMS application over the primary somatosensory cortex (S1) has no effect on behavioral performance in either group. Adapted from Burton et al. (2003) (A) and Amedi et al. (2004) (B).*

In another fMRI study (Amedi et al., 2003), congenitally blind and sighted control participants covertly recalled a list of previously learned abstract words in the absence of any sensory stimulation. Congenitally blind but not sighted controls showed increased activations in striate and extrastriate occipital areas during this verbal memory task relative to a rest condition (Figure 3, left-hand). At the behavioral level, congenitally blind participants outperformed the sighted in an old/new recognition test conducted 6 months later as well as in verbal memory tests from the Wechsler Intelligence Scale. Interestingly, individual performance on these tests positively correlated with the magnitude of V1 activation measured during covert recall of the words in the scanner (Amedi et al., 2003) (Figure 3, right-hand): the higher the behavioral performance in the memory tests, the higher the activity measured in V1. A follow-up study (Raz, Amedi, & Zohary, 2005) conducted one year later with the same blind participants measured brain activity when these participants performed a recognition task on the words initially learned before the first scan. This study revealed that individual magnitude of activation in V1 during the recognition task was positively correlated to online memory performance. Altogether, these findings suggest a functional involvement of the visually-deprived occipital cortex in episodic verbal memory and further indicate that this crossmodal recruitment may account for the superior verbal memory abilities observed in the blind at the behavioral level (Amedi et al., 2003; Röder & Rösler, 2003; Röder, Rösler, & Neville, 2001).

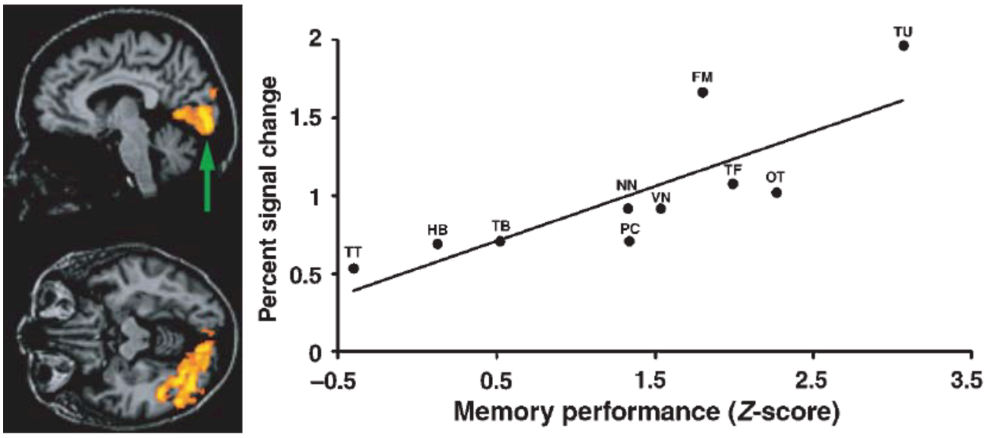

Figure 3. Occipital involvement in episodic verbal memory in the early blind brain. *Left-hand image displays activity observed in a group of congenitally blind subjects during the covert recall of a list of previously learned words (no sensory stimulation) compared to a rest condition. Right-hand graph plots activation of V1 during this task in each blind subject relative to this subject's own behavioral performance in a verbal memory test from the Wechsler Intelligence Scale (immediate recall). Adapted from Amedi et al. (2003).*

In summary, early neuroimaging studies demonstrated a massive reorganization of brain functions in early blind subjects so that the occipital cortex, typically devoted to vision, is activated during numerous non-visual tasks. Importantly, this crossmodal plasticity is considered compensatory because it may correlate with superior non-visual performance and TMS delivered on the occipital cortex alters non-visual functions in the blind. Based on these findings, one might wonder whether the occipital cortex of the blind reorganizes in a general manner so that it is indifferently devoted to various tasks and sensory modalities, or whether sub-regions within the occipital cortex may develop specialized functional characteristics after early visual deprivation. Amedi and colleagues (2003) reported that different portions of the occipital cortex in congenitally blind subjects were preferentially responsive to Braille reading on the one hand, and verb generation and verbal memory on the other hand (Amedi et al., 2003). These authors were among the first to propose that, rather than being generally-responsive to the non-visual modalities, the visually-deprived occipital cortex may be organized in a topographical fashion, much like the visual cortex is for specific visual functions in the sighted brain.

2. Functional specialization in crossmodal plasticity

In sighted individuals, the existence of separate hierarchical pathways for object identification (the ventral "what" stream) and object localization/grasping in space (the dorsal "where" stream) appears as a general principle of organization of the visual cortices (Goodale & Milner, 1992; Haxby et al., 1991). Beyond this general dual-stream segregation, a division of labor further characterizes the visual cortices, whereby different functional regions or modules process different aspects of vision. In the last decade, increasing evidence has accounted for the idea that crossmodal plasticity in individuals deprived of vision early in life follows organizational principles that maintain a similar segregation of the "visual" cortex for non-visual processing (for reviews see Collignon, Voss, Lassonde, & Lepore, 2009b; Dormal & Collignon, 2011; Voss & Zatorre, 2012). In this perspective, specialized regions of the "visual" cortex in early blind individuals continue to serve the same function although there is a shift in the primary sensory modality on which these regions operate (Pascual-Leone & Hamilton, 2001).

2.1. Dorsal visual pathway and spatial processing[3]

Visual areas hMT+/V5 and dorsal V3/V3A have been extensively described as underlying motion perception in the visual modality (Sunaert, Van Hecke, Marchal, & Orban, 1999; Tootell et al., 1995; Watson et al., 1993). In blind individuals who have lost vision at birth or soon after birth, the putative homolog of these regions show responses to motion albeit in the auditory (Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone, 2010; Poirier et al., 2006) and in the tactile (Matteau, Kupers, Ricciardi, Pietrini, & Ptito, 2010; Ricciardi et al., 2007) modalities. Moreover, activation in response to auditory motion in putative homolog of area hMT+/V5 in blind individuals reflects the direction of perceived moving sounds (Wolbers, Zahorik, & Giudice, 2011b), a property that is known to characterize this region in the sighted brain for visually moving stimuli (Born & Bradley, 2005). These findings have accounted for the notion

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[3] This section is a modified version of published work: Dormal, G., Lepore F., & Collignon, O. (2012). Plasticity of the dorsal "spatial" stream in visually deprived individuals. *Neural Plasticity*, 2012, 687659.

that crossmodal activations in response to auditory dynamic stimulation in these regions have a functional role in non-visual motion processing rather than representing unspecific activation. In the same vein, several studies using different paradigms and neuroimaging techniques have consistently demonstrated that spatial hearing in the early blind leads to dorsal occipital recruitment, mainly in the right, spatially-dominant, hemisphere. In a PET study, Weeks and collaborators (2000) reported that sound localization, compared to rest, strongly activated association areas in the right dorsal occipital cortex of early blind individuals but not sighted controls (Weeks et al., 2000). Another PET study extended these findings demonstrating that several regions in the right dorsal extrastriate cortex correlated with sound localization performance, accounting for the functional relevance of these activations (Gougoux et al., 2005). Similar findings were later reported by Voss and colleagues (2008) in the left dorsal extrastriate cortex during a monaural sound source discrimination task (Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008). Interestingly, specific recruitment of right dorsal occipital regions in early blind individuals for spatial processing occurs not only for auditory but also for tactile inputs (Renier et al., 2010).

Recently, Collignon and colleagues (2011) characterized brain activity in congenitally blind and sighted individuals while participants were performing a discrimination task on pairs of sounds differing either in terms of location in space or in pitch (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). In this study, a staircase paradigm was used in order to equalize the difficulty level across tasks and participants. The spatial localization task relative to the pitch discrimination task was shown to preferentially map onto specialized sub-regions of the right dorsal occipital stream in the congenitally blind group but not in the sighted group (Figure 4A). The two main activated regions were the right cuneus and the right middle occipital gyrus in the vicinity of regions that have previously been described in the sighted as the dorsal V3/V3A and the complex hMT+/V5, involved in visuospatial and visual motion processing (Haxby et al., 1991; Sunaert et al., 1999). Although the task implicated auditory localization rather than motion processing, the authors hypothesized that hMT+/V5 was activated because the task generated a vivid perception of apparent motion (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). Functional connectivity analyses further demonstrated that these occipital regions were part of a larger parieto-frontal network including multisensory regions (i.e. the inferior parietal lobules, the intraparietal sulcus and the superior frontal gyrus) that are typically involved in spatial attention and awareness (Szczepanski, Konen, & Kastner, 2010) (Figure 4A). In other words, it appears that the dorsal occipital regions recruited by spatial hearing in the early blind are inherently part of the network involved in auditory localization (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). Hence, these authors proposed that this pattern of connectivity may constrain regions with a similar function to reorganize in a functionally specific manner.

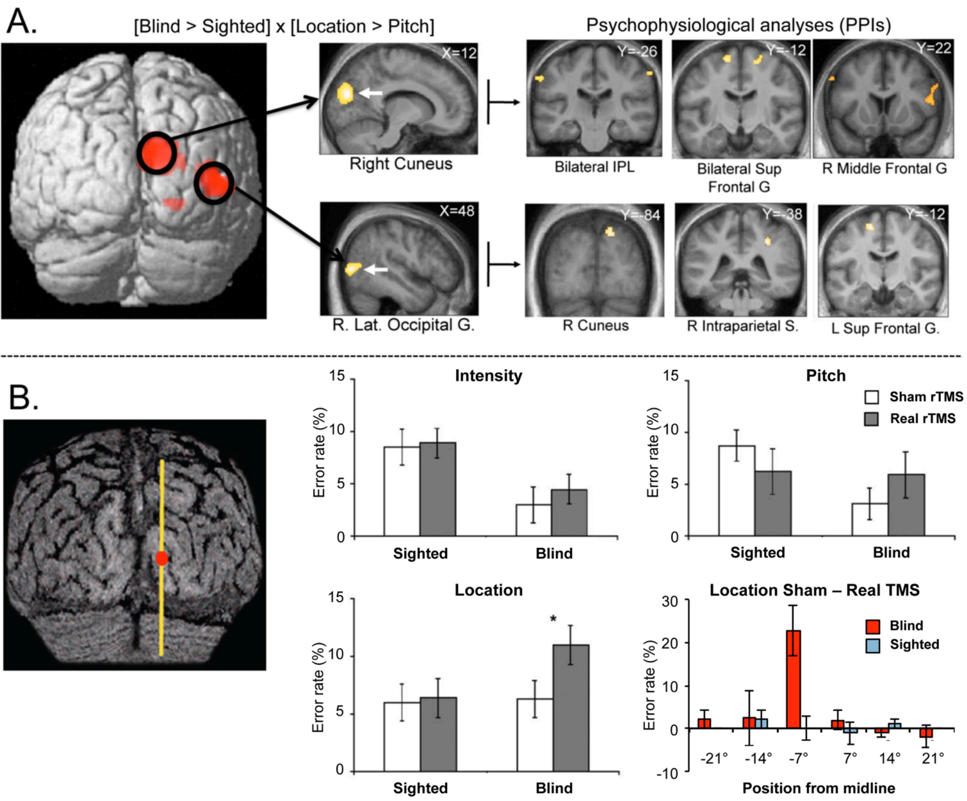

Figure 4. Recruitment of right dorsal occipital regions for spatial hearing in early blind individuals. *(A) Activations for the spatial over the pitch processing of sounds in early blind subjects relative to sighted controls. The right part of the figure displays psychophysiological interaction results using the two main activity peaks as seed areas. (b) Real rTMS applied over the right dorsal extrastriate occipital cortex (BA 18) leads to a significant increase in error rate in early blind subjects and selectively for the sound location/spatial task. The histogram on the right bottom of the figure represents the percentage of errors in the spatial location task in early blind and sighted subjects for the real rTMS condition minus the sham TMS condition (isolating the effect of the TMS), as a function of sound position. Negative values on the x-axis are refer to the left external space, positive values on the x-axis refer to the right external space. Adapted from Collignon et al. (2011b (A), 2007 (B)).*

TMS studies have further accounted for the functional relevance of the right dorsal occipital recruitment observed for spatial hearing in the early blind brain (Collignon et al., 2007; Collignon, Davare, Olivier, & De Volder, 2009a). Notably, Collignon and collaborators (2007) demonstrated that the stimulation of the right dorsal extrastriate occipital cortex disrupted auditory spatial localization abilities in early blind but not sighted controls participants, while pitch and intensity perception remained unaffected in either group (Collignon et al., 2007) (Figure 4B). Interestingly, the detrimental effect of TMS in the early blind group during the spatial localization task was strongly driven by a disruption in the ability of blind individuals to locate sounds presented at the closest position relative to the reference sound in the contralateral (left) field relative to the right-sided site of stimulation (Dormal, Lepore, & Collignon, 2012). This is consistent with evidence from the sighted literature documenting a contralateral field preference in several visual areas along the dorsal pathway including V3/V3A and the posterior portion of hMT+/V5 (Dukelow et al., 2001; Tootell et al., 1995; 1997). These results further stress the notion that crossmodal recruitment of the dorsal stream in early blind individuals is functionally-relevant and somehow follows similar computational constraints as those observed in sighted individuals when processing visual inputs.

2.2. Ventral visual pathway and object identification

Aside from the dorsal occipital recruitment for motion and spatial processing documented in the early blind, other studies reported activations along the ventral occipito-temporal pathway during tasks involving the identification/recognition of an auditory or a tactile stimulus. Among early neuroimaging studies described in the first section of this chapter, several found occipito-temporal activations that were more extended in the left – language-dominant – hemisphere during tasks involving semantic decisions (Noppeney et al., 2003), covert speech production (Amedi et al., 2003; Burton et al., 2003; Burton, Snyder, Diamond, & Raichle, 2002b; Ofan & Zohary, 2007) and during the retrieval (Amedi et al., 2003) (Figure 3, left-hand) and recognition of verbal material (Raz et al., 2005). Left-lateralized striate and extrastriate occipital activations were reported more recently in a group of congenitally blind subjects (but not sighted subjects) for speech comprehension compared to meaningless or reversed speech (Bedny, Pascual-Leone, Dodell-Feder, Fedorenko, & Saxe, 2011). Similarly, several early studies exploring the neural correlates of Braille reading in early blind individuals using different control tasks (see section 1 of this chapter), reported more extended occipital activations in the left hemisphere (Amedi et al., 2003; Burton, Snyder, Conturo, Akbudak, Ollinger, et al., 2002a; Büchel, Price, Frackowiak, & Friston, 1998b; Gizewski et al., 2003).

Most interestingly, Büchel and colleagues (1998) compellingly demonstrated that the reading of Braille words, when contrasted to the reading of non-words Braille strings, elicits focal activations in an area localized in the anterior portion of the left fusiform gyrus in congenitally blind subjects (Büchel, Price, & Friston, 1998a) (Figure 5A). In the same study (Büchel, Price, & Friston, 1998a), an independent visual experiment performed in a group of sighted participants revealed that this region overlapped with a region responding selectively to written strings (Figure 5A), later referred to as the Visual Word Form Area (VWFA) (L. Cohen et al., 2000). These findings were recently replicated by Reich and colleagues (2011) in a separate group of congenitally blind and sighted participants (Reich, Szwed, Cohen, & Amedi, 2011) (Figure 5B).

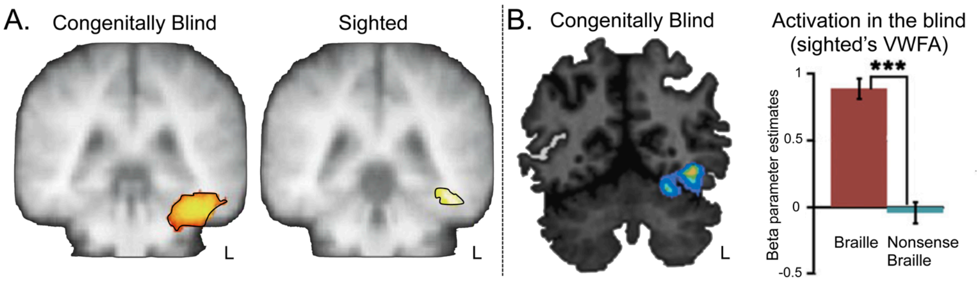

Figure 5. Braille reading in the early blind brain. *Braille reading of words compared to non-words activates a region in the left fusiform gyrus in congenitally blind subjects as shown on coronal slices in (A, left-hand) and (B). This region overlaps with the VWFA responding selectively to written words in sighted subjects (A, right-hand). The graphic on the right-hand of the figure represents estimated activity for Braille reading of words compared to non-words in a region-of-interest corresponding to the sighted's VWFA. Adapted from Büchel et al. (1998a) (A) and Reich et al. (2011) (B).*

In sighted subjects, a large portion of the lateral and ventral visual cortices, referred to as the lateral occipital complex (LOC), is preferentially responsive to pictures of objects relative to scrambled objects (Malach et al., 1995) and is well known for its involvement in object recognition (Grill-Spector, Kourtzi, & Kanwisher, 2001). Several studies have documented selective activations within LOC when early blind individuals process shape information about objects using the preserved non-visual modalities. Notably, increased activity within sub-regions of LOC in early blind subjects was demonstrated during the tactile exploration of objects (Amedi, Raz, Azulay, & Malach, 2010), during shape imagery tasks triggered by sounds of objects (De Volder et al., 2001) or by their names (Peelen, He, Han, Caramazza, & Bi, 2014) and when processing object's shape with auditory "soundscapes" provided by prosthetic visual-to-auditory devices (Amedi, Stern, Camprodon, & Bermpohl, 2007a; Merabet et al., 2009).

Studies in the field have further attempted to examine the role of visual experience in shaping category-specific representations of objects within the ventral visual cortex, by investigating the presence of similar category-related responses in people who are born blind or have lost sight early in life. For example, the presence of category-related patterns of activations for faces versus manmade objects within the fusiform gyri was reported in 4 early blind subjects, suggesting that visual experience is not necessary for category-related representations to develop in these regions (Pietrini et al., 2004). In the same vein, another study found that regions of the ventral stream characterized by category preferences for nonliving versus living objects in sighted participants (viewing pictures) displayed similar category preferences in 3 congenitally blind individuals performing a size judgment task on heard nouns of the same objects (Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009a). Using the same task, similar findings were recently reported in a group of congenitally blind subjects for manipulable objects (tools) in the posterior left middle temporal gyrus (Peelen et al., 2013) and large non-manipulable objects in the parahippocampal gyri bilaterally (He et al., 2013)[4]. Human voices are a very specific category of sounds considered as the auditory counterpart of faces for person identification (Campanella & Belin, 2007). Interestingly, regions within the right fusiform gyrus in the vicinity of areas involved in face processing in the sighted brain (Kanwisher, McDermott, & Chun, 1997; Rossion, Hanseeuw, & Dricot, 2012) display stronger responses to human voices relative to object sounds (Gougoux et al., 2009) and larger voice priming effects in congenitally blind individuals compared to sighted subjects (Hölig, Föcker, Best, Röder, & Büchel, 2014).

In summary, whereas specific dorsal occipital regions with a right hemispheric dominance are activated during tasks involving spatial localization and motion, ventral occipital regions in the early blind seem to maintain a preferential coding for the processing of stimulus identity. This suggests that the dual-stream segregation of ventral and dorsal cortical pathways develops in the absence of early visual experience (Dormal & Collignon, 2011; Voss & Zatorre, 2012). A recent study noted that the major difference characterizing tasks

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[4] see also Wolbers, Klatzky, Loomis, Wutte, & Giudice, 2011a for related findings

evoking activations in the dorsal or the ventral “visual” areas in the blind may be their reliance on semantic information (Hölig et al., 2014). Speech comprehension and production, semantic processing, verbal memory, objects and voice identification, in contrast to spatial and motion processing, are cognitive functions that imply the retrieval of semantic information and its association with the percept such as its name or its meaning.

Beyond this dual-stream organization of the “visual” cortex, the anatomo-functional similarity observed between occipital regions activated by specific non-visual tasks in the early blind and the ones associated to analogue functions in the visual modality in the sighted, suggests that these areas may retain their functional coding ability despite visual deprivation. Hence, rather than being a tabula rasa at birth, the “visual” cortex appears to be organized into specific computational units that are biased towards the accomplishment of a particular function. However, the sensory input to perform this function appears to be experience-dependent, so that the “visual cortex” may be reoriented towards the non-visual modalities, at least when vision is lost early in life.

2.3. Non-visual activations in the visual cortex of the sighted

A growing body of evidence suggests that tactile and auditory processing may elicit task-specific activations in the visual cortex even in subjects with typical visual experience. For instance, several groups have shown that hMT+/V5 responds to auditory (Alink, Singer, & Muckli, 2008; Poirier et al., 2005; Strnad, Peelen, Bedny, & Caramazza, 2013; Warren, Zielinski, Green, Rauschecker, & Griffiths, 2002) and tactile motion (Blake, Sobel, & James, 2004; Hagen et al., 2002; Ricciardi et al., 2007; van Kemenade et al., 2014) in sighted subjects. Likewise, sub-regions of LOC are responsive when sighted individuals process shape information through the haptic exploration of objects (Amedi et al., 2010; Amedi, Jacobson, Hendler, Malach, & Zohary, 2002; Amedi, Malach, Hendler, Peled, & Zohary, 2001; Amedi et al., 2007; Snow, Strother, & Humphreys, 2014; Zhang, Weisser, Stilla, Prather, & Sathian, 2004) but not when they must recognize objects by their characteristic sound (Amedi et al., 2002; 2007b). In the same vein, size judgment tasks based on heard nouns of living versus non-living objects (Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009b), manipulable (Peelen et al., 2013) and non-manipulable objects (He et al., 2013) lead to category-specific patterns of activation in the ventral visual pathway of sighted subjects.

Observations of overlapping task-related increases of activation in response to visual and non-visual stimuli in the sighted visual cortex, joined to reports of co-localized non-visual responses in the sighted and the early blind brain, have lead some researchers to propose an influential theory of the brain as a metamodal or supramodal structure (Pascual-Leone & Hamilton, 2001; Reich et al., 2012; Ricciardi & Pietrini, 2011). According to this theory originally proposed by Pascual-Leone and Hamilton (2001), distinct functional areas, including regions that are classically considered as purely unisensory, are characterized by the computation or function they execute (i.e. spatial processing, shape processing) regardless of the sensory input modality on which they operate (Pascual-Leone & Hamilton, 2001). These so-called "operators" may show a preference for a given sensory modality according to the suitability of this sensory modality for a given computation. For example, right dorsal extrastriate areas are thought to be "visual" regions only because these regions are originally suited to perform spatial processing, a computation for which vision (compared to touch or sound) provides the most informative cues (e.g. distance, space, size). In the case of visual deprivation however, these regions would execute their assigned function based on the remaining sensory information. According to more recent interpretations of this theory (Reich et al., 2012; Ricciardi & Pietrini, 2011), the "visual" cortex (and the brain in general) represents information in a highly abstract form and its functional organization develops in the absence of any visual experience. For instance, LOC was proposed to act as a metamodal operator for shape, subtending form processing independently of the modality through which this information is provided and independently of previous visual experience with shape (Amedi et al., 2001; 2002; 2007b; 2010; Peelen et al., 2014; Ptito et al., 2012). In the same vein, the hMT+/V5 complex is considered by some as a metamodal operator for motion (Ricciardi et al., 2007) and the VWFA as a metamodal reading center (Reich et al., 2011) for reviews see (Reich et al., 2012; Ricciardi & Pietrini, 2011).

Most of the studies reporting crossmodal occipital task-related activations in sighted subjects have discussed the possible implication of mental visual imagery and have considered it unlikely. Nevertheless, clear evidence has accounted for the fact that mental visual imagery in the absence of any stimulation elicits reliable responses in the visual cortex of sighted subjects (Kosslyn et al., 1993; Slotnick, Thompson, & Kosslyn, 2005) for a review see (Kosslyn & Thompson, 2003), and that such mechanisms may in fact facilitate performance during non-visual tasks and mediate occipital cortical involvement (Sathian, Zangaladze, Hoffman, & Grafton, 1997; Zhang et al., 2004). In other words, occipital crossmodal activation reported in sighted individuals may simply stem from top-down visual imagery processes triggered by somatosensory or auditory input, casting doubt on the idea that this involvement is "metamodal" or independent of sensory modality. In support of this assumption, De Volder and colleagues (2001) demonstrated robust and selective activations in bilateral LOC when sighted participants listened to object sounds and were explicitly asked to mentally visualize the shape of the corresponding objects (De Volder et al., 2001). Moreover, the observation of crossmodal responses in the sighted visual cortex during non-visual tasks is far from being unequivocal. Many studies haven't reported such findings and others have even demonstrated *de*activations in extrastriate visual regions of the sighted brain during non-visual tasks (Bedny et al., 2010; Collignon et al., 2013; Gougoux et al., 2005; Lewis, Beauchamp, & DeYoe, 2000; Renier et al., 2010; Saenz, Lewis, Huth, Fine, & Koch, 2008; Voss, Lepore, Gougoux, & Zatorre, 2011), possibly as a result of inhibitory mechanisms acting in order to reduce interference from distracting visual inputs (Laurienti et al., 2002).

3. Sensitive periods for crossmodal plasticity in the blind

Most research demonstrating crossmodal reorganization and superior behavioral performance in the blind has been carried out in individuals who are blind since birth or have lost sight early in life. Investigating those who have lost sight later in life, after the development of the visual system, provides a unique window into the existence of sensitive periods modulating the effects of visual deprivation on the reorganization of the occipital cortex. One of the pioneer studies investigating glucose metabolism in blind human adults at rest also examined late blind individuals (Veraart et al., 1990). Early blind subjects displayed larger activity in the occipital cortex compared to sighted control individuals with eyes closed, whereas late blind individuals showed the opposite pattern (Figure 6). Hence, the onset of visual deprivation is likely to play a determining role in the changes encountered by the occipital cortex following visual deprivation. In line with this assumption, a couple of studies suggested the existence of a critical period, beyond which visual deprivation leads to little or no crossmodal reorganization in the occipital cortex, especially in V1 (Cohen et al., 1999; Sadato et al., 2002). However, this view was challenged by studies demonstrating that the visually-deprived brain is capable of experience-dependent plasticity even in adulthood, albeit to a lesser extent than in early blind individuals.

In a PET study, Büchel and colleagues (1998) were among the first to demonstrate the existence of task-dependent activations of occipital areas in late-onset blind individuals during Braille reading and auditory word processing (Büchel, Price, Frackowiak, & Friston, 1998b). Similar findings were subsequently reported for a variety of tactile and of verbal auditory tasks in a series of studies conducted by Burton and collaborators (Burton et al., 2003; Burton, Sinclair, & McLaren, 2004; Burton, Snyder, Conturo, Akbudak, Ollinger, et al., 2002a; Burton, Snyder, Diamond, & Raichle, 2002b). In all of these studies except one (Büchel, Price, Frackowiak, & Friston, 1998b), task-dependent occipital activations during non-visual processing were somewhat more extended in early blind compared to late blind subjects. Aside from these *quantitative* differences, crossmodal plasticity in those who have lost sight later in life seems to also differ *qualitatively* from the one that characterizes the occipital cortex of early blind individuals (for a review see Voss, 2013), notably in terms of functional relevance, and of functional specialization.

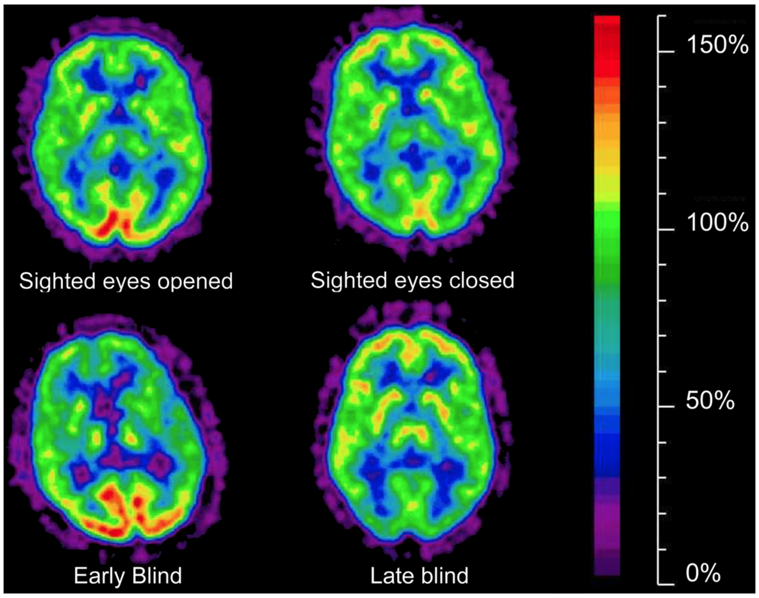

Figure 6. Glucose metabolism at rest in sighted and blind subjects. *Glucose metabolism maps are displayed in a sighted subject with eyes opened (top-left) and eyes closed (top-right), in an early blind subject (bottom-left) and in a late blind subject (bottom-right). Glucose utilization is more elevated in the occipital cortex of early blind subjects than in sighted subjects with eyes closed and in late blind subjects. Adapted from Veraart et al. (1990).*

3.1. Functional relevance of late acquired blindness

Although occipital activations were documented in late blind subjects when performing an auditory spatial localization task (Voss et al., 2008; Voss, Gougoux, Lassonde, Zatorre, & Lepore, 2006), this crossmodal activity has not been associated with enhanced behavioral abilities, unlike what is typically reported in early blind individuals. Voss and collaborators (2008) reported that occipital regions that were negative predictors of behavioral performance in an auditory localization task were the regions most strongly activated in late blind subjects (Voss et al., 2008). Hence, far from being beneficial, crossmodal activity may even be detrimental in cases of late onset visual deprivation. This observation parallels the finding of a recent fMRI study conducted in a group of late blind participants scanned while performing pitch and spatial discrimination tasks (Collignon et al., 2013). In this study, regression analyses were performed between the number of years of total blindness and brain activity triggered by auditory processing. Surprisingly, the strength of auditory activity measured in several regions of the occipital cortex was *inversely* related to the total duration of blindness. In other words, those individuals who were in the dark for a shorter amount of time were the ones displaying the largest crossmodal activity in these occipital regions. This finding is thus opposed to what would have been expected if activity in these regions reflected a compensatory effect of visual deprivation (related for example, to a longer experience in relying on auditory and tactile modalities). Further accounting for the functional irrelevance of crossmodal occipital activations observed in late blind, Cohen and colleagues (1999) demonstrated that transient disruption of the medial occipital cortex using TMS affected Braille reading performance in congenitally and early blind participants, but not in late blind subjects (Cohen et al., 1999). Together, these findings argue against a compensatory effect of crossmodal activity in late-onset blind individuals.

3.2. Functional specialization of late acquired blindness

As described in Section 2 of this chapter, increasing evidence has accounted for the notion that the functional organization of the “visual” cortex is somewhat preserved after visual deprivation, at least when occurring early in life. Recent research has begun to examine the existence of sensitive periods for the maintenance of functional specialization in crossmodal plasticity. Collignon and colleagues (2013) reported robust crossmodal recruitment of occipital cortex during auditory processing in both congenitally blind and late blind individuals irrespective of the task. Crucially however, the preferential activation of right dorsal occipital regions for auditory spatial (over pitch) processing and its increased connectivity with a fronto-parietal network was only observed in the former group (Collignon et al., 2013) (Figure 7A, left-hand). Similar findings were reported in another study investigating speech comprehension in congenitally blind and late blind individuals (Bedny, Pascual-Leone, Dravida, & Saxe, 2012). Again, while robust crossmodal occipital activations were observed in both blind groups for unspecific auditory processing (speech relative to rest), only the congenitally blind displayed left-lateralized occipital responses for speech (over backward speech) processing (Bedny et al., 2012) (Figure 7A, right-hand). In the same vein albeit using a region-of-interest approach, Bedny and colleagues (2010) demonstrated that the putative homolog of hMT+/V5 responded to auditory moving sounds in congenitally blind subjects but not in sighted controls or late blind participants (Bedny et al., 2010) (Figure 7B). Interestingly, no motion preference was observed in an early-blind individual who had functional vision until he lost it between 2 and 3 years of age (Figure 7B). Taken as a whole, these observations are suggestive of an early sensitive period during which the absence of visual input drives different occipital regions to develop selective crossmodal responses to specific non-visual inputs.

Altogether, these findings support the notion that the expression of blindness-induced plasticity is critically dependent on the developmental period of blindness onset. Unlike crossmodal plasticity observed in early-blind subjects, the same phenomenon in late-onset blind subjects appears to be less extended and, most importantly, to be neither compensatory, nor functionally specific.

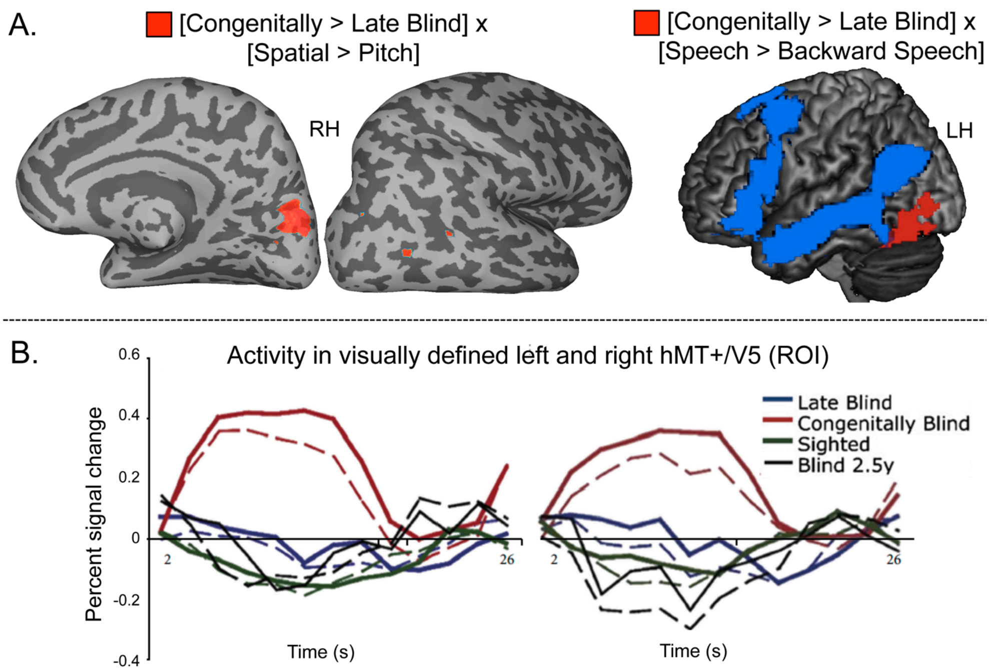

Figure 7. Sensitive periods for functional specialization in the occipital cortex of the blind. *Although crossmodal unspecific activations for auditory processing are present in the occipital cortex of the late blind (not shown here), only congenitally blind display specific responses for spatial localization of sounds in right dorsal extrastriate occipital areas (A, left-hand), and specific responses to heard speech in the left ventral occipito-temporal cortex (A, right-hand). Similarly, visual area hMT+/V5 responds to auditory looming sounds with high (straight lines) and low motion content (dashed lines) only in congenitally blind subjects, but not in sighted or late blind subjects, nor in an early blind subject who lost sight at the age of 2.5 years old. RH: right hemisphere, LH: left hemisphere. Adapted from Collignon et al. (2013) (A, left-hand), Bedny et al. (2010) (B) and Bedny et al. (2012) (A, right-hand).*

4. Outcomes for visual restoration and rehabilitation[5]

Understanding the plastic changes occurring along the visual pathway of the early- and the late- blind is of primary importance given current advances in the field of sensory rehabilitation technologies, whether they are of the invasive or of the non-invasive type (Collignon, Champoux, Voss, & Lepore, 2011a; Merabet, Rizzo, Amedi, Somers, & Pascual-Leone, 2005; Reich et al., 2012; Veraart, Duret, Brelén, Oozeer, & Delbeke, 2004).

4.1 Non-invasive interventions

Non-invasive interventions such as sensory-substitution devices, may take advantage of added neural resources in the processing of the remaining senses resulting from crossmodal plasticity (Reich et al., 2012). The concept of sensory substitution refers to the use of one sensory modality to supply information normally gathered from another sense (Bach-y-Rita, Collins, Saunders, White, & Scadden, 1969). Probably the most well-known and successful example is Braille reading, which allows provinding reading material to the blind brain through the spared tactile modality. Other examples concern the use of the long-cane as an extension of the body (Serino, Bassolino, Farnè, & Làdavas, 2007) and the use of sounds reverberation to locate obstacles and discriminate object size (Arnott, Thaler, Milne, Kish, & Goodale, 2013; Stroffregen & Pittenger, 1995). Such abilities represent domains of high proficiency in blind individuals, resulting from the combination of extensive training programs and neuroplastic changes. For instance, Braille reading skills are the result of extensive practice (Wong & Gnanakumaran, 2011) and, as reviewed earlier in this chapter, are associated with occipital function in the early blind brain (Büchel, Price, Frackowiak, & Friston, 1998b; Cohen et al., 1997; Hamilton et al., 2000; Kupers et al., 2007; Sadato et al., 1996; 1998; 2002). Other more sophisticated devices aimed at transforming visual information into auditory or tactile signals have also been developed (Bach-y-Rita, Kaczmarek, Tyler, & Garcia-Lara, 1998; Capelle, Trullemans, Arno, & Veraart, 1998) and have proven their efficacy for the recognition of complex shape information (Amedi et al., 2007; Arno, Capelle,

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[5] This section is a modified version of published work: Collignon, O., Dormal, G. & Lepore, F. (2012). Building the brain in the dark: functional and specific crossmodal reorganization in the occipital cortex of blind individuals. In: Jenkin, M., Steeves, J. & Harris, L. (Eds). *Plasticity in sensory systems,* Cambridge, University Press.

Wanet-Defalque, Catalan-Ahumada, & Veraart, 1999; Arno et al., 2001; Striem-Amit, Dakwar, Reich, & Amedi, 2012), the localization of objects (Proulx, Stoerig, Ludowig, & Knoll, 2008; Renier & De Volder, 2010; Renier et al., 2005; Striem-Amit et al., 2012) or the navigation in a "virtual" environment (Segond, Weiss, & Sampaio, 2005). While these devices presently suffer from a poor ergonomic value, as they are not yet at a point were they can be used efficiently in everyday life, they represent a potentially promising tool for rehabilitation in blind individuals. Moreover, because these non-invasive techniques of rehabilitation take advantage of the preserved non-visual abilities in the blind, they may be expected to be more efficient in early blind individuals rather than in late blind subjects.

4.2. Invasive interventions

Surgical interventions to restore sight rely on the integrity of the deprived visual system. In this case, crossmodal reorganization following visual deprivation might prevent the reorganized cortex from performing its original function efficiently, especially in those who have lost sight early in life (Collignon, Champoux, Voss, & Lepore, 2011a; Merabet et al., 2005; Reich et al., 2012; Veraart et al., 2004). In fact, the functional relevance and functional specificity characterizing crossmodal plasticity in the early blind brain is likely to interfere with the proper reacquisition of vision. In the same vein, the deterioration of optic and geniculo-cortical tracts associated to early visual deprivation[6] (Bridge, Cowey, Ragge, & Watkins, 2009; Noppeney, Friston, Ashburner, Frackowiak, & Price, 2005; Pan et al., 2007; Park et al., 2007; Ptito, Schneider, Paulson, & Kupers, 2008b; Shimony, 2005; Shu, Li, Li, Yu, & Jiang, 2009; Wang et al., 2013) is likely to compromise visual recovery. Support for the assumption that crossmodal plasticity might interfere with visual restoration comes from cases of sight recovery after longstanding blindness on the one hand, and from research conducted on deaf cochlear implant users on the other.

4.2.1. Cases of sight-recovery

Reported cases of sight-recovery individuals in adulthood following early-onset blindness have been associated with poor recovery of visual functions

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[6] Disuse-atrophy of the geniculo-cortical tracts has also been reported in late blind subjects (Voss, Pike, & Zatorre, 2014; Wang et al., 2013) although such findings are somewhat inconsistent (Schoth, Burgel, Dorsch, Reinges, & Krings, 2006; Zhang, Wan, Ge, & Zhang, 2012).

(Ackroyd, Humphrey, & Warrington, 1974; Carlson, Hyvärinen, & Raninen, 1986; Fine et al., 2003; Gregory, 2003; Gregory & Wallace, 1974; von Senden, 1960). Animals deprived of visual input during the critical period are functionally blind after re-opening of the eyes (Carlson, Pertovaara, & Tanila, 1987; Hyvärinen, Carlson, & Hyvärinen, 1981). These poor outcomes have been attributed to the idea that early visual deprivation deeply and permanently affects the development of the visual cortex and its ability to process visual information. In humans, two cases of sight-recovery, SB and MM, have been quite extensively described in the scientific literature (Fine et al., 2003; Gregory, 2003; Gregory & Wallace, 1974). SB lost effective sight at 10 months of age and received a corneal graft after fifty years as a blind person. MM became blind at 3 years old and received stem-cell transplant in his right eye at the age of 46. SB and MM presented striking similarities in their visual disabilities following sight restoration. Despite the fact that their retinas regained some functionality, they both encountered extreme difficulties interpreting what they saw, suggesting that these deficiencies were from central rather than from peripheral origins. Although they could recognize colors and simple shapes quite accurately, recognition of complex shapes (including faces and everyday life objects), perception of depth cues as well as detection of illusory contours were all abilities that were highly altered. In MM, these visual deficits were further accounted by neuroimaging evidence showing a massive reduction of activation to faces and objects in the fusiform and lingual gyri bilaterally (i.e., brain areas usually devoted to object and face perception) (Fine et al., 2003) (Figure 8C, left-hand) and an abnormal neural representation of the visual field (Levin, Dumoulin, Winawer, Dougherty, & Wandell, 2010) (Figure 8B). Seven years after the intervention, he still had poor spatial resolution and limited visual abilities that prevented him from efficiently relying on his vision in every day life (Levin et al., 2010; Saenz et al., 2008). In contrast to these marked difficulties encountered by SB and MM, motion perception abilities appeared to be quite well preserved in both cases despite years of blindness. MM for instance performed within normal limits in several motion tasks, whether he had to detect the direction of a moving pattern, or perceive the orientation or the shape of a moving object. Similarly, Gregory and Wallace (1963) reported that SB was only able to recognize certain objects in the environment provided they were moving. As such, motion cues constituted information on which these patients could rely more confidently in order to use their newly acquired vision in their day-to-day activities. Consistently with these preserved motion perception abilities, fMRI measures in MM documented normal size of area hMT+/V5 and normal activation in response to moving versus stationary visual stimuli when tested within months following sight restoration (Fine et al., 2003) (Figure 8C, right-hand) as well as 7 years later (Saenz et al., 2008) (Figure 10). In marked contrast to deficiencies observed in several aspects of vision, the preservation of motion perception abilities in both patients were interpreted as resulting from an earlier development of motion compared to form processing, the former being therefore more established prior to visual deprivation (Fine et al., 2003; Saenz et al., 2008)[7].

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[7] The pattern of preserved and deficient visual abilities reported in these patients parallels observations reported in individuals who were visually-deprived for a short period of time early during development because they were born or developed dense bilateral cataracts which were then surgically removed. These studies have documented epochs of time during development in which visual experience is necessary for the later undisturbed development of specific aspects of vision and have stressed that specific visual functions may have different sensitive periods (Lewis & Maurer, 2005). For instance, visual deprivation at birth, even when ending in the first two years of life, causes permanent deficits in visual acuity (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002), sensitivity to mid- and high- spatial frequencies (Ellemberg, Lewis, Maurer, Lui, & Brent, 1999; Maurer, Ellemberg, & Lewis, 2006), configural/holistic face processing (Le Grand, Mondloch, Maurer, & Brent, 2001; 2004), discrimination of faces from different viewpoints (Geldart, Mondloch, & Maurer, 2002; Putzar, Hötting, & Röder, 2010), detection of illusory contours (Putzar, Hötting, Rösler, & Röder, 2007) and sensitivity to the global direction of a unidirectionally moving stimulus (Ellemberg et al., 2002; Hadad, Maurer, & Lewis, 2012). In contrast, sensitivity to low spatial frequencies (Ellemberg et al., 1999) and perception of biological motion (Hadad et al., 2012) can fully recover from a period of early deprivation since birth. Interestingly, the loss of sight after a few months of age preserves the global detection of motion even when the period of blindness is extended as it is the case for SB and MM (Fine et al., 2003; Gregory & Wallace, 1974) but still can dramatically impair letter acuity (Lewis & Maurer, 2005) and peripheral light sensitivity (Bowering, Maurer, Lewis, & Brent, 1993). Although behavioral studies have suggested that detection of large shapes including facial features and face external contour can resist a period of early visual deprivation (Geldart et al., 2002; Le Grand et al., 2001; 2004; Mondloch et al., 2013; Putzar et al., 2010), recent EEG studies have demonstrated that the electrophysiological markers of face detection (Bentin, Allison, Puce, Perez, & McCarthy, 1996) differ in individuals lacking early visual experience compared to individuals with typical visual experience (Mondloch et al., 2013; Röder, Ley, Shenoy, Kekunnaya, & Bottari, 2013) and to individuals who have developed visual impairment later in life (Röder et al., 2013).

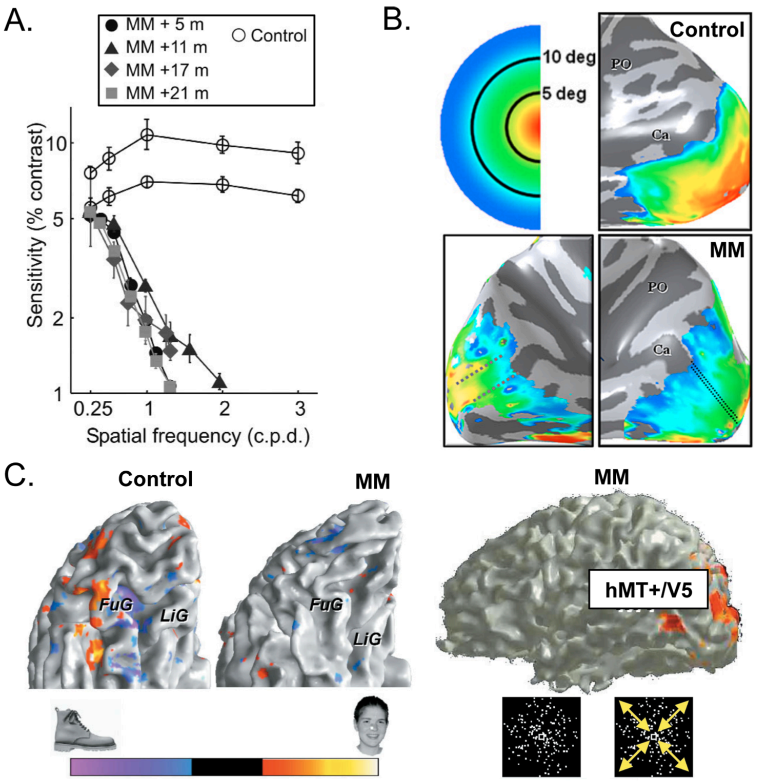

Figure 8. Findings collected in studies carried out with sight-recovery subject MM. *(A) MM's contrast sensitivity as a function of spatial frequency measured psychophysically 5 to 21 months after surgery. (B) Visual field eccentricity representation (central 14°) in medial occipital cortex of MM's left (left panel) and right (right panel) hemispheres. For comparison, visual field representation is also displayed for a sighted control subject. MM’s eccentricity map in peri-calcarine cortex differs from the controls as it shows a more extended representation of the peripheral visual (beyond about 10°) together with a lack of foveal representation at the occipital pole (below about 3°). (C, left-hand) Left hemisphere activation in response to faces versus objects (red−orange regions respond more to faces and green−blue regions respond more to objects). The control subject shows a typical pattern of activation, with large contiguous regions responding more either to faces or objects in the fusiform gyrus (FuG) and lingual gyrus (LiG). In contrast, MM shows little activity to objects, and almost no activity to faces. (C, right-hand) In contrast, motion selective responses in area hMT+/V5 in MM are comparable to controls both in terms of strength and extent. Adapted from Fine et al. (2003) (A, C) and Levin et al. (2010) (B).*

A recent study reported the case of two congenitally blind subjects treated for bilateral cataract after 7 and 13 years of blindness, respectively, and of an early-onset visually-impaired individual (pre-corrective visual acuity: 20/900) who received optical correction at the age of 29 years old (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009). As observed in SB and MM, these patients presented strong deficits in form perception. They perceived objects as distinct and separate patches of colors and had a hard time putting them together as a whole. However, performance in form and object recognition was greatly improved by the introduction of motion cues. Further, their ability to recognize static images of objects was higher for images of objects that typically move (i.e. a face, a bird as opposed to a flower or a telephone). Hence, it was suggested that motion information in an object might favor binding of the constituent parts together into a unique representation, allowing these subjects to recognize these objects even when they were still. Despite the fact that the human brain appears to retain an impressive capacity for visual learning well into late childhood (Held et al., 2011; Kalia et al., 2014; Ostrovsky et al., 2009; Ostrovsky, Andalman, & Sinha, 2006), an important point raised by these studies in sight-restored patients is that early intervention is often a good predictor of visual abilities in adults. In the particular case of congenital blindness, sight restoration in adults may be less beneficial than intuitively expected, notably because of the structural (deterioration of the visual tracks) and functional (crossmodal plasticity) changes that are encountered by the deprived visual cortices (Bavelier & Neville, 2002; Noppeney, 2007).

4.2.2. Insights from deaf cochlear implant users

Another more straightforward line of evidence accounting for the idea that crossmodal plasticity is likely to challenge sensory recovery stems from research conducted on deaf individuals who receive cochlear implants to restore auditory input. Paralleling findings in the blind, research conducted on deaf individuals has revealed task-related crossmodal visual activity in the sensory-deprived auditory cortices (for reviews see Bavelier & Neville, 2002; Frasnelli et al., 2011). Recent research on early deaf cats further suggests that this crossmodal reorganization may be functionally specific (Lomber, Meredith, & Kral, 2010; Meredith et al., 2011; for a review see Dormal & Collignon, 2011).

It was initially thought that hearing abilities following cochlear implants were mainly predicted by the duration of deafness (Lee et al., 2001; O'Donoghue, Nikolopoulos, & Archbold, 2000). However, the latter was shown to only account for 9% of the variance in implant outcome (Green et al., 2007), suggesting that other factors should be taken into consideration. A related predictor was identified by Lee et al. (2001) who measured glucose metabolism at rest using PET in a group of pre-lingually deaf children before they underwent cochlear implantation (Lee et al., 2001). These authors demonstrated that as children grew older and the duration of deafness increased, the extent of hypometabolism (i.e. number of hypometabolic voxels) measured in the auditory-deprived temporal cortices decreased. Most importantly, the extent of pre-operative hypometabolism measured in these regions was a positive predictor of the speech abilities of these children assessed post-implantation. In other words, a longer duration of deafness was associated with a smaller extent of hypometabolism in the auditory cortices before cochlear implantation and to a worse outcome in speech performance after cochlear implantation. In the same vein, it was later demonstrated that weak pre-operative resting state metabolic activity in the superior temporal sulcus and to some extent in the right primary auditory cortex were associated to higher speech performance scores assessed 3 years post-implantation, even when factoring out the confounding effect of age at implantation (Lee et al., 2007) (Figure 9A). These authors proposed that the lack of hypometabolism observed in auditory-deprived temporal cortices may reflect their colonization by the remaining senses, a phenomenon that may hinder the ability of these regions to process auditory input provided by cochlear implants (Lee et al., 2001; Lee et al., 2007).

Accounting for this hypothesis, visual evoked potential studies have reported a negative impact of crossmodal reorganization in temporal cortices on the outcome of cochlear implant use (Buckley & Tobey, 2011; Doucet, Bergeron, Lassonde, Ferron, & Lepore, 2006; Sandmann et al., 2012). More specifically, visual crossmodal responses measured over the right auditory cortex in cochlear implant users are negatively correlated with speech perception scores (Buckley & Tobey, 2011; Sandmann et al., 2012). Although Buckley and Toby (2011) reported that crossmodal activity accounted for speech performance only in pre- but not in post-lingually hearing impaired cochlear implant users, Sandmann et al. (2012) identified this effect in a group of post-lingually deaf cochlear implant users. In fact, similar findings were reported in a PET study (Strelnikov et al., 2013) (Figure 9B). In this study, resting state brain activity in the right superior temporal gyrus measured shortly after cochlear implantation (T0) was negatively correlated to speech performance assessed 6 months later, extending the findings of Lee et al. (2007) to post-lingually deaf cochlear implant users. Interestingly, the same finding was reported when participants were scanned during a challenging visual (speech lip-reading) discrimination task, suggesting that crossmodal reorganization of the auditory association cortices may compromise auditory recovery (Strelnikov et al., 2013). The same group of post-lingually deaf participants were scanned again between 3 to 15 months after cochlear implantation (T1) (Rouger et al., 2012). In two auditory areas, namely the right posterior and anterior STS, crossmodal activations during the visual task were significant at T0 but not at T1, although this difference reached significance only in the anterior area.

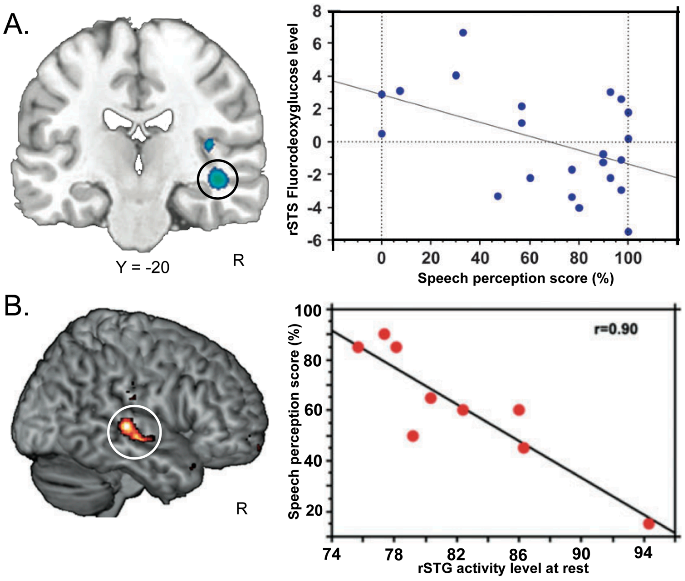

Figure 9. Inverse correlation between crossmodal plasticity in the deaf auditory cortex measured with PET and speech performance after cochlear implantation*. (A) Pre-operative resting state glucose metabolism in the superior temporal sulcus is inversely related to 3 years post-operative speech performance in pre-lingually deaf cochlear users. (B) Similar findings are shown for the right superior temporal gyrus in post-lingually deaf cochlear users at rest when relating brain activity shortly after cochlear implantation to speech performance 6 months later. Adapted from Lee et al. (2007) (A) and Strelnikov et al. (2013) (B).*

Together, these studies suggest that crossmodal plasticity in the deprived sensory cortices may be detrimental for sensory recovery not only in early onset sensory-deprived individuals but, to some extent, even in those individuals who lose sensory input later in life. As stated earlier, empirical investigations of this question in visually-deprived individuals are very scarce. Since the advent of neuroimaging, only one fMRI study jointly investigated occipital visual and crossmodal responses in MM and in another early blind patient whose vision was partially restored in adulthood (Saenz et al., 2008). This study demonstrated robust and specific crossmodal auditory motion responses coexisting with regained visual motion responses in area hMT+/V5 (Figure 10). However, since this study was carried out several years after sight restoration, no observations were reported about the evolution of the occipital cortex functional tuning before and after sight was regained.

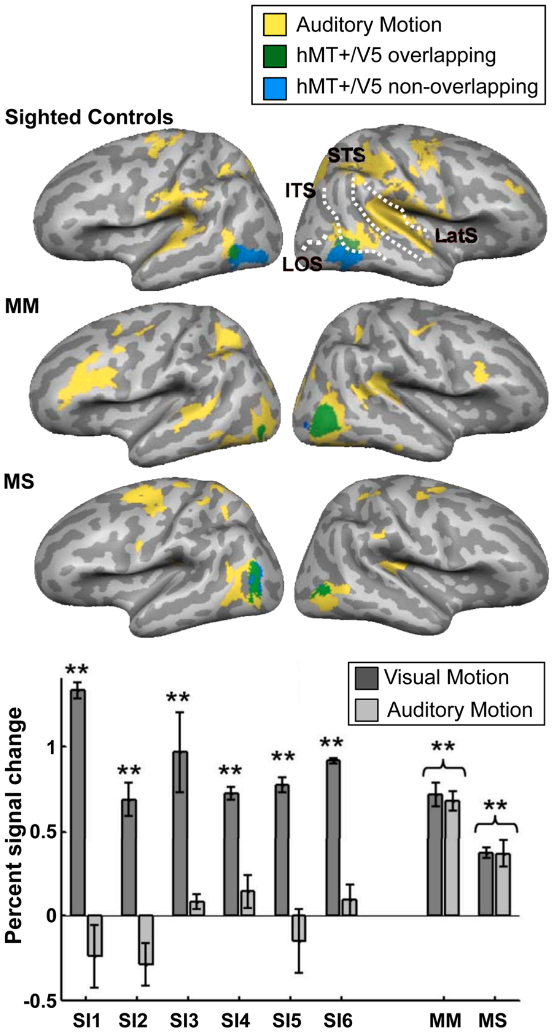

Figure 10. Surface maps of auditory and visual motion responses in hMT+/V5 in sighted controls subjects and in two sight-recovery subjects, MM and MS*. Yellow regions responded more to moving relative to stationary auditory white noise. Shown in green and blue are hMT+/V5 location as determined by a visual motion localizer in the same subjects. Note the near complete overlap (very little blue) in subjects MM and MS indicating co-localization of hMT+/V5 for visual and auditory motion processing. Adapted from Saenz et al. (2008).*

5. Summary and conclusions

In the present chapter, we have reviewed compelling evidence that the visually-deprived occipital cortex strongly responds to auditory and tactile stimulation, a phenomenon referred to as crossmodal plasticity. In those who lost sight early in life, this crossmodal reorganization is thought to be functionally relevant since it may be associated with compensatory behavioral abilities in the remaining senses (Amedi et al., 2003; Gougoux et al., 2005) and TMS delivered on the occipital cortex alters behavioral performance in several non-visual tasks (Amedi et al., 2004; Cohen et al., 1997; Collignon et al., 2007; Kupers et al., 2007). Moreover, accumulating evidence suggests that the functional organization of the occipital cortex is preserved in early blind individuals (for reviews see (Dormal & Collignon, 2011; Reich et al., 2011; Ricciardi & Pietrini, 2011). Interestingly, the nature of the neuroplastic changes observed in blind individuals seems to depend on the period of development during which vision is lost.

Within this theoretical framework, the empirical work presented in the following chapters aimed at investigating the role of visual experience in shaping the modality- and functional specialization of neural systems typically associated with functions of the dorsal and of the ventral visual pathways. Using fMRI, we characterized brain responses to different types of auditory stimuli aiming at targeting these two streams in a group of early-onset totally blind participants and in a group of matched sighted control participants. These studies are presented in chapter 2 and chapter 3, respectively. In chapter 2, we revisited the question of auditory motion selectivity in the reorganized occipito-temporal cortex of early blind individuals by using whole-brain analyses and stimuli only differing in motion content. Indeed, because previous studies exploring this question have used conditions differing in terms of low-level features of the stimuli or focused their analyses within regions of interest, the question of whether specific "visual" regions (e.g., hMT+/V5) may show a unique and selective contribution to auditory motion processing in the early blind remained unanswered. Moreover, we tested whether looming/receding sounds, as compared to laterally moving sounds, elicited specific reorganizations in the blind occipito-temporal cortex. Indeed, in-depth motion in the visual modality is a crucial cue for efficient locomotion and heading (Britten & van Wezel, 1998), and relies on specific visual cortical structures (De Jong, Shipp, Skidmore, Frackowiak, & Zeki, 1994; Morrone, Tosetti, Montanaro, & Fiorentini, 2000; Wunderlich et al., 2002).

In the second study presented in chapter 3, we investigated whether category-specific and topographically organized crossmodal responses to voices and object sounds exist in the ventral occipito-temporal cortex. Regarding object sounds more specifically, we investigated whether sounds of objects that do not explicitly convey shape-related information may elicit selective responses within LOC in early blind individuals. Indeed, an influential theoretical account proposes that cross-modal involvement of LOC (e.g. tactile exploration of objects) underlies knowledge of shape independently of modality through which this information is conveyed and independently of visual experience (Amedi et al., 2007; 2010; Peelen et al., 2014; Ptito et al., 2012). However, whether crossmodal responses in LOC during object identification are solely related to the processing of shape remains unknown.

In the third study presented in chapter 4, we had the opportunity to jointly investigate the evolution of crossmodal plasticity and visual recovery in an early-onset visually impaired individual, KL, who partially recovered sight at the age of 47 years old. KL was tested on 3 separate sessions taking place 3 weeks prior to as well as 1.5 and 7 months after surgery using identical behavioral, structural and functional MRI paradigms. This unique case study provides unprecedented information about how regained visual functions interplay with the crossmodally reorganized occipital cortex of a person with longstanding and severe visual impairment.

Chapter 2.

Investigating auditory motion processing in the occipito-temporal cortex of early blind and sighted individuals[8]

Abstract

Early blindness represents a unique model for investigating the role of visual experience in the functional development of specific brain regions that are normally devoted to a particular aspect of vision. The hMT+/V5 complex has been extensively documented as a region underlying visual motion perception in the sighted brain. In-depth motion in particular elicits distributed activations in ventral extrastriate occipital regions. Here, we aimed at identifying how the occipital cortex selectively engages in motion processing depending on visual experience since birth. Using fMRI, brain responses to in-depth, laterally moving, and static sounds were recorded in a group of early blind (EB) and blindfolded sighted control participants (SI). Univariate whole brain analyses demonstrated that a single region in the right middle temporal gyrus showed a strong functional selectivity for both in-depth and laterally moving sounds in EB. This region largely overlapped with the right hMT+/V5 area localized in an independent visual experiment performed in the SI group. Moreover, in-depth moving sounds elicited specific activity in bilateral ventral occipital cortex in EB compared to SI, whereas a similar finding was observed in SI in the visual modality. Despite the absence of auditory-driven motion activity in area hMT+/V5 in SI, multivariate pattern analyses indicated that crossmodal motion information was present in this region in both EB and SI, although it was significantly more robust in EB. Altogether, these results demonstrate that the reorganized occipito-temporal cortex of EB is segregated into distinct functional areas showing preference for the computation of motion over static information, and for the computation of specific motion trajectories, while preserving a domain selectivity that is strikingly similar to the one observed in the sigthed brain when presented with similar information in the visual modality.

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[8] This chapter is a slightly different version of a paper with the same title by Dormal, Tawfik, Yakobov, Lepore, & Collignon that is currently under review.

Investigating auditory motion processing in the occipito-temporal cortex of early blind and sighted individuals

1. Introduction

Perception of visual motion is a crucial skill for survival. In line with its evolutionary importance, this visual ability is known to rely on a set of highly specialized brain regions. Neuroimaging studies in humans have identified a strong motion-responsive region in the ascending limb of the inferior temporal sulcus (Dumoulin et al., 2000) considered as the human homologue of the macaque's MT-MST (Duffy & Wurtz, 1991; Mikami, Newsome, & Wurtz, 1986; Saito et al., 1986; Tanaka & Saito, 1989) and referred to as the hMT+/V5 complex (Tootell et al., 1995; Watson et al., 1993; Zeki et al., 1991). The first markers of visual motion perception in humans emerge soon after birth, as infants as young as 1 month of age preferentially look at moving over stationary stimuli (Volkmann and Dobson, 1986). Visual evoked potentials studies have identified directional selective cortical responses in infants between 2 and 4 months of age (Braddick, Birtles, Wattam-Bell, & Atkinson, 2005; Hou, Gilmore, Pettet, & Norcia, 2009) and responses to coherent patterns of motion by 5 months of age (Gilmore, Hou, Pettet, & Norcia, 2007; Shirai et al., 2009; Wattam-Bell et al., 2010). Together, the findings that visual motion perception is phylogenetically conserved (with a set of similar brain regions in both humans and non-human primates), and that its cortical markers emerge early during development, provide evidence that this visual ability may at least partially rely on innate predispositions.

Yet, the role of visual experience in shaping visual motion perception, and presumably the neural system on which it relies is widely accepted. For instance, global motion perception (i.e. the ability to perceive the overall direction of motion of a stimulus), which relies on the integrity of area hMT+/V5 (Becker, Haarmeier, Tatagiba, & Gharabaghi, 2013; Newsome & Paré, 1988), is permanently altered if vision is absent at birth because of congenital cataracts, even if the period of deprivation is short (Ellemberg et al., 2002; Hadad et al., 2012). However, this function is preserved in cases where the loss of sight occurs after a few months of age (Ellemberg et al., 2002). These observations thus suggest that motion-selective regions of the brain, and notably hMT+/V5, may tune to visual motion information early in life provided normal visual experience was acquired soon after birth (for a review see Dormal et al., 2012).

Early blindness represents a unique model to unravel the interplay between intrinsic constraints and experience in shaping the sensory-functional development of cortical regions that are typically devoted to vision. Studies on early visually-deprived individuals have shown that brain areas typically subtending visual abilities massively reorganize in order to support non-visual functions (for a review see Bavelier & Neville, 2002). Despite this reorientation in modality tuning, the visually-deprived occipital cortex appears to maintain a division of computational labor somewhat similar to the one that characterizes the sighted brain (for reviews see Dormal & Collignon, 2011; Reich et al., 2012; Ricciardi & Pietrini, 2011). In particular, consistent with its role in vision, hMT+/V5 has been shown to respond to auditory (Bedny et al., 2010; Poirier et al., 2006) and tactile (Ricciardi et al., 2007) motion signals in the early blind brain, suggesting that the absence of early visual input may tune this cortical region to the remaining non-visual modalities while preserving its original function for motion computation.

However, this interpretation of selective crossmodal reorganization of hMT+/V5 for non-visual motion processing has been challenged by recent studies in the field (Lewald & Getzmann, 2013; Watkins et al., 2013). In an fMRI study, Watkins and colleagues (2013) demonstrated the presence of a tonotopic organization for auditory trains of different frequencies within area hMT+/V5 in congenitally blind (anophtalmic) subjects, suggesting that crossmodal reorganization of this area as a result of early visual deprivation may be unrelated to motion processing per se (Watkins et al., 2013). Moreover, in a recent electrophysiological study, Lewald and Getzmann (2013) identified a widespread activity within the occipital cortex of blind compared to sighted individuals in response to auditory motion, suggesting that motion selectivity may not be restricted to area hMT+/V5 but rather is a more general attribute of the visually-deprived and reorganized occipital cortex (Lewald & Getzmann, 2013). Together, these findings stress the importance of controlling the low-level features of the contrasted stimuli in order to unequivocally determine that hMT+/V5 is selective to motion processing in EB. Moreover, they stress the necessity of adopting a whole-brain approach, as opposed to a region-of-interest approach when investigating motion selectivity in the reorganized occipital cortex of EB. Because previous studies exploring motion selectivity in early blind individuals have used conditions differing in terms of low-level features of the stimuli (not only differing in their motion content), or focused their analyses within regions of interest, the question of whether specific occipital regions in the blind (eg. hMT+/V5) may show a unique and selective contribution to auditory motion processing remains unanswered.

In addition, the question of whether different non-visual motion signals simulating different trajectories, such as translational/unidirectional or rotational/radial motion, may elicit specific responses in the visually-deprived occipito-temporal cortex has received little research attention. In the sighted brain, visual signals that mimic in-depth motion such as optic flow patterns and radially moving patterns, compared to other moving stimuli, generate selective distributed activations in bilateral extrastriate occipital regions (De Jong et al., 1994; Ptito, Kupers, Faubert, & Gjedde, 2001; van der Hoorn, Beudel, & De Jong, 2010; Wunderlich et al., 2002), presumably because of the importance of such dynamic cues for effective heading orientation, locomotion, and navigation in the environment. Hence, non-visual signals that mimic in-depth motion may be expected to lead to specific adaptations and reorganizations compared to other types of moving sounds in the visually-deprived brain. To date, one fMRI study investigated brain responses to translational (unidirectional) and rotational tactile patterns delivered on the tip of the fingers in four early blind subjects (Ricciardi et al., 2007). This study reported indistinguishable patterns of brain activity between these two conditions (Ricciardi et al., 2007). However, beyond their informational utility for object localization outside of peri-personal space, in-depth auditory signals such as approaching and receding sounds represent a more meaningful non-visual counterpart to visual motion in-depth. Supporting this assumption, strong associations between auditory signals and perception of visual in-depth motion have been observed in sighted individuals. For example, adaptation to visual motion in-depth (either approaching or receding) leads to the subsequent perception of a steady sound as changing in loudness in the opposite direction (increasing or decreasing, a physical correlate of auditory motion in-depth) (Jain, Sally, & Papathomas, 2008; Kitagawa & Ichihara, 2002). Similarly, a static auditory stimulus can be perceived as moving together (approaching or receding) with a visually presented in-depth moving stimulus (Jain et al., 2008; Kitajima & Yamashita, 1999). When the visual stimulus is ambiguous, similar cross-modal effects have been reported from audition to vision so that approaching and receding sounds lead to the perception of a simultaneously presented visual pattern as moving in-depth in the same direction (Jain et al., 2008; B. Schouten, Troje, Vroomen, & Verfaillie, 2011). When lacking visual input, such in-depth auditory motion cues, and particularly looming signals, are likely to play a crucial role in guiding locomotion and anticipating the arrival of potentially dangerous objects (Neuhoff, 1998).

A largely debated question in the field concerns the extent to which the sighted brain itself displays crossmodal responses to non-visual motion signals in area hMT+/V5. Whereas some studies have reported absent (Alink, Euler, Kriegeskorte, Singer, & Kohler, 2011; Bedny et al., 2010; Bremmer et al., 2001; Saenz et al., 2008) or suppressed (Lewis et al., 2000) responses to tactile and/or auditory dynamic stimuli in the vicinity of area hMT+/V5 in sighted subjects, others have found activation for non-visual motion stimuli in this region (Alink et al., 2008; Blake et al., 2004; Hagen et al., 2002; Poirier et al., 2005; Ricciardi et al., 2007; Strnad et al., 2013; Warren et al., 2002). Similar inconsistent findings in sighted subjects stem from studies that used multivariate pattern analyses in order to decode auditory and tactile motion information from the activation pattern of area hMT+/V5 localized visually. Whereas one study reported that the direction of leftward and rightward moving sounds could not be decoded above chance level in area hMT+/V5 in sighted subjects (Alink et al., 2011), two studies demonstrated opposite findings for auditory (sounds with high versus low motion content Strnad et al., 2013) and tactile motion signals (leftward versus rightward tactile motion van Kemenade et al., 2014), although mean decoding accuracy was below 60% in both studies (Strnad et al., 2013; van Kemenade et al., 2014). Observation of cross-modal responses to non-visual motion information in the vicinity of area hMT+/V5 even in subjects with typical visual experience has lead some to suggest that this region may act as a metamodal/supramodal structure for motion computation (Ricciardi et al., 2007; for reviews see Pascual-Leone & Hamilton, 2001; Reich et al., 2012; Ricciardi & Pietrini, 2011). According to this theoretical perspective, hMT+/V5 may act as a motion processor, independently from the modality on which it operates and independently of visual experience.

In the present study, we aimed at investigating the role of visual experience in setting the modality and functional tuning of the occipito-temporal cortex to motion processing. Our goals were threefold. First, we performed whole-brain univariate analyses in order to investigate crossmodal responses to auditory motion within and between-groups by comparing brain responses to moving sounds relative to static control sounds matched in terms of low-level properties (e.g. energy and frequency spectrum). For this purpose, we tested whether unequivocal selectivity for auditory motion processing was present in occipito-temporal regions and whether these regions overlapped with regions selective to visual motion as assessed by and independent visual localizer in the sighted. Secondly, we characterized specific crossmodal responses elicited by different types of moving sounds, namely in-depth versus laterally moving sounds, within and between-groups. Again, we aimed at comparing any specific activation patterns elicited by different types of auditory moving signals in early blind (relative to sighted) to the activation patterns elicited by different types of visual dynamic signals, namely radially moving dots (simulating in-depth motion) and translationally moving dots (in analogy to laterally moving sounds). Finally, we performed multivariate pattern analyses in the regions of interest defined by our univariate approach in order to further investigate the presence of crossmodal responses to different auditory moving signals relative to static sounds in the occipito-temporal cortex of early blind and sighted subjects.

2. Materials and Methods

2.1. Participants

Two groups were included in this experiment: a group of sixteen early blind (EB) (5 females, range 23 to 62 years, mean ± SD = 45 ± 12 years), and a group of fifteen sighted controls (SI) matched to the EB group for age, sex, handedness, educational level and musical experience (5 females, range 22 to 61 years, mean ± SD = 42 ± 12 years). EB participants were either totally blind or had only rudimentary sensitivity for brightness differences and no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment (Supplemental Table 1). All the procedures were approved by the research ethic and scientific boards of the “Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR)” and the “Quebec Bio-Imaging Network (QBIN)”. Experiments were undertaken with the consent of each participant.

2.2. Task and general experimental design

Participants in both groups were scanned in an auditory run and were blindfolded throughout the fMRI acquisition. SI participants were also scanned in a visual run on a separate day. In order to familiarize the participants to the fMRI environment before an fMRI acquisition, participants underwent a training session in a mock scanner. During that session participants practiced the tasks in the bore of the simulator while listening to recorded scanner sounds. In the scanner, auditory stimuli were delivered by means of circumaural, fMRI-compatible headphones (Mr Confon, Magdeburg, Germany). Visual stimuli were projected on a screen at the back of the scanner and visualized through a mirror (127 mm x 102 mm) that was mounted at a distance of approximately 12 cm from the eyes of the participants.

2.2.1. Auditory experiment*.* Auditory stimuli consisted of pink noise sounds from 3 different categories: (1) in-depth motion, (2) lateral motion, and (3) stationary sounds (no motion) (Figure 1A). Pink noise (44.1 Hz sampling rate) sounds were created and edited using Audacity (http://audacity.sourceforge.net) and MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). They lasted either 1s (standard) or 1.8s (target) in duration. In the in-depth motion condition, sounds (mono) either rose or decreased exponentially in intensity (from 10% to maximal intensity and from maximal intensity to 10% intensity) creating the vivid perception of a sound moving towards or away from the listener. In the lateral motion condition, the same sounds were presented separately in the left and the right ear (stereo) with intensity increasing in one ear while decreasing simultaneously in the other one, creating the vivid perception of a sound moving from one ear to the other in the azimuth. In the static condition, 1s and 1.8s pink noise sounds (mono) of constant intensity. A 25 ms ascending/descending ramp was applied at the beginning/end of the static sounds. In order to ensure equal global acoustic energy across conditions despite the application of a ramp in the static condition, the static sounds were normalized based on the mean Root Mean Square (RMS) of the sounds from the motion conditions.

The whole run consisted of 30 consecutive blocks (10 repetitions/category) separated by rest periods of 7s. Each block included 18 consecutive auditory stimuli (no ISI) (Figure 1A). Stimuli within the motion blocks always alternated between the two opposite directions (approaching and receding in the in-depth condition, left-to-right and right-to-left in the lateral motion condition). The task consisted of detecting longer (1.8s) sounds by pressing the response button with the index finger of the right hand. Subjects were asked to respond as accurately as possible. Response speed was not emphasized. Within each category, there were 4 blocks with one such target (18.8s duration), 4 blocks with 2 such targets (19.6s duration) and 2 blocks with 3 such targets (20.4s duration). The whole run thus contained a total of 18 targets/category.

2.2.2. Visual experiment. Visual stimuli were generated from random-dot patterns consisting of 3 different categories in analogy to the auditory experiment: (1) radial motion, (2) translation (vertical) motion, and (3) flicker (no motion) (Figure 1B). The use of vertically rather than laterally moving stimuli in the translational condition was introduced in order to minimize the generation of saccades (Morrone et al., 2000). In the auditory experiment, we used laterally moving sounds because the perception of vertically moving sounds is difficult to achieve with the use of headphones. Moreover, it was shown that the processing of vertically and laterally moving sounds (over static sounds) leads to common and undifferentiated brain responses, suggesting that the same neural substrates subtend auditory motion processing in both directions (Pavani, Macaluso, Warren, Driver, & Griffiths, 2002). Stimuli consisted of 90 frames of 512 x 384 pixels (about 30° x 24° of visual angle in the scanner). Each frame contained 200 white dots of 4 pixels diameter (about 0.25° in the scanner), randomly placed at a minimum radius of 25 pixels (about 1.5° in the scanner) from a central white fixation cross (29 pixels in width and height, about 1.7° in the scanner). From one frame to the other, each dot shifted 4 pixels towards the periphery in the radial condition (i.e. expanding from the center to the periphery) and 4 pixels toward the upward direction in the vertical condition. In the radial condition, the magnitude of the dot displacement from one frame to the next one was always constant across space so that it did not differ from the vertical condition in terms of local speed (Burr & Santoro, 2001). In the flickering condition, each dot remained stationary from one frame to another. In all conditions, each dot had a limited lifetime so that it disappeared after 12 frames and reappeared somewhere else in the display. All 90 frames were presented sequentially at a rate of 16.667 ms from frame 1 to frame 90 (expanding motion in the radial condition, upward motion in the vertical condition and flickering) and from frame 89 to frame 1 (contracting motion in the radial condition, downward motion in the vertical condition and flickering), creating moving/flickering stimuli of 1.5s duration each. Therefore dots had a limited lifetime of 200 ms and moved (in the radial and vertical condition only) with a velocity of approximately 15°/s in the scanner. Limited lifetime dots were used in order to ensure that the global direction of motion could only be determined by integrating local signals over a larger summation field rather than by following a single dot (especially in the vertical condition where all dots move in the same direction) (Bex, Simmers, & Dakin, 2003). Additionally, limited lifetime dots allowed the use of control flickering (as opposed to purely static) stimuli that were matched in terms of temporal resolution with the moving stimuli.

The whole run consisted of 30 consecutive blocks (10 repetitions/category) of 21s duration each, separated by rest periods of 7s. Each block included 14 stimuli presented with no ISI. Stimuli within motion blocks always alternated between the two opposite directions (expanding and contracting in the radial condition, moving upward and downward in the vertical motion condition). In the radial condition, stimuli were designed to simulate in-depth motion (towards or away from the viewer). The task consisted of detecting a 500 ms (30 frames) color change (from white to grey) in the central fixation cross by pressing the response button with the index finger of the right hand. Subjects were asked to respond as accurately as possible. Response speed was not emphasized. For each category, there were 5 blocks with one target and 5 blocks with 2 targets. The whole run thus contained a total of 15 targets/category.

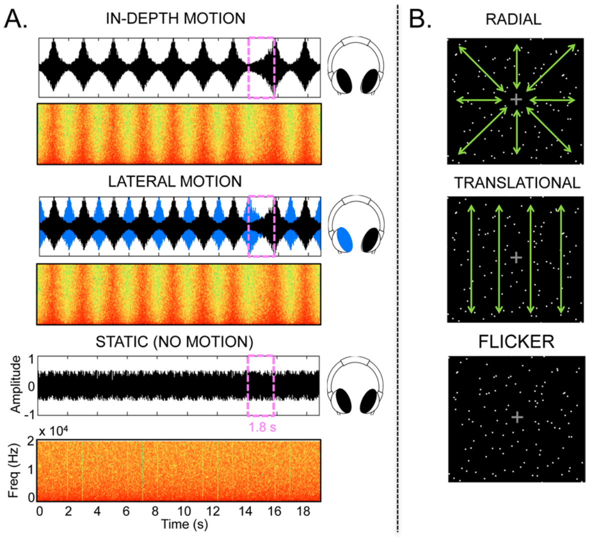


Figure 1. Illustration of the stimuli used in the (A) auditory and (B) visual experiments. *(A) Sound properties of a representative block from the in-depth (looming/receding) motion, lateral motion (leftward/rightward) and static (no motion) condition. Graphs represent the amplitude of a block as a function of time (waveform) and the spectrum of frequencies as a function of time (frequency spetcrum). Pink dashed lines indicate the occurrence of a 1.8 s target sound (the standard sound duration was of 1 s). The sounds delivered to each ear were in-phase in the in-depth motion condition, and in the static condition (black waveforms represent the sound delivered to the two ears), and out-of-phase in the lateral motion condition (black/blue waveforms represent the sounds delivered to the right/left ear).*

2.3. Behavioral analysis

Performance in the auditory run was analyzed by submitting accuracy scores (hits minus false alarms) to a 2 (between-subjects factor *Group*) × 3 (within-subjects factor *Condition*) repeated measures ANOVA. In the sighted group, a repeated measures ANOVA (3 within-subjects factor *Condition*) was also performed in the visual run.

2.4. MRI data acquisition

Functional MRI-series were acquired using a 3-T TRIO TIM system (Siemens, Erlangen, Germany), equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (TR = 2200 ms, TE = 30 ms, FA = 90°, 35 transverse slices, 3.2 mm slice thickness, 0.8 mm inter-slice gap, FoV = 192×192 mm^2, matrix size = $64\times64\times35$, voxel size = $3\times3\times3.2$ mm^3). Slices were sequentially acquired along the z-axis in feet-to-head direction. The 4 initial scans were discarded to allow for steady state magnetization. Participants' head was immobilized with the use of foam pads that applied pressure onto the headphones. A structural T1-weigthed 3D MP-RAGE sequence (voxel size= 1x1x1.2 mm^3; matrix size= 240x256; TR= 2300 ms, TE= 2.91 ms, TI= 900 ms, FoV= 256; 160 slices) was also acquired for all participants.

2.5. Functional MRI analysis

2.5.1. Univariate analyses. Functional volumes from the auditory and the visual experiment were pre-processed and analysed separately using SPM8 (Welcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), implemented in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States).

Pre-processing included slice timing correction of the functional time series (Sladky et al., 2011), realignment of functional time series, co-registration of functional and anatomical data, creation of an anatomical template using DARTEL (a template including participants from both groups in the auditory experiment, and a template including sighted participants only in the visual experiment) (Ashburner, 2007), spatial normalization of anatomical and functional data to the template, and spatial smoothing (Gaussian kernel, 8mm full-width at half-maximum, FWHM). The creation of a study-specific template using DARTEL was performed to reduce deformation errors that are more likely to arise when registering single subject images to an unusually shaped template

(Ashburner, 2007). This is particularly relevant when comparing early blind and sighted subjects as early blindness is associated with significant structural changes, particularly within the occipital cortex (Jiang et al., 2009; Noppeney et al., 2005; Pan et al., 2007; Park et al., 2009).

After these pre-processing steps, the analysis of fMRI data, based on a mixed effects model, was conducted in two serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated by a general linear model including the responses to the 3 experimental conditions (In-depth motion, Lateral motion and Static conditions in the auditory experiment; Radial, Translational and Flicker in the visual experiment). These regressors consisted of boxcar function convolved with the canonical hemodynamic response function. The movement parameters derived from realignment of the functional volumes (translations in x, y and z directions and rotations around x, y and z axes) and a constant vector were also included as covariates of no interest. High-pass filtering was implemented in the design matrix using a cut-off period of 128 seconds to remove low-frequency noise and signal drift from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

In the auditory experiment, linear contrasts were used to test the main effect of each condition ([In-depth], [Lateral], [Static], the contrasts between conditions ([In-depth>Static], [Lateral>Static], [In-depth>Lateral], [Lateral>In-depth]), the main effect of general auditory processing ([In-depth+Lateral+Static]) and generated statistical parametric maps [SPM(T)]. These summary statistics images were further spatially smoothed (Gaussian kernel 6mm FWHM) and entered in a second-level analysis, corresponding to a random effects model, accounting for inter-subject variance. One-sample t-tests characterized the main effect of conditions ([In-depth], [Lateral], [Static], [In-depth>Static], [Lateral>Static], [In-depth>Lateral], [Lateral>In-depth], [In-depth+Lateral+Static]) in each group separately. Two-sample t-tests were then performed to identify group effect for each condition separately, group effects independent of the condition, and to explore group-by-condition interaction effects. In the visual experiment, linear contrasts tested the main effect of each condition ([Radial], [Vertical], [Flicker]) and the contrasts between conditions ([Radial>Flicker], [Vertical>Flicker], [Radial>Vertical], [Vertical>Radial]) and generated statistical parametric maps [SPM(T)]. These summary statistics images were further spatially smoothed (Gaussian kernel 6mm FWHM) and entered in a second-level analysis, corresponding to a random effects model, accounting for inter-subject variance. One-sample t-tests characterized the main effect of conditions ([Radial], [Vertical], [Flicker], [Radial>Flicker], [Vertical>Flicker], [Radial>Vertical], [Vertical>Flicker].

The resulting set of voxels values for each contrast constituted a map of the t statistic [SPM(T)], thresholded at $p < 0.001$ (uncorrected for multiple comparisons). We only report group-by-condition interaction effects driven by the EB group. For this purpose, interaction effects were inclusively masked by the main effects in the EB group ($p < 0.001$ uncorrected). Statistical inferences were performed at a threshold of $p < 0.05$ after correction for multiple comparisons (Family Wise Error method) over either the entire brain volume, or over small spherical volumes (15 mm radius) located in structures of interest. Significant clusters were anatomically labeled using brain atlases (http://www.thehumanbrain.info/; Petrides, 2012). To select the coordinates of interest, we consulted a body of litterature examining brain activations related to auditory motion/spatial processing in blind and sighted subjects, and visual motion processing in sighted subjects. Before performing any small-volume correction (SVC), peaks reported in Talairach space (Talairach & Tournoux, 1988) were transformed to Montreal Neurological Institute space using Matthew Brett's bilinear transformation (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Standard stereotactic coordinates (x,y,z) used for SVC are listed below.

Frontal locations: Right middle frontal gyrus : 50, 38, 26 and 56, 22, 36 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b) ; left middle frontal gyrus : -48, 28, 26 (Poirier et al., 2005); right superior frontal gyrus : -3, 14, 47 (Lewis et al., 2000) and 6, 6, 60 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b); left inferior frontal gyrus : -40, 50, 6 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b), right inferior frontal gyrus : 52, 10, 6 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b); left precentral gyrus: -54, 14, 6 (Bedny et al., 2010). *Parietal locations*: Left superior parietal lobule: -30, -54, 64 (Pavani et al., 2002); left inferior parietal lobule: -66, -24, 40 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b); right inferior parietal lobule: 30, -38, 40 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b); right intraparietal sulcus: 48, -40, 56 and 28, -62, 62 (Pavani et al., 2002); right posterior intraparietal sulcus : 16, -77, 44 (Sunaert et al., 1999); left posterior intraparietal sulcus: -14, -84, 38 (Poirier et al., 2006); right ventral intraparietal sulcus : 24, -76, 28 (Sunaert et al., 1999); right dorsal intraparietal sulcus anterior : 33, -44, 61 (Sunaert et al., 1999). *Temporal locations:* Left superior temporal gyrus : -44, -34, 18 (Griffiths & Green, 1999); right superior temporal gyrus : 64, -26, 10 (Pavani et al., 2002); right inferior temporal gyrus: 44, -70, 2 (Bedny et al., 2010); left inferior temporal gyrus: -48, -74, -8 (Bedny et al., 2010); right middle temporal gyrus: 48, -72, 10 (Bedny et al., 2010); left hMT+/V5 : -42, -66, -2 (Sunaert et al., 1999); right hMT+/V5: 42, -62, 6 (Sunaert et al., 1999). *Insular cortex:* Left insula : -32, 18, 6 (Bedny et al., 2010); right insula : 34, 20, 4 (Bedny et al., 2010); posterior insular cortex : 45, -31, 24 (Sunaert et al., 1999). *Cingulate cortex:* Posterior cingulate gyrus: 14, -22, 46 (Sunaert et al., 1999). *Occipital locations*: Left superior occipital gyrus: -20, -80, 30 (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b); left cuneus : 0, -90, 22 (Bedny et al., 2010); left lingual gyrus: -20, -80, -8 (Sunaert et al., 1999); left fusiform gyrus: -40, -64, -12 (Sunaert et al., 1999); left pericalcarine cortex (V1/V2) : -24, -88, -8 (Poirier et al., 2006).

2.5.2. Multivariate pattern analyses. Preprocessing steps were identical to the ones performed for univariate analyses, with one exception; In the current analyses, functional time series were smoothed with a Gaussian kernel of 2 mm (FWHM), and first order linear detrending and demeaning was applied to the data.

MVPA analyses targeted 2 regions-of-interests (ROIs) defined on the basis of the resulting activations from the univariate analyses in the auditory and the visual experiments, respectively. For this purpose, two spherical ROIs (5-mm radius) were created, one at the middle temporal gyrus peak resulting from the conjunction analysis of the 2 contrasts comparing brain responses to each auditory motion condition relative to the static condition in EB (46 -60 4, Supplemental Table 4.3), the other at the right hMT+/V5 peak resulting from the conjunction analysis of the 2 contrasts comparing brain responses to each visual motion condition relative to the flicker (no motion) condition in SI (40, -60, 6, Figure 3C, Supplemental Table 6.3). To ensure that the decoding accuracies did not result from spurious factors (e.g. task-correlated head movements), the same classification analyses were also ran in two non-brain ROIs where above-chance decoding should not be expected: the right ventricle (RV) (4mm sphere) and outside of the brain (OB) (5mm sphere) (Gallivan, McLean, Valyear, & Culham, 2013; Schrouff et al., 2013).

Analyses were performed using the PRoNTo toolbox (Schrouff et al., 2013) implemented in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). Because of the slow nature of the BOLD signal, only functional data starting 6s after the onset of each block (i.e. typically corresponding to the peak of the BOLD signal) were considered for the analyses (training and testing). In the auditory experiment, 3 linear binary support vector machine (SVM) classifiers were created for each participant (within each group) in order to discriminate response patterns corresponding to different auditory conditions pairwise (In-depth versus Static, Lateral versus Static, In-depth versus Lateral) in the ROIs and control regions. Similarly, in the visual experiment, 3 linear binary SVM classifiers were created for each participant of the sighted group in order to discriminate response patterns corresponding to different visual conditions pairwise (Radial versus Flicker, Translation versus Flicker, Radial versus Translation) in the ROI and the control regions. A N-fold "Leave One Block Out" cross-validation scheme was implemented within each subject, where a classifier was trained on all the blocks except one, and then tested on the left-out block. A single decoding accuracy was obtained for each subject by averaging accuracies resulting from each cross-validation fold (10 in total).

Statistical analyses were performed in two steps. Firstly, one-sided one-sample t-tests were performed in order to test whether group average decoding accuracy in each ROI was significantly above chance level (50%). Secondly, repeated-measures ANOVAs were performed separately in the auditory and the visual experiment. In the auditory experiment, decoding accuracies were entered into a 2 (between-subjects factor *Group:* blind and sighted) × 4 (within-subjects factor *ROI:* rhMT+/V5, rMTG, RV, OB) x 3 (within-subjects factor *Classification:* in-depth versus static, lateral versus static, in-depth versus lateral) repeated measures ANOVA. In the visual experiment, average accuracies were entered into a 3 (within-subject factor *ROI:* rhMT+/V5, RV, OB) x 3 (within-subject factor *Classification:* radial versus flicker, translation versus flicker, radial versus translation) repeated-measures ANOVA.

3. Results

3.1. Behavioral Results

3.1.1. Auditory experiment. One participant from the blind group and two participants from the sighted group were excluded from further analyses because their target detection performance (hits – false alarms) in the scanner was below 2 standard deviations from the mean performance of their group. fMRI data was analyzed with and without these outliers. Excluding the outliers from the analyses had no effect on the results. The main effect of group was not significant ($p > 0.08$), indicating that overall target detection accuracy (hits – false alarms) did not differ between the EB (mean ± SD = 94.7% ± 4.9%) and the SI group (mean ± SD = 90.03% ± 8.54%). There was however a significant main effect of condition ($F_{(2,52)} = 11.107$; $p = 0.001$). The interaction was not significant ($p > 0.2$). Two-tailed paired-sample t-tests indicated overall lower detection accuracy in the in-depth motion condition (mean ± SD = 86.9% ± 13.37%) compared to the lateral motion (mean ± SD = 94.25% ± 8.07%; $t_{(27)}= -2.908$, $p = 0.007$) and to the static conditions (mean ± SD = 96.43% ± 6.45%; $t_{(27)}= -3.905$, $p = 0.001$).

3.1.2. Visual experiment. Two participants from the sighted group were excluded from further analyses because their target detection performance (hits – false alarms) in the visual experiment was below 2 standard deviations from the mean performance of the group. fMRI data was analyzed bwith and without these outliers., Removing the outliers from the analyses did not affect the results. The remaining twelve sighted participants performed close to ceiling in all conditions (radial: mean ± SD = 77.2% ± 4.21%; translational: mean ± SD = 77.35% ± 8%; flicker: mean ± SD = 76.5% ± 8.22%). The main effect of condition was not significant ($p > 0.6$), indicating that detection accuracy was equivalent across conditions.

3.2. fMRI Results – Univariate analyses

3.2.1. Auditory motion related activity in early blind and sighted subjects. We first conducted a between-group conjunction analysis (examining regions that were jointly activated in both groups) separately in the in-depth motion relative to the static condition ([BLIND In-depth > Static] ∩ [SIGHTED In-depth > Static]), and in the lateral motion relative to the static condition ([BLIND Lateral > Static] ∩ [SIGHTED Lateral > Static]). In line with previous studies, the right superior temporal gyrus was activated in both groups for both in-depth moving sounds (Seifritz et al., 2002) and laterally moving sounds (Pavani et al., 2002; Warren et al., 2002) relative to static sounds (Supplemental Table 2.1). Laterally moving sounds (relative to the static sounds) additionally activated the superior parietal lobule and supramarginal gyrus bilaterally. Looming/receding sounds (relative to the static condition) elicited additional activations in the right frontal cortex encompassing the middle and inferior frontal gyri, as well as in the left middle frontal gyrus (Supplemental Table 2.2).

3.2.2. Crossmodal plasticity in the occipito-temporal cortex of early blind subjects. To test the effect of early blindness on the general processing of sounds, we compared brain responses of blind relative to sighted subjects when combining all auditory conditions ([Blind>Sighted] x [In-depth+Lateral+Static]). This analysis yielded substantial activity in most of the right occipito-temporal cortex, encompassing the middle temporal gyrus, the middle and inferior occipital gyri, the pericalcarine cortex, the cuneus and the superior occipital gyrus. In the left hemisphere, activations were observed in the middle occipital and superior occipital gyri (Figure 2, Supplemental Table 3).

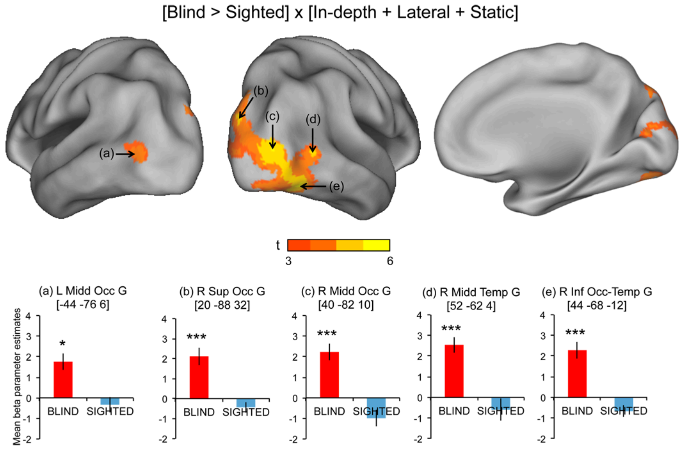


Figure 2. Unspecific crossmodal plasticity in the blind. *Upper panel : Activations obtained from contrasts testing the main effects of group independently of condition [Blind > Sighted] x [In-depth + Lateral + Static] (displayed at* $p_{uncorr} < 0.001$*). Images show the lateral surface of the left and right hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen, 2005). Color bars represent t-values. Lower panel : Mean activity estimates (arbitrary units ± SEM) associated with sound processing (in-depth + Lateral + Static) in the blind and the sighted. Significant main effects within each group are indicated with asterisks :* $*p < 0.05$ *SVC (FWE),* $**p=0.05$ *whole brain corrected (FWE),* $***p<0.05$ *whole brain corrected (FWE).*

3.2.3. Functional specialization for auditory motion processing in the occipito-temporal cortex of early blind subjects. The group [EB>SI] x condition [In-depth>Static] interaction analysis revealed large bilateral activations in the occipito-temporal cortex with a right hemispheric dominance (Figure 3A, Supplemenary Table 4.1). In the right hemisphere, these activations encompassed the inferior occipital gyrus extending to the lingual gyrus, the cuneus, the medial occipital gyrus and the temporal gyrus. In the left hemisphere, activations were restricted to the lingual and fusiform gyri. The group [Blind>Sighted] x condition [Lateral>Static] interaction analysis revealed one cluster in the right middle temporal gyrus (Figure 3B, Supplemental Table 4.2). A conjunction (AND) analysis was then conducted on these two contrasts in order to identify if any regions were commonly activated in EB (relative to SI) during the processing of both moving conditions (in-depth and lateral motion) relative to the static condition. This analysis revealed a single right lateralized cluster in the middle temporal gyrus ((46, -62, 4), Figure 3C, Supplemental Table 4.3) overlapping with the right hMT+/V5 as localized visually in the group of sighted subjects using the conjunction of the contrasts [Radial motion > Flicker] and [Translational motion > Flicker] ((40, -60, 6), Figure 3C, Supplemental Table 6.3).

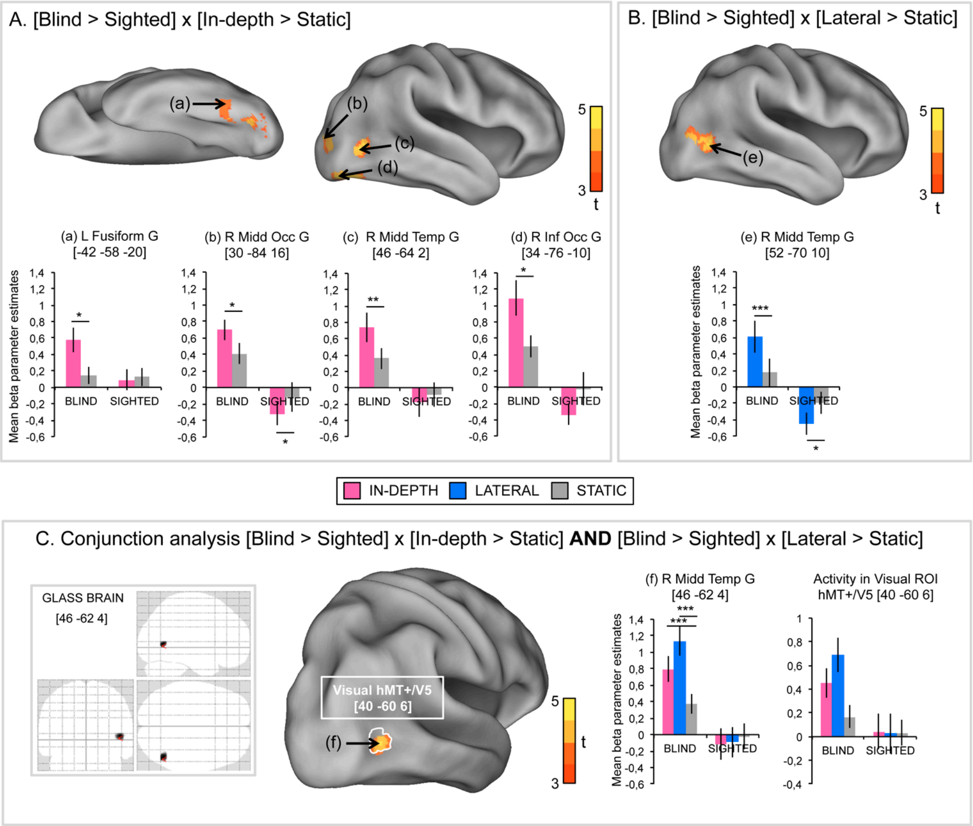


Figure 3. Auditory motion-specific (compared to static) crossmodal plasticity in the blind. *Activations obtained from (A) the contrast testing the group by condition interaction ([Blind > Sighted] x [Looming > Static], (B) the contrast testing the task by group interaction ([Blind > Sighted] x [Lateral > Static] and (C) from the conjunction of (A) and (B) are displayed at ($p_{uncorr} < 0.001$). Templates represent the ventral surface of the left hemisphere and the lateral surface of the right hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen, 2005). Color bars represent t-values. Graphs show mean activity estimates (arbitrary units ± SEM) associated with in-depth motion (pink), lateral motion (dark blue) and static conditions (grey) in blind and sighted subjects. Significant main effects within each group are indicated with asterisks : *p < 0.05 SVC (FWE), **p=0.05 whole brain corrected (FWE), ***p<0.05 whole brain corrected (FWE).*

3.2.4. Specific reorganization for in-depth motion in the occipito-temporal cortex of early blind subjects. Looming/receding sounds relative to laterally moving sounds (group [EB>SI] x condition [In-depth>Lateral] interaction) yielded specific activations in bilateral ventral portions of the occipito-temporal cortex (Figure 4, Supplemental Table 5). These activations included the middle occipital, inferior occipital, lingual and fusiform gyri in the left hemisphere and the inferior occipital gyrus in the right hemisphere. Interestingly, in the visual modality, activations obtained in the sighted group for radially moving dots relative to translationally moving dots elicited similar posterior activations encompassing bilateral middle occipital gyri, left pericalcarine cortex, and right superior occipital gyrus (Figure 4, Supplemental Table 6.4). There were no specific activations for laterally moving sounds relative to in-depth moving sounds in blind relative to sighted subjects (group interaction [Blind>Sighted] x [Lateral>In-depth]).

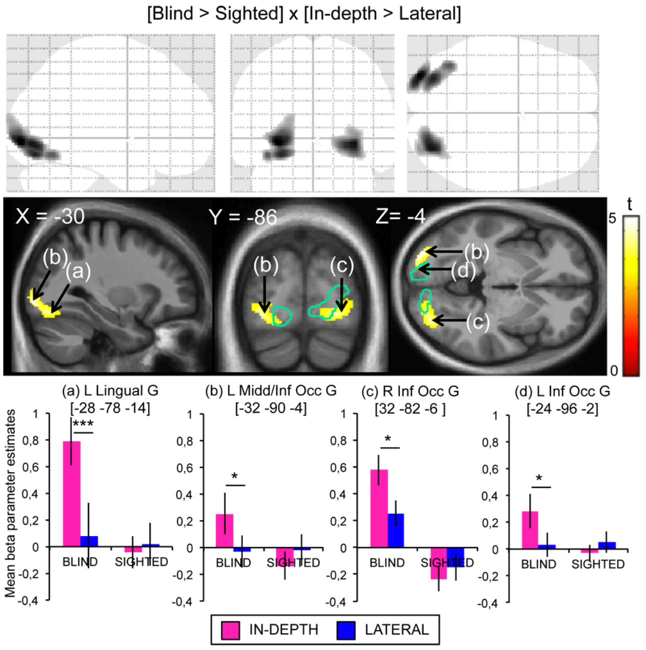


Figure 4. In-depth motion specific (compared to lateral motion) crossmodal plasticity in the blind. *(Upper) Activations obtained from the contrast testing the group by condition interaction ([Blind > Sighted] x [In-depth > Lateral] are displayed at* $p_{uncorr} < 0.001$*. Outlined in green are activations obtained in the corresponding contrast from the visual experiment in sighted subjects [Sighted Radial > Translational]. Color bar represent t-values. (Lower) Mean activity estimates (arbitrary units ± SEM) associated with the processing of in-depth (pink) and lateral (dark blue) motion in blind and sighted subjects. Results are displayed (*$p_{uncorr} < 0.001$*) over sagittal, coronal and tranversal slices of the mean structural image of all subjects normalized to the same stereotaxic space. Significant main effects within each group are indicated with asterisks : *p < 0.05 SVC (FWE), **p=0.05 whole brain corrected (FWE), ***p<0.05 whole brain corrected (FWE).*

3.3. fMRI Results – Multivariate pattern analyses

3.3.1. Auditory experiment. In order to further investigate the sensitivity of hMT+/V5 to auditory motion signals in EB and SI, multivariate pattern analyses (MVPA) using binary classifiers were performed in two regions of interests: (1) the right middle temporal gyrus (rMTG) that was commonly activated during each auditory motion condition compared to the static condition in EB (46 -60 4), Supplemental Table 4.3) and (2) the right hMT+/V5 (rhMT+/V5) peak commonly activated in sighted individuals during each visual motion condition compared to the flicker condition (40 -60 6), Figure 3B, Supplemental Table 6.3). MVPA analyses were also performed in two controls regions (see Methods).

Binary decoding accuracy for all 3 classifications (In-depth versus Static, Lateral versus Static, In-depth versus Lateral) was significantly above chance level (50%) in rMTG and rhMT+/V5 in EB (all ts > 4, all ps (one-tailed) < 0.0002) and SI (all ts > 2, all ps (one-tailed) < 0.02) (Figure 5). In contrast, decoding accuracy in control regions did not differ from chance (all ts < 1, all ps > 0.1) (Figure 5). An ANOVA with *Group* (EB, SI) as a between-subjects factor and *ROI* (rMTG, rhMT+/V5, OB, RV) and *Classification* (In-depth vs. Static, Lateral vs. Static, In-depth vs. Lateral) as within-subjects factors revealed a significant main effect of Group (F(1,26) = 6.552, p = 0.017) and a significant main effect of ROI (F(3,78) = 7.48, p < 0.001) that were modulated by a significant interaction between these two factors (F(3,26) = 6.312, p = 0.001). The effect of classification was not significant (p > 0.2), and no other interaction was significant. Follow-up analyses (two-tailed independent sample t-tests) performed for each ROI separately indicated that decoding accuracy was significantly higher in EB than in SI in rMTG (75.89% ± 11.6% vs. 63.72% ± 11.85%; t(26) = 2.74, p = 0.01) and in rhMT+/V5 (74.4% ± 13.9% vs. 59.87% ± 9.96%; t(26) = 3.107, p = 0.005) whereas decoding accuracy did not differ between the two groups in the control regions OB and RV (ts < 0.4, ps > 0.6).

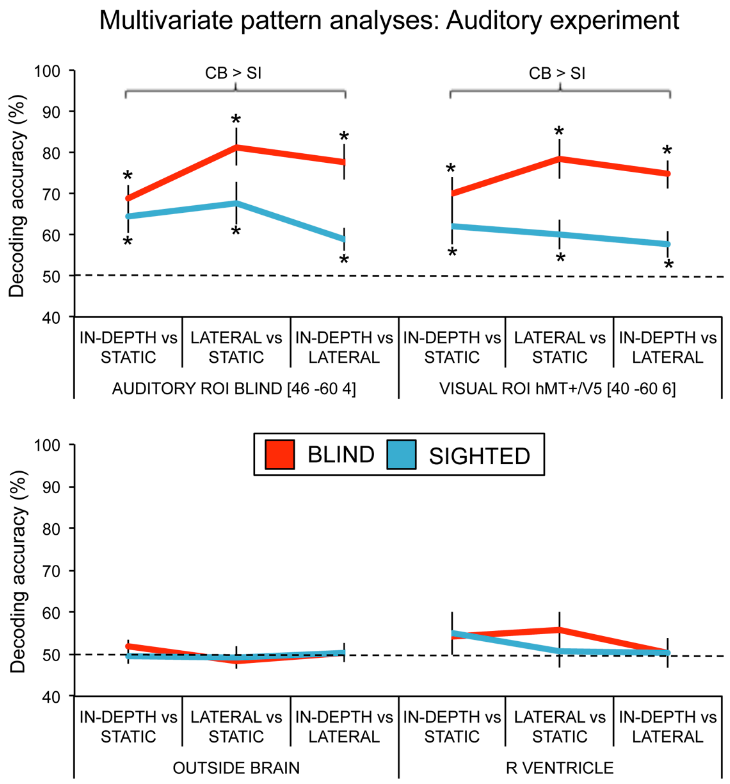


Figure 5. Results of multivariate pattern analyses in the auditory experiment. *Classification accuracy (mean % ± SEM) is plotted for regions of interest and for 2 control regions. Dotted lines represent chance level (50%). Asterisks denote classification significantly above chance level.*

<u>3.3.2. Visual experiment</u>. Multivariate pattern analyses (MVPA) were also performed in rhMT+/V5 with visual stimuli in the sighted group (Figure 6). Decoding accuracy was significantly above chance level in rhMT+/V5 for all classifications (all ts > 3, all ps (one-tailed) < 0.002) but did not differ from chance in the control regions OB and OV (all ts > -1.35 and <-0.13, all ps > 0.2) (Figure 6). A repeated measures ANOVA with *ROI* (rhMT+/V5, OB, RV) and *Classification* (Radial vs. Flicker, Translation vs. Flicker, Radial vs. Translation) as within-subject factors revealed a significant main effect of ROI (F(2,24) =46.6, p < 0.001). No other main effect or interaction was significant. Follow-up analyses (two-tailed paired sample t-tests) indicated higher decoding accuracies in rhMT+/V5 (mean ± SD = 75.9% ± 10.44%) relative to both control regions OB (mean ± SD = 48.3% ± 6%, t(12) = 7.42, p < 0.001) and RV (mean ± SD = 48.7% ± 6%, t(12) = 7.27, p < 0.001).

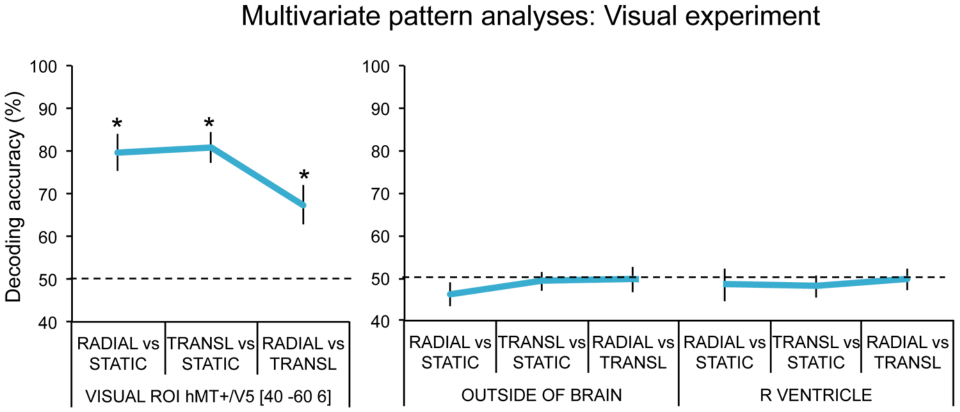


Figure 6. Results of multivariate pattern analyses in the visual experiment. *Classification accuracy (mean % ± SEM) is plotted for regions of interest and for 2 control regions. Dotted lines represent chance level (50%). Asterisks denote classification significantly above chance level.*

4. Discussion

In the present study, we investigated the role of visual experience in setting the modality and functional tuning of the occipito-temporal cortex to motion processing. Specifically, we aimed at (1) exploring the presence of crossmodal selectivity for auditory motion processing in early blind individuals with the use of whole-brain analyses and stimuli well-matched for low-level properties; (2) testing whether specific reorganizations occur for in-depth auditory motion perception in particular (compared to lateral motion) as a result of early blindness and (3) clarifying whether cross-modal responses to auditory motion may be found even in subjects with typical visual experience. Using univariate analyses, we found that a region in the right middle temporal gyrus showed a very specific functional preference for both in-depth and laterally moving sounds in EB but not in SI (Figure 3C, Supplemental Table 4.3). An independent visual experiment in SI confirmed that this region strikingly overlapped with the right hMT+/V5 area (Tootell et al., 1995; Watson et al., 1993) (Figure 3C, Supplemental Table 6.3). Importantly, in-depth moving sounds relative to laterally moving sounds elicited specific activity in bilateral ventral occipital cortex in EB compared to SI (Figure 4, Supplemental Table 5), a finding that was also observed in the visual modality when contrasting activations elicited by radially moving relative to translationally moving dots in SI (Figure 4, Supplemental Table 6.4). Despite the absence of auditory-driven activity in the right occipito-temporal cortex of SI, multivariate pattern analyses revealed that right hMT+/V5 contains information about auditory motion signals in both groups, although such information (decoding accuracy) was more robust in EB compared to SI (Figure 5). Altogether, these results demonstrate that the reorganized occipito-temporal cortex of EB is segregated into distinct functional areas showing preference for the computation of motion over static information, and for the computation of specific motion trajectories, preserving a domain selectivity remarkably similar to the one observed in vision in SI.

4.1. Auditory motion related activity in sighted and blind subjects

The existence of regions responsive to auditory motion has been previously demonstrated for in-depth moving sounds (Seifritz et al., 2002) and laterally/vertically moving sounds (Pavani et al., 2002; Warren et al., 2002). So far, existing imaging data suggests that these moving sounds share a common location in the right planum temporale (for a review see Hall & Moore, 2003). Consistent with previous findings, and confirming that our paradigm was efficient in eliciting auditory motion related brain activity, we found that both EB and SI displayed stronger activity for in-depth relative to static sounds and for laterally moving sounds relative to static sounds in the right planum temporale (Supplemental Table 2).

4.2. Functional specialization for auditory motion processing in the occipito-temporal cortex of blind subjects

In line with several previous studies investigating crossmodal processing associated with blindness, the findings of the present study demonstrated substantial activity in the occipital cortex of EB compared to SI in response to sound processing (Figure 2, Supplemental Table 3). A subset of these regions showed a preference for in-depth moving over static sounds (Figure 3A, Supplemental Table 4.1), and for laterally moving over static sounds (Figure 3B, Supplemental Table 4.2). The common neural substrate elicited by both in-depth and laterally moving sounds relative to static sounds in EB overlapped with hMT+/V5 localized visually in SI (Figure 3C, Supplemental Table 6.3). This finding strongly suggests that when hMT+/V5 is deprived of visual input early in life, this cortical area redirects its modality tuning toward a non-visual modality, here audition, but maintains its functional role in selective processing of information related to motion. These results are in line with findings reported in our previous studies showing that this region preferentially responds to spatial over pitch attributes of sounds in congenitally blind but not in sighted (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b) or late-blind individuals (Collignon et al., 2013). Our results are also consistent with studies who focused on hMT+/V5 (ROI approach) and demonstrated higher responses for laterally moving relative to static sounds (Poirier et al., 2006) and for looming sounds with high motion content relative to looming sounds with low motion content in this region (Bedny et al., 2010). In the latter study (Bedny et al., 2010), however, significant differences between looming stimuli with high and low motion content were found only in left hMT+/V5. We found the opposite results: whereas left hMT+/V5 showed substantial auditory-driven activity (Figure 2) but unspecific to motion content (Figure 3), a cluster overlapping with right hMT+/V5 displayed strong motion-specific responses to both looming/receding and laterally moving sounds in EB subjects (Figure 3C). This conflicting finding may be due to the different stimuli used in these studies. Unlike the stimuli used in the present study (Figure 1A), the high and low motion content stimuli used in the study of Bedny and colleagues (2010) differed in many aspects in terms of low-level properties and perceptual salience (Bedny et al., 2010; Strnad et al., 2013), so that any difference observed between conditions might be putatively associated to differences in the physical attributes of the sounds or in the level of arousal they generate, rather than to differences in motion content itself. Indeed, hMT+/V5 was recently shown to display a tonotopic mapping in response to pure tones of varying frequencies, suggesting that this region might be sensitive to early aspects of auditory processing (Watkins et al., 2013). To our knowledge, the present study is the first to demonstrate that when using a whole-brain approach and well-matched moving and static stimuli differing solely in their motion content, the right hMT+/V5 is the only region that responds to both types of moving sounds compared to static in EB (compared to SI).

4.3. Specific reorganization for in-depth motion in the occipito-temporal cortex of blind subjects

Another novel finding of the present study concerns the preferential responses observed for in-depth motion over lateral motion in EB relative to SI subjects in bilateral ventral extrastriate occipital regions (Figure 4). Stronger responses for visual radial motion over visual translational motion were observed in partially overlapping regions in SI although extending more medially in the occipital cortex, in line with observations previously reported in the literature (Koyama et al., 2005; Ptito et al., 2001; Wunderlich et al., 2002) (Figure 4). The pattern of extrastriate regions displaying larger responses to looming/receding over laterally moving sounds in EB subjects was also strikingly similar to the ones reported in visual studies contrasting radially moving patterns (mimicking in-depth motion) to rotational (Wunderlich et al., 2002) and randomly moving patterns (De Jong et al., 1994; Ptito et al., 2001). In line with these studies and with our own findings, these regions were localized more ventrally and posteriorly compared to the location of hMT+/V5. These findings therefore bring the first evidence for specific reorganizations for looming/receding signals compared to laterally moving signals in the early visually deprived occipito-temporal cortex, in the vicinity of regions underlying the perception of visual motion in-depth in the sighted brain (De Jong et al., 1994; Ptito et al., 2001; van der Hoorn et al., 2010; Wunderlich et al., 2002).

4.4. Decoding auditory motion content within the right middle temporal gyrus

In order to further investigate motion selectivity in hMT+/V5, multivariate pattern analyses with binary classifiers were performed in two ROIs, namely at the rMTG peak commonly activated during each auditory motion condition compared to the static condition in EB (46 -60 4), Supplemental Table 4.3) and at the rhMT+/V5 peak commonly activated in sighted during each visual motion condition compared to the flicker condition (40 -60 6), Figure 3C, Supplemental Table 6.3). In both ROIs, decoding accuracy was significantly above chance level in EB not only between each motion condition compared to the static condition (a result that was already present in the univariate analyses) but, importantly, between the two motion conditions as well (Figure 5). Similarly, in the visual modality in SI, multivariate pattern analyses performed in rhMT+/V5, revealed above level decoding accuracy between each visual motion condition relative to flicker but also between the two motion conditions, whereas this last dissociation was not observed with univariate analysis (Figure 6). In sum, activity pattern in the same right hMT+/V5 region differentiated specific motion trajectories in the auditory modality in EB, and in the visual modality in SI.

Importantly, univariate analyses revealed that, in stark contrast to EB, SI did not show motion-selective activations to auditory moving sounds in the “visual” cortex (Supplemental Figure 1). In all of the motion-selective reorganized regions of the occipito-temporal cortex of EB, including the right middle temporal gyrus overlapping with visually-defined hMT+/V5, activity was silent or even suppressed in SI when processing sounds (Figure 3 and Figure 4). In line with these findings, several other studies have reported silent or suppressed responses in motion-selective visual cortex, notably hMT+/V5, when sighted individuals were engaged in the processing of auditory (Alink et al., 2011; Bedny et al., 2010; Lewis et al., 2000; Saenz et al., 2008) and tactile dynamic information (Bremmer et al., 2001). Deactivations of extrastriate occipital regions during non-visual processing in sighted subjects have been typically associated with an attempt to reduce interference from distracting visual inputs (Laurienti et al., 2002). In contrast, other studies have reported the presence of crossmodal responses to auditory (Alink et al., 2008; Poirier et al., 2005; Warren et al., 2002) and tactile motion signals (Blake et al., 2004; Hagen et al., 2002; Ricciardi et al., 2007; van Kemenade et al., 2014) in the vicinity of area hMT+/V5 in sighted subjects.

This conflicting finding may be resolved when examining the results obtained from our complementary multivariate pattern analyses in SI. Indeed, despite the absence of significant auditory-driven activations in visually-defined hMT+/V5 in SI (Figure 3C), multivariate pattern analyses targeting this area (and a closeby rMTG selectively activated in EB for auditory motion processing) indicated that auditory motion conditions could be decoded significantly above chance level even in SI (Figure 5). A previous study demonstrated relatively low (even if significant) decoding accuracy for looming stimuli with low versus high motion content within area hMT+/V5 in sighted and congenitally blind individuals, with no significant difference between groups (Strnad et al., 2013). In the present study, even if motion content could also be decoded in both rhMT+/V5 and rMTG in the sighted group, the decoding accuracy was less accurate in SI compared to EB (Figure 5). In sum, despite no crossmodal motion activity was found in area hMT+/V5 in SI subjects with univariate analyses (Supplemental Figure 1), traces of auditory motion information could be detected using multivariate pattern analyses in this area, although the distance between the patterns of activity related to each auditory condition was not as robust as the one observed in EB.

Different theoretical accounts may explain the presence of non-visual motion information in a region that strongly responds to visual motion in sighted subjects. According to the metamodal/supramodal theory of the brain (for reviews see Pascual-Leone & Hamilton, 2001; Reich et al., 2012; Ricciardi & Pietrini, 2011), area hMT+/V5 may act as a supramodal processor for motion, performing motion computations independently of the modality over which it operates. Findings from our univariate analyses showed large responses to visual but not to auditory motion in this area, and in combination with our multivariate analyses, demonstrated high decoding accuracy for visual motion and relatively weak (even if significant) decoding of auditory motion in area hMT+/V5. Together, these findings argue against the notion that the computational implementation underlying motion processing in hMT+/V5 of the sighted is "independent" of the input modality. Similarly, even in studies that reported overlapping visual and non-visual motion responses in area hMT+/V5 in sighted subjects, the results consistently demonstrated markedly larger and more robust responses for visual compared to non-visual motion information in this area (Alink et al., 2008; Blake et al., 2004; van Kemenade et al., 2014). An alternative explanation for the presence of crossmodal motion information in area hMT+/V5 of sighted subjects may be their reliance on mental visual imagery. According to this assumption, activation of hMT+/V5 may subtend auditory motion processing *per se* in blind subjects whereas it may subtend auditorily triggered visual mental imagery in the sighted. In fact, reliable responses of area hMT+/V5 during visual imagery of motion have been previously reported (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998). We do not exclude the possibility that non-visual motion information might be present in hMT+/V5 of the sighted aside of visual imagery. However, no study to date, including ours, can compellingly reject the visual imagery hypothesis. This also holds true for studies reporting overlapping crossmodal responses to non-visual information in both sighted and blind subjects, as similar activation patterns in these two populations may be subtended by different cognitive processes.

5. Conclusions

Our findings demonstrate that the occipito-temporal cortex responds to auditory dynamic stimuli radically differently in sighted and early blind subjects – with specific activations present only in the latter. Moreover, our results indicate that even if auditory motion signal can be reliably decoded in hMT+/V5 of SI, it is significanly less robust than the one observed in EB. These findings, in addition to the major differences observed in the sighted between the visual and the auditory modality, argue against the view that the computation implemented in hMT+/V5 for processing motion information is abstract or independent from the sensory information conveying the motion signal. The findings of the present study rather suggest that developmental visual experience, or the absence of it, shapes motion-selective regions of the occipito-temporal cortex to process dynamic information related to a specific sensory modality.

6. Supplemental Material

Subject	Age	Gender	Hand	Light perception	Onset	Etiology	Educational Level	Musical Experience
EB1	48	M	R	No	1y	Glaucoma	University	Yes
EB2	44	M	R	Diffuse light	0	Leber’s congenital amaurosis	University	No
EB3	60	F	R	No	0	Retinopathy of prematurity	High school	Yes
EB4	43	M	R	No	0	Retinopathy of prematurity	High school	Yes
EB5	36	F	R	No	10m (OS) / 3.5y (OD)	Retinoblastoma	Cegep	No
EB6	31	M	R	No	0	Leber’s congenital amaurosis	University	Yes
EB7	55	M	R	No	2m	Electrical burn of optic nerves	High School	No
EB8	51	M	R	No	0	Glaucoma	University	Yes
EB9	45	M	R	No	0	Retinopathy of prematurity	University	Yes
EB10	31	F	A(R)	No	0	Retinopathy of prematurity	High School	No
EB11	51	M	A(R)	No	0	Major eye infection (Thalidomide's victim)	University	Yes
EB12	62	M	R	Diffuse light	0	Congenital cataracts	Cegep	Yes
EB13	23	M	R	Diffuse light	0	Glaucoma and microphtalmia	University	Yes
EB14	28	M	R	No	0	Retinopathy of prematurity	University	Yes
EB15	57	F	R	No	0	Chorioretinal atrophy associated to Toxoplasmosis	Cegep	Yes
EB16	58	F	R	No	0	Retinopathy of prematurity	Cegep	Yes

Supplemental Table 1. Characteristics of the blind participants. *Handedness was evaluated using an adapted version of the Edinburgh inventory. EB and SI participants were classified as musicians if they had practiced a musical instrument or vocal for at least 2 years on a regular basis (at least 2 h a week). M: male, F: female, m: months, y: years, OS: left eye, OD: right eye.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
(1) Between-Groups Conjunction [In-depth > Static]					
R Middle Frontal G	54	30	28	3.72	0.009*
R Inferior Frontal G (triangular part)	48	36	26	3.61	0.013*
R Inferior Frontal G (triangular part)	46	44	14	3.14	0.049*
L Middle Frontal G (anterior)	-38	50	4	3.23	0.039*
R Superior Temporal Gyrus	60	-34	14	3.26	0.035*
(2) Between-Groups Conjunction [Lateral > Static]					
R Superior Parietal Lobule	34	-40	52	3.78	0.006*
L IPS/ Superior Parietal Lobule	-32	-46	52	3.38	0.02*
L Supramarginal Gyrus	-42	-34	26	2.93	$0.052^{\#}$
R Supramarginal Gyrus	50	-28	28	3.03	$0.053^{\#}$
R Superior Temporal Gyrus	66	-36	14	2.96	$0.062^{\#}$

Supplemental Table 2. *Summary of the functional results obtained for the between-group conjunctions (common activations between EB and SI) testing for specific responses to (1) In-depth moving relative Static sounds, and (2) Laterally moving compared to Static sounds. (*) Coordinates significant (p_{corr} < 0.05 FWE) after correction over small spherical volumes (SVC, 15 mm radius). (#) Coordinates marginally significant after correction over small spherical volumes (SVC, 15 mm radius).*

Area	X (mm)	Y (mm)	Z (mm)	Z	p	X (mm)	Y (mm)	Z (mm)	Z	p
[Blind > Sighted] X [In-depth + Lateral + Static]						**Blind [In-depth + Lateral + Static]**				
R Inferior Occipito-Temporal Gyrus	44	-68	-12	4.40	0.001*	44	-70	-14	4.80	0.019***
R Middle Occipital Gyrus	40	-82	10	4.33	0.001*	32	-84	12	4.77	0.022***
R Inferior/Middle Occipital Gyrus	46	-80	-2	4.09	0.003*	44	-70	-14	4.80	0.019***
R Middle Temporal Gyrus	52	-62	4	4.01	0.004*	50	-60	4	4.62	0.04***
R Peri-calcarine Cortex	10	-82	16	3.67	0.013*	12	-80	14	6.37	<0.001***
R Cuneus	12	-96	18	3.39	0.028*	12	-98	12	5.39	0.001***
R Cuneus/Superior Occipital Gyrus	20	-88	32	4.04	0.004*	18	-90	32	4.74	0.025***
R Superior Occipital Gyrus	22	-76	38	3.87	0.007*	22	-86	48	3.34	0.032*
L Superior Occipital Gyrus	-18	-82	36	3.98	0.005*	-16	-82	34	3.92	0.006*
L Middle Occipital Gyrus	-44	-76	6	3.53	0.019*	-44	-76	6	4.12	0.003*

Supplemental Table 3. *Summary of the functional results obtained for the interaction analysis testing for larger responses to all auditory conditions in EB relative to SI, inclusively masked by the main effect of all auditory conditions in EB. For each region significant in the interaction analyses (left-hand table), corresponding statistics in the main effect in EB is depicted in the right-hand table. None of the regions were significantly activated or deactivated in SI. Coordinates are significant ($p_{corr} < 0.05$ FWE) after correction over (*) small spherical volumes (SVC, 15 mm radius) or over (***) the whole brain.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p	X (mm)	Y (mm)	Z (mm)	Z	p
(1) [Blind > Sighted] x [In-depth > Static]						**(1) Blind [In-depth > Static]**				
R Inferior Occipital/Lingual Gyrus	34	-76	-10	4.22	0.002*	34	-74	-10	3.87	0.006*
R Middle Occipital Gyrus	34	-76	0	4.14	0.002*	36	-82	4	3.25	0.035*
R Middle Temporal Gyrus	46	-64	2	3.93	0.005*	46	-60	4	4.5	0.054**
R Middle Occipital Gyrus (TOS)	30	-84	16	3.99	0.004*	32	-84	14	3.20	0.042*
R Superior Occipital Gyrus	30	-86	22	3.97	0.004*	30	-88	24	3.20	0.042*
L Lingual Gyrus	-30	-84	-14	3.89	0.006*	-26	-84	-16	4.06	0.003*
L Fusiform Gyrus	-30	-60	-16	3.62	0.013*	-28	-60	-18	4.15	0.002*
L Fusiform Gyrus	-42	-58	-20	3.46	0.021*	-42	-58	-22	4.15	0.002*
(2) [Blind > Sighted] x [Lateral > Static]						**(2) Blind [Lateral > Static]**				
R Middle Temporal Gyrus	52	-70	10	4.13	0.002*	48	-60	6	4.8	0.014***
(3) Conjunction Analysis of (1) and (2)						**(3) Conjunction Analysis of (1) and (2)**				
R Middle Temporal Gyrus	46	-62	4	3.88	0.005*	46	-60	4	4.15	0.002***

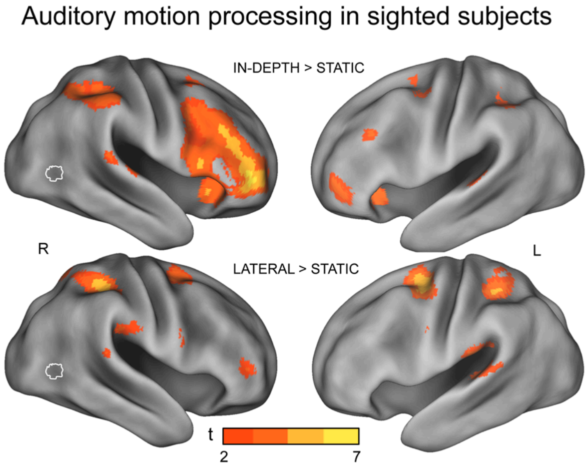
Supplemental Table 4. *Summary of the functional results obtained for the Group by Task interaction analyses (inclusively masked by the main effect in EB) testing for (1) larger responses to In-depth moving sounds relative to Static sounds in EB relative to SI, (2) larger responses to Laterally moving sounds relative to Static sounds in EB relative to SI, (3) common responses obtained in (1) and (2). For each region significant in the interaction analyses (left-hand table), corresponding statistics in the main effect in EB is depicted in the right-hand table. Regions underlined denote regions that were significantly deactivated (Static > In-depth, and Static > Lateral) in SI: R Middle Occipital Gyrus (TOS): 28,-80,16, Z=3.27, p=0.035*; R Middle Temporal Gyrus: 56, -74, 6, Z=3.24, p=0.031*. Coordinates are significant (p_{corr} < 0.05 FWE) after correction over (*) small spherical volumes (SVC, 15 mm radius) or over (***) the whole brain. (**) Coordinate marginally significant (p_{corr} = 0.05 FWE) after correction over the whole brain. TOS, Tranverse Occipital Sulcus.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p	X (mm)	Y (mm)	Z (mm)	Z	p
[Blind > Sighted] x [In-depth > Lateral]						**Blind [In-depth > Lateral]**				
L Lingual/Fusiform Gyrus	-28	-78	-14	4.19	0.002*	-26	-80	-14	5.92	0.029***
L Midd/inf Occipital Gyrus	-32	-90	-4	4.41	0.001*	-28	-90	-6	4.23	0.002*
L Inferior Occipital Gyrus	-24	-96	-2	4.14	0.002*	-24	-94	-4	4.29	0.001*
R Inferior Occipital Gyrus	32	-82	-6	4.28	0.001*	32	-82	-6	4.31	0.001*

Supplemental Table 5. *Summary of the functional results obtained for the interaction analysis testing for selective responses to In-depth over laterally moving sounds in EB relative to SI, inclusively masked by the main effect in EB. For each region significant in the interaction analyses (left-hand table), corresponding statistics in the main effect in EB is depicted in the right-hand table. None of the regions were significantly activated or deactivated in SI. Coordinates are significant ($p_{corr} < 0.05$ FWE) after correction over (*) small spherical volumes (SVC, 15 mm radius) or over (***) the whole brain.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
(1) [Radial > Flicker]					
R Middle Temporal Gyrus (hMT+/V5)	40	-60	4	5.05	0.008***
L Middle Occipito Gyrus (hMT+/V5)	-34	-66	4	3.53	0.013*
R Superior Occipital Gyrus	24	-82	24	3.45	0.016*
(2) [Translational > Flicker]					
R Middle Temporal Gyrus (hMT+/V5)	40	-62	6	5.12	0.006***
R Rolandic Operculum (Lateral fissure)	46	-32	20	4.10	0.003*
R Superior Parietal Lobule	26	-50	60	3.93	0.005*
R Postcentral Gyrus	30	-38	62	3.22	0.035*
L Inferior Parietal Lobule	-24	-50	54	3.28	0.030*
R Middle Cingulate Gyrus	14	-20	44	3.15	0.042*
(3) Conjunction of (1) and (2)					
R Middle Temporal Gyrus (hMT+/V5)	40	-60	6	4.86	0.016***
(4) [Radial > Translational]					
R Middle/Superior Occipital Gyrus	24	-96	10	4.97	0.015***
L Pericalcarine Cortex	-14	-94	-4	4.17	0.003*
L Middle Occipital Gyrus	-40	-72	4	3.49	0.020*
R Middle Occipital Gyrus	38	-68	6	3.40	0.025*

Supplemental Table 6. *Summary of the functional results obtained in the visual experiment for responses to (1) radially moving patterns relative to flicker, (2) Translational moving patterns relative to flicker; (3) common regions obtained in (1) and (2); (4) Radially moving patterns relative to translationally moving patterns. Coordinates are significant (p_{corr} < 0.05 FWE) after correction over (*) small spherical volumes (SVC, 15 mm radius) or over (***) the whole brain.*



Supplemental Figure 1. Auditory motion processing in sighted subjects. *Activations obtained from the contrasts [In-depth > Static] and [Lateral > Static] in sighted subjects. Functional data are displayed at a threshold of* $p_{uncorr} < 0.005$. *Even at this liberal threshold, no significant activity is observed in the vicinity of visually localized area hMT+/V5 (outlined in white). Images show the lateral surface of the left and right hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen, 2005).*

Chapter 3.

Selectivity for sounds of objects in the occipito-temporal cortex of early blind individuals[9]

Abstract

The ventral occipito-temporal cortex (VOTC) is organized in partially distinct regions displaying a preferential tuning for specific categories of visual objects in sighted individuals. Recent studies in early blind subjects have suggested that some aspects of this functional organization are independent of visual experience. The lateral occipital complex (LOC), traditionally involved in visual form and object identification (LOC), is thought to underlie object identification through shape processing in the blind. However, it remains unknown whether object sound processing might trigger preferential activity in the VOTC independently of shape processing. Using fMRI, we recorded brain responses to object sounds and voices during a task that minimized the potential involvement of shape imagery in a group of early blind individuals (EB) and in sighted participants (SI). Sounds of objects elicited selective crossmodal responses in the occipital cortex of EB but not SI, including regions traditionally involved in visual object identification (LOC), and more posterior occipital regions that have been previously associated to semantic processing in the blind. In contrast, human voices did not elicit selective crossmodal responses in either group. These findings suggest that the absence of developmental vision leads the occipital cortex, including LOC, to represent object sounds in the absence of shape information. We propose that LOC and more posterior regions in the blind may support the extraction of low-level auditory cues in order to allow auditory object identification and support higher-level semantic processes related to the automatic processing of the meaning of object sounds.

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[9] This chapter is a manuscript in preparation for submission by authors Dormal, Pelland, Lepore, & Collignon.

Selectivity for sounds of objects in the occipito-temporal cortex of early blind individuals

1. Introduction

A principle of organization of the human visual cortex is functional specialization, whereby different functional regions are preferentially responsive to different aspects of a visual scene (Goodale & Milner, 1992; Haxby et al., 1991; Zeki et al., 1991). Within this division of labor, the ventral occipito-temporal cortex (VOTC) partially separates into distinct areas displaying preferences for specific categories of objects such as faces, bodies, animals, words, tools or places (Chao, Haxby, & Martin, 1999; Cohen & Dehaene, 2004; Downing, Jiang, Shuman, & Kanwisher, 2001; Epstein & Kanwisher, 1998; Kanwisher et al., 1997). What drives such functional organization in VOTC remains however the matter of intense debates (Bracci & Peelen, 2013; Downing, Chan, Peelen, Dodds, & Kanwisher, 2006; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999; Konkle & Caramazza, 2013; Levy, Hasson, Avidan, Hendler, & Malach, 2001; Mahon et al., 2007).

In the last decade, early blindness has emerged as a unique model for investigating the role of intrinsic constraints and experience in shaping the functional organization of the high-level ventral visual cortex. Studies on early visually-deprived individuals have shown that brain areas typically subtending visual abilities massively reorganize in order to support non-visual functions (for a review see Bavelier & Neville, 2002). Despite this reorientation in modality tuning, a rapidly increasing number of studies have demonstrated that at least some aspects of category-selectivity are present in the VOTC of congenitally blind individuals, suggesting they may develop in the absence of any visual experience (Büchel, Price, & Friston, 1998a; He et al., 2013; Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009b; Peelen et al., 2013; Pietrini et al., 2004; Reich et al., 2011).

The lateral occipital complex (LOC) is a large portion of the lateral and ventral OTC that is preferentially responsive to pictures of objects relative to scrambled objects (Malach et al., 1995), and is well known for its involvement in visual form/object processing (Grill-Spector et al., 2001). Accounting for the critical role of shape processing for visual object recognition, lesion to LOC causes visual object agnosia, a permanent deficit in object recognition (Bridge et al., 2013; James, Culham, Humphrey, Milner, & Goodale, 2003; Milner et al., 1991). Numerous studies have demonstrated that in early blind individuals, this region displays selective responses during the active exploration of object's shape through touch or, when provided with sufficient training, even audition. Such crossmodal responses were observed during the haptic exploration of objects (Amedi et al., 2007; 2010; Pietrini et al., 2004), during a shape imagery task triggered by the presentation of sounds of objects previously explored by touch (De Volder et al., 2001), during size judgment tasks based on objects' heard names (Peelen et al., 2014) as well as during objects' exploration through echolocation (Arnott et al., 2013) and through the use of sensory-substitution devices (Amedi et al., 2007). Selective activations in LOC were also reported in sighted participants performing similar non-visual tasks (Amedi et al., 2001; 2002; 2007b; 2010; Peelen et al., 2014; Snow et al., 2014; M. Zhang et al., 2004). Based on these observations, LOC was proposed to act as a metamodal operator for shape, reflecting knowledge of object shape regardless of sensory modality and independent of the modality through which this knowledge was acquired (Amedi et al., 2007; 2010; Peelen et al., 2014). However, the question of whether sounds produced by objects may elicit selective crossmodal activation of LOC in early blind individuals in the absence of shape discrimination has been barely addressed in the literature (Amedi et al., 2007). This is of crucial interest since, in contrast to vision or touch, the recognition of object sounds relies on the extraction of spectro-temporal acoustic attributes not intrinsically linked to the shape of the object. In sighted individuals, the extraction of these acoustic perceptual features and the conceptual representation it triggers relies on a specific regions within the superior and middle temporal cortices (Bizley & Cohen, 2013). It remains unknown whether object sound processing in the blind might trigger preferential activity in the VOTC independently of shape processing.

Other regions of the VOTC in the sighted brain, notably the fusiform and inferior occipital gyri, have been extensively described as being preferentially responsive to pictures of faces relative to non-face objects (Kanwisher et al., 1997; Rossion et al., 2012). Interestingly, a functional magnetic resonance imaging (fMRI) study reported category-selective responses in the vicinity of these regions in congenitally blind individuals (but not sighted individuals) when passively listening to voices compared to objects sounds (Gougoux et al., 2009). These findings are in line with the notion that voices represent "auditory faces"

(Belin, Fecteau, & Bédard, 2004; Yovel & Belin, 2013) and suggest that, in case of early visual deprivation, regions that would have typically developed to perform face processing may reorganize in order to support person identification via the preserved auditory modality. In this study however, sounds presented in the two conditions differed in several aspects other than their categorical belonging so that the differential responses observed for voices compared to objects may be driven by stimuli counfounds. On the one hand, the voice category consisted of a large variety of human vocalizations including emotional content (e.g. baby cries, laughs), speech, singing, etc. On the other hand, since voices and object sounds were only matched in terms of overall energy (RMS), they differed in many constituent acoustic features. Moreover, the use of a passive task in this study cannot rule out the possibility that participants attended more to human vocalizations than to object sounds, for example via mechanisms of attentional capture similar to the ones that have been described for faces (Yovel & Belin, 2013).

In the present study, we used fMRI to further investigate the role of visual experience in shaping the functional organization of the VOTC. Specifically, we investigated the existence of functional selectivity for voices and object sounds, by controlling that this selectivity was specific to the perceptual category and independent from basic constituent acoustic features. We used an orthogonal task in the scanner (i.e. not related to category) in order to maintain attention and arousal constant across categories. Moreover, we used short stimuli that were presented at a fast rate in order to minimize the potential intervention of shape representations (and visual imagery in the sighted). We tested whether putative object-selective responses in the blind overlapped with visual shape selective cortex (LOC). Similarly, we tested whether putative voice-selective responses in the blind overlapped with face selective areas.

2. Materials and Methods

2.1. Participants

Two groups were included in this experiment: a group of sixteen early blind (EB) (5 females, range 23 to 62 years, mean ± SD = 45 ± 12 years), and a group of fifteen sighted controls (SI) matched to the EB group for age, sex, handedness, educational level and musical experience (5 females, range 22 to 61 years, mean ± SD = 42 ± 12 years). EB participants were either totally blind or had only rudimentary sensitivity for brightness differences and no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment (Supplemental Table 1). All the procedures were approved by the research ethic and scientific boards of the "Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR)" and the "Quebec Bio-Imaging Network (QBIN)". Experiments were undertaken with the consent of each participant.

2.2. Task and general experimental design

Participants in both groups were scanned in an auditory run and were blindfolded throughout the fMRI acquisition. SI participants were also scanned in a visual run on a separate day. In order to familiarize the participants to the fMRI environment before an fMRI acquisition, participants underwent a training session in a mock scanner. During that session participants practiced the tasks in the bore of the simulator while listening to recorded scanner sounds..In the scanner, auditory stimuli were delivered by means of circumaural, fMRI-compatible headphones (Mr Confon, Magdeburg, Germany). Visual stimuli were projected on a screen at the back of the scanner and visualized through a mirror (127 mm x 102 mm) that was mounted at a distance of approximately 12 cm from the eyes of the participants.

2.2.1. Auditory experiment. Auditory stimuli consisted of 4 different categories: human voices, object sounds, and their respective scrambled version (Figure 1). All sounds were monophonic, 16-bit and sampled at 44.1 Hz. Voices and object sounds were cut at 995ms and were applied a 5ms ascending ramp in the beginning and a 5ms descending ramp in the end. A 5ms silence was added at the beginning of the stimuli to avoid them from clicking.

Human voices consisted of 8 exemplars of each of 5 vowels ("a", "e", "i", "o", "u"), pronounced by 40 different francophone speakers (half male) recorded in the lab (Figure 1A). Object sounds consisted of 40 sounds of non-living objects from the environment that were compiled from professional CD collections (Figure 1B). To ensure that the sounds would be well-recognized by the participants, they were first selected in a pilot study from a larger database, based on the recognition performance of 10 sighted participants who did not participate in the fMRI study. In this pilot study, participants performed a recognition task where they were asked to name each sound and subsequently rate it on a scale from 1 to 10 according to how the sound was characteristic (representative) of the object. The 40 sounds with the highest rates (all above 7) were selected for the experiment.

Scrambled versions of the vocal and object sounds were performed in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) (Figure 1C and 1D). Each vocal and object sound was submitted to a fast Fourier transformation and the resulting components were separated into frequency windows of ~700 Hz based on their center frequency. Scrambling was then performed by randomly intermixing the magnitude and phase of each Fourier component (Belin, Zatorre, & Ahad, 2002; Belin, Zatorre, Lafaille, Ahad, & Pike, 2000) within each of these frequency windows separately. The inverse Fourier transform was then applied on the resulting signal. The output was a sound of the same length of the original sound with similar energy within each frequency band. For scrambled vocal sounds only, the envelope of the original voice was further applied on the output signal (Figure 1C). This was not done for scrambled object sounds because the application of the original envelope in this case lead many scrambled object sounds to be recognizable despite the scrambling (Figure 1D). Hence, for these sounds, a 5ms ramp was applied in the beginning and at the end and a 5 ms silence was added at the beginning. Following standard practices, voices, object sounds and their scambled versions were equalized in root mean square (RMS) level (Belin et al., 2000; 2002; Giordano, McAdams, Zatorre, Kriegeskorte, & Belin, 2013).

The run lasted about 18 minutes and consisted of 10 repetitions of each of the 4 conditions alternating in blocks of 21s duration and separated by silent periods of 7s. Each block consisted of the presentation of 20 stimuli with a 50ms ISI (Figure 1). Participants were instructed to detect a repetition in the sounds (same sound presented twice in a row) by pressing the response button with the index finger of the right hand. Emphasis was put on accuracy rather then speed. Within each condition, there were 4 blocks with one such repetition, 4 blocks with 2 repetitions and 2 blocks with 3 repetitions, for a total of 18 targets/condition. This design aimed at matching as best as possible attention, arousal and motor components between conditions.

2.2.2. Visual experiment. Stimuli consisted of 4 different categories: pictures of faces, objects and their phase-scrambled version (Rossion et al., 2012). The *face* category consisted of full front pictures of 50 different faces (half male) (between 170 and 210 pixels width and 250 pixels height), that were cropped for external features and embedded in a white rectangle (220 pixels width x 270 pixels height). Similarly, the *objects* category consisted of pictures of 50 different objects (between 170 – 210 pixels width and 250 pixels height) inserted in a white rectangle (220 pixels width x 270 pixels height). The phase-scrambled pictures were used in order to control spatial frequencies and pixel intensity in each color channel (RGB) in the *face* and in the *object* categories. They were created using a Fourier phase randomization procedure by replacing the phase of each original image by the phase of a uniform noise allowing for amplitude to be conserved in each frequency band (Sadr & Sinha, 2004).

The run lasted about 18 minutes and consisted of 10 repetitions of each of the 4 conditions, alternating in blocks of 21s. Blocks were separated by a baseline condition consisting of a white fixation cross on a black background. In each block, 20 pictures were presented on a black background for 1000ms with a 50ms ISI. Participants were instructed to detect a repetition in the pictures (the same picture presented twice in a row) by pressing a key with the right index finger. Emphasis was put on accuracy rather then speed. Stimuli in each block were presented centrally, but their location varied either in the x or in the y axis in steps of 30 pixels from trial to trial (average location is centered). This was done so that specific elements of the stimuli did not appear at the same location in consecutive trials, forcing the participants to pay more attention. Within each condition, there were 4 blocks with one such repetition, 4 blocks with 2 repetitions and 2 blocks with 3 repetitions, for a total of 18 targets/condition. This design aimed at matching as best as possible attention, arousal and motor components between conditions.

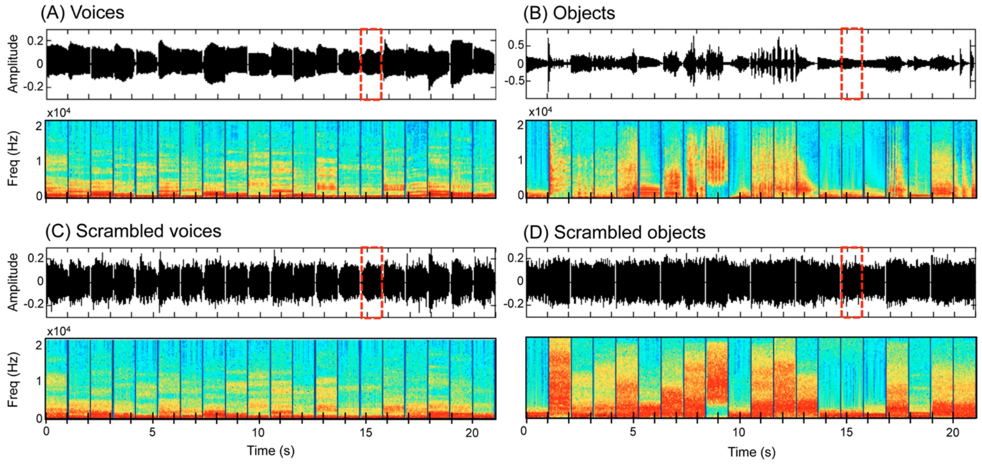


Figure 1. Illustration of the stimuli used in the auditory experiment. *Sound properties of a representative block from the (A) Voice condition, (B) Object sounds condition and (C,D) the respective scrambled (control) conditions. Graphs represent the amplitude of a block as a function of time (waveform) and the spectrum of frequencies as a function of time (frequency spectrum). Red dashed lines indicate the occurrence of a target sound (repetition of a sound twice in a row).*

2.3. Behavioral analysis

Performance in the auditory run was analyzed by submitting accuracy scores (hits minus false alarms) to a 2 (*Group*: Blind, Sighted; between-subjects factor) × 4 (*Condition*: voices, scrambled voices, objects, scrambled objects) repeated measures ANOVA. Performance in the visual run was analyzed by submitting accuracy scores (hits minus false alarms) to a repeated measures ANOVA with *Condition* (faces, scrambled faces, objects, scrambled objects) as a within-subjects factor.

2.4. MRI data acquisition

Functional MRI-series were acquired using a 3-T TRIO TIM system (Siemens, Erlangen, Germany), equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (TR = 2200 ms, TE = 30 ms, FA = 90°, 35 transverse slices, 3.2 mm slice thickness, 0.8 mm inter-slice gap, FoV = 192×192 mm^2, matrix size = 64×64×35, voxel size = 3×3×3.2 mm^3). Slices were sequentially acquired along the z-axis in feet-to-head direction. The 4 initial scans were discarded to allow for steady state magnetization. Participants' head was immobilized with the use of foam pads that applied pressure onto the headphones. A structural T1-weigthed 3D MP-RAGE sequence (voxel size= 1x1x1.2 mm^3; matrix size= 240x256; TR= 2300 ms, TE= 2.91 ms, TI= 900 ms, FoV= 256; 160 slices) was also acquired for all participants.

2.5. Functional MRI analysis

Functional volumes from the auditory and the visual experiment were pre-processed and analysed separately using SPM8 (Welcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), implemented in MATLAB R2008a (The MathWorks, Inc., Natick, Massachusetts, United States).

Pre-processing included slice timing correction of the functional time series (Sladky et al., 2011), realignment of functional time series, co-registration of functional and anatomical data, creation of an anatomical template using DARTEL (a template including participants from both groups in the auditory experiment, and a template including sighted participants only in the visual experiment) (Ashburner, 2007), spatial normalization of anatomical and functional data to the template, and spatial smoothing (Gaussian kernel, 8mm full-width at half-maximum, FWHM). The creation of a study-specific template using DARTEL was performed to reduce deformations errors that are more likely to arise when registering single subject images to an unusually shaped template (Ashburner, 2007). This is particularly relevant when comparing blind and sighted subjects as blindness is associated with significant changes in the structure of the brain itself, particularly within the occipital cortex (Jiang et al., 2009; Noppeney et al., 2005; Pan et al., 2007; Park et al., 2009).

After these pre-processing steps, the analysis of fMRI data, based on a mixed effects model, was conducted in two serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated by a general linear model including the responses to each of the 4 conditions (Objects, ScrO, Voices, ScrV). These regressors consisted of boxcar function convolved with the canonical hemodynamic response function. The movement parameters derived from realignment of the functional volumes (translations in x, y and z directions and rotations around x, y and z axes) and a constant vector were also included as covariates of no interest. High-pass filtering was implemented in the design matrix using a cut-off period of 128 seconds to remove low-frequency noise and signal drift from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

Linear contrasts tested the main effect of each condition [Object], [ScrO], ([Voice], [ScrV]), the contrasts between conditions ([Object>ScrO], [Voice>ScrV], [Object>Voice], [Voice>Object]), the main effect of general auditory processing ([Object+ScrO+ Voice+ScrV]) and generated statistical parametric maps [SPM(T)]. These summary statistics images were then further spatially smoothed (Gaussian kernel 6mm FWHM) and entered in a second-level analysis, corresponding to a random effects model, accounting for inter-subject variance. One-sample t tests characterized the main effect of conditions ([Object], [ScrO], [Voice], [ScrV], [Object>ScrO], [Voice>ScrV], [Object>Voice], [Voice>Object], [Object+ScrO+Voice+ScrV] in each group separately. Two-sample t-tests were then performed to identify group effects for each condition separately, group effects independent of the condition and to explore group-by-condition interaction effects. Identical analyses were conducted on the visual experiment based on the 4 visual conditions (Objects, ScrO, Faces, ScrF).

The resulting set of voxels values for each contrast constituted a map of the t statistic [SPM(T)], thresholded at $p < 0.001$ (uncorrected for multiple comparisons). Statistical inferences were performed at a threshold of $p < 0.05$ after correction for multiple comparisons (Family Wise Error method) over either the entire brain volume, or over small spherical volumes (15 mm radius) located in structures of interest. Significant clusters were anatomically labeled using brain atlases (http://www.thehumanbrain.info/; Petrides, 2012). In the auditory experiment, main effects of condition in each group were used as inclusive ($p_{uncorr} < 0.001$) or exclusive ($p_{uncorr} < 0.005$) masks in order to identify which group was driving the interaction effect.

3. Results

3.1. Behavioral Results

3.1.1. Auditory experiment. Two participants from each group were excluded from further analyses because their repetition detection performance in the scanner was below 2 standard deviations from the mean performance of their respective group. The main effect of Group was significant ($F_{(1,25)} = 9.837$, $p = 0.004$), indicating that EB were overall more accurate (hits – false alarms) than SI in detecting repetitions (EB: mean ± SD = 95.53% ± 3%; SI: mean ± SD = 88.14% ± 8.25%). There was also a significant main effect of condition ($F_{(3,75)} = 7.740$, $p < 0.001$). The interaction between the 2 factors was not significant ($p > 0.3$). Follow-up analyses (two-tailed paired t-tests) indicated that accuracy was lower in the scrambled objects condition (mean ± SD = 87.44% ± 10.63%) compared to the voices (mean ± SD = 92.4% ± 8.73%, $t_{(26)} = -2.975$, $p = 0.006$), the scrambled voices (mean ± SD = 93.62% ± 8.8%, $t_{(26)} = -3.844$, $p = 0.001$) and the objects conditions (mean ± SD = 94.44% ± 6.16%, $t_{(26)} = -4.132$, $p < 0.001$).

3.1.2. Visual experiment. One sighted participant was excluded from further analyses because her target detection performance in the scanner was below 2 standard deviations from the mean performance of the group. The main effect of condition was significant ($F_{(3,39)} = 7.601$, $p < 0.001$). Follow-up analyses (two-tailed paired t-tests) indicated that accuracy (hits minus false alarms) was significantly lower in the scrambled faces condition (mean ± SD = 76.98% ± 13.05%) compared to remaining conditions (faces: mean ± SD = 85.32% ± 10.8%, $t_{(13)} = -2.215$, $p = 0.045$; objects: mean ± SD = 93.25% ± 8.48%, $t_{(13)}$

= -5.147, $p < 0.001$; scrambled objects: mean ± SD = 89.3% ± 10.33%, $t_{(13)}$ = -3.613, $p = 0.003$).

3.2. fMRI Results

3.2.1. Object-specific activity in both early blind and sighted subjects. We first conducted a between-group conjunction (AND) analysis (looking at what is jointly activated in both groups of subjects) testing for specific object-related activity relative to both scrambled objects and voices ([BLIND Object > ScrO] ∩ [BLIND Object > Voice] ∩ [SIGHTED Object > ScrO] ∩ [SIGHTED Object > Voice]) (Figure 2, Supplemental Table 2). This analysis identified bilateral activations - although stronger in the left hemisphere - in the medial part of the transverse temporal gyrus (A1) extending laterally along the lateral fissure and posteriorly to the planum temporale. Bilateral activations were also found in the intraparietal sulci. In the left hemisphere, additional clusters of activation were found within the frontal cortex, in the inferior and middle frontal gyri, and within the temporal cortex, in the posterior middle temporal gyrus extending to the inferior temporal sulcus and in the fusiform gyrus (Supplemental Figure 1, Supplemental Table 2).

3.2.2. Voice-specific activity in both early blind and sighted subjects. In the same vein, we conducted a between-group conjunction (AND) analysis (looking at what is jointly activated in both groups of subjects) testing for specific voice-related activity relative to both scrambled voices and objects ([BLIND Voice > ScrV] ∩ [BLIND Voice > Object] ∩ [SIGHTED Voice > ScrV] ∩ [SIGHTED Voice > Object]). This analysis yielded specific activity in the superior temporal sulcus bilaterally (Figure 2, Supplemental Table 2).

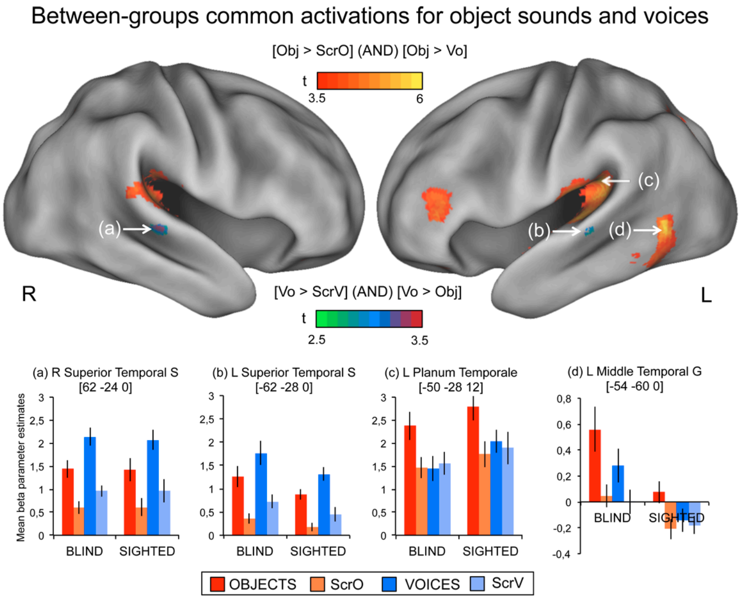


Figure 2. Selective responses to object sounds and voices common to early blind and sighted subjects. *Activations obtained for the conjunction contrasts testing selectivity to object sounds ([Obj > ScrO] (AND) [Obj > Vo]) and voices ([Vo > ScrV] (AND) [Vo > Obj]) common to blind and sighted participants (displayed at* $p_{uncorr} < 0.001$ *and* $p_{uncorr} < 0.005$*). Images show the lateral surface of the left and right hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen, 2005). Color bar represents t-values. Graphs show mean activity estimates (arbitrary units ± SEM) in blind and sighted subjects.*

3.2.3. Crossmodal plasticity in the occipital cortex of early blind subjects.

To test the effect of early blindness on the general processing of sounds, we compared brain responses of blind relative to sighted subjects when combining all auditory conditions (group [EB>SI] x condition [Object+ScrO+Voice+ScrV]). This analysis yielded substantial activity in bilateral occipito-temporal cortices (Figure 3, Supplemental Table 3). In the left hemisphere, activations were observed in the middle occipito-temporal gyrus and the inferior occipital gyrus as well as in the superior occipital gyrus. In the right hemisphere, a large cluster of activation was found in the inferior occipito-temporal gyrus, extending ventrally and anteriorly to the lateral occipito-temporal sulcus, and extending posteriorly and superiorly to the middle occipital gyrus. This interaction effect was driven by the EB group since an inclusive mask of the main effect in EB ($p_{uncorr}<0.001$) did not affect this analysis.

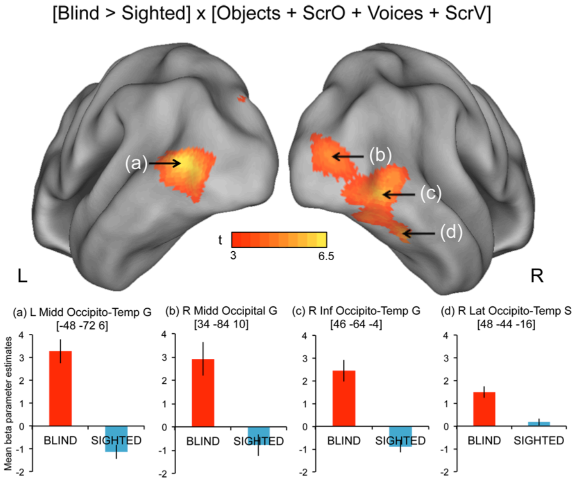


Figure 3. Unspecific crossmodal plasticity in the blind. *Activations obtained from the contrast testing the main effect of group independently of condition [Blind > Sighted] x [Objects + ScrO + Voices + ScrV] (displayed at $p_{uncorr} < 0.001$). Graphs show mean activity estimates (arbitrary units ± SEM) in blind and sighted subjects.*

3.2.4. Functional specialization for object sounds in the occipital cortex of early blind subjects. The group [EB>SI] x condition [Object>ScrO] interaction analysis revealed bilateral activations in the lateral and ventral portions of the occipito-temporal cortex bilaterally (Supplemental Table 4.1). These activations encompassed the middle and inferior occipital gyri and extended medially to the fusiform gyri. The group [EB>SI] x condition [Object>Voice] interaction analysis revealed a very similar activation pattern although this analysis yielded additional activations in the superior occipital gyrus and cuneus bilaterally (Supplemental Table 4.2). In both analyses, activations were bilateral although more extended in the left hemisphere. These interaction effects were both driven by the EB group since an inclusive mask of the corresponding main effects in EB ($p_{uncorr}<0.001$) did not affect these analyses.

A conjunction (AND) analysis was then conducted on these 2 contrasts in order to identify the regions specifically activated in EB (relative to SI) for the processing of object sounds relative to both scrambled objects and voices (Figure 4, Supplemental Table 4.3). This analysis revealed bilateral activations, in the middle and inferior occipital gyri, which, in the left hemisphere, extended to the fusiform gyrus. Peaks of activations on the lateral portion of the occipito-temporal cortex in the left (xyz = -36, -78, -4) and right (xyz = 40, -64, 4) (Figure 4, Supplemental Table 4.3) hemisphere were in close vicinity to left and right LOC peaks (left LOC xyz = -46, -82, -6; Z=4.92; p=0.022; right LOC xyz = 48, -70, -12; Z = 5.24; p=0.006 (whole-brain corrected)) that were localized visually in SI using the contrast [Object pictures>Scrambled].

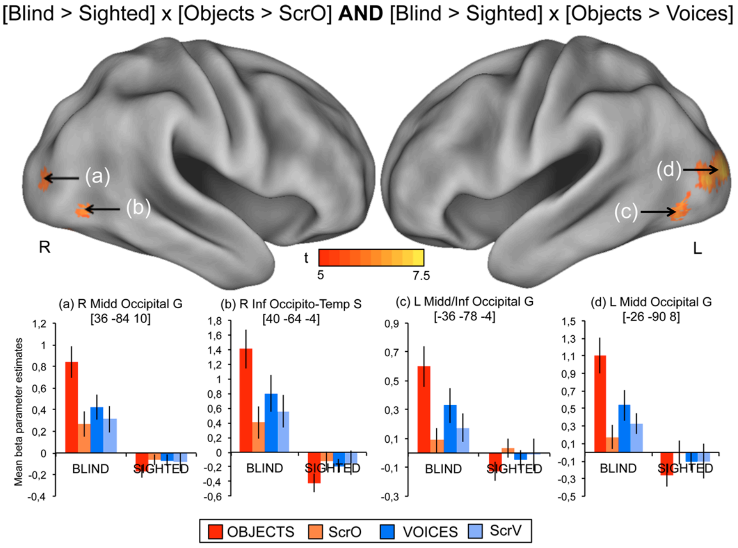


Figure 4. Object-specific crossmodal responses in the blind. *Conjunction analysis of the contrasts testing the group by condition interactions [Blind > Sighted] x [Objects > ScrO] AND [Blind > Sighted] x [Objects > Voices] (displayed at* $p_{corr} < 0.05$*). Images show the lateral surface of the left and the right hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen, 2005). Color bar represents t-values. Graphs show mean activity estimates (arbitrary units ± SEM) in blind and sighted subjects*

3.2.5. Larger activation to voices relative to scrambled voices but not to object sounds in the fusiform gyrus of early blind subjects. The group [EB>SI] x condition [Voice>ScrV] interaction analysis revealed activations in the fusiform gyrus bilaterally (Figure 5, Supplemental Table 5). This interaction effect was driven by the EB group since an inclusive mask of the main effect in EB ($p_{uncorr}<0.001$) did not affect this analysis. There were no significant activations in the group [EB>SI] x condition [Voice>Object] interaction.

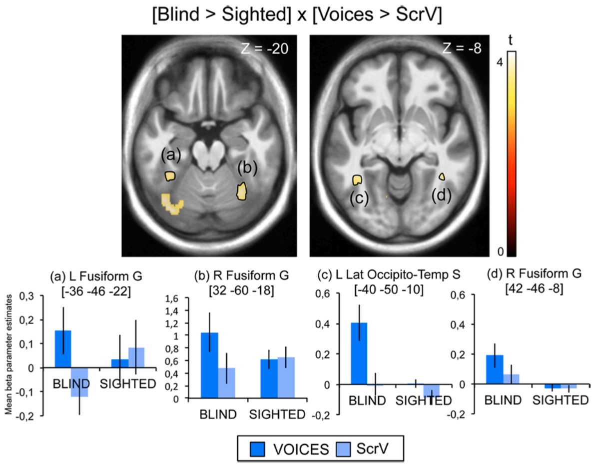


Figure 5. Crossmodal responses to voices relative to scrambled voices in the blind. *Results of the contrast testing the group by condition interaction [Blind > Sighted] x [Voices > ScrV] are displayed at* $p_{uncorr} < 0.001$ *over transversal slices of the mean structural image of all subjects normalized to the same stereotaxic space. Color bar represents t-values. Graphs show mean activity estimates (arbitrary units ± SEM) in blind and sighted subjects.*

4. Discussion

Mirroring the functional organization that characterizes the VOTC for the representation of distinct visual categories of objects, previous studies have shown that the auditory system also hosts a topographical organization where distinct areas preferentially respond to different categories of complex environmental sounds such as voices, animal vocalizations, tools or musical instruments (Belin et al., 2000; Engel, Frum, Puce, Walker, & Lewis, 2009; Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; Lewis, Talkington, Puce, Engel, & Frum, 2011; Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002). In line with previous studies, non-living object-specific activity was observed along the lateral fissure bilaterally and extending to the planum temporale (Giordano et al., 2013; Lewis, Talkington, Tallaksen, & Frum, 2012) whereas human voice-specific activity was found in bilateral superior temporal sulci (Belin et al., 2000; 2002) in both groups of participants (Figure 2, Supplemental Table 2). In EB (relative to SI), selective responses to sounds of objects were also found in the middle and inferior occipital gyri bilaterally and were stronger and more extended in the left hemisphere (Figure 4, Supplemental Table 4.3). Interestingly, crossmodal object-selective responses over the lateral portions of the occipital cortex in EB (relative to SI) partially overlapped with LOC (Malach et al., 1995) as independently localized with visual stimuli in our group of sighted participants. In contrast, no selective responses to voices, when compared to object sounds, were observed in the VOTC of EB (or SI).

Previous studies have shown that regions within LOC display crossmodal responses in both early blind individuals and sighted subjects during tasks involving the active processing of object-related *shape* information (Amedi et al., 2007; 2010; Peelen et al., 2014). These findings, together with the observation that typical sounds produced by objects do not elicit crossmodal activity in LOC of sighted individuals (Amedi et al., 2002; 2007b) nor in two blind individuals (Amedi et al., 2007) – unless these sounds explicitly triggered a mental shape imagery task (De Volder et al., 2001) – were taken as evidence that LOC acts as a metamodal operator for shape. It was therefore suggested that LOC supports the processing of object shape independently from the input modality providing the information, and even develops independently from previous visual experience with object shape (Amedi et al., 2007; 2010; Peelen et al., 2014). However, similar crossmodal involvement of LOC in early blind and sighted individuals does not necessarily imply that this region supports identical representations in these two populations. In fact, crossmodal involvement of LOC reported in sighted individuals in previous studies may simply stem from top-down visual imagery processes triggered by somatosensory or auditory input, casting doubt on the idea that this involvement is independent of sensory modality. The fact that sighted individuals display activations in LOC when haptically exploring objects but not when hearing the typical sounds produced by objects (Amedi et al., 2002; 2007b) – unless associated to an explicit visual imagery task (De Volder et al., 2001) – may be simply due to the fact that the former (haptic processing) is more susceptible to implicitly trigger mental visual imagery of shape. In fact, visual imagery abilities are tightly linked to the extent of tactile object activation of LOC in sighted individuals (Zhang et al., 2004).

In the present study, we used a task that minimized the potential intervention of shape representations and visual imagery and demonstrate that sounds of objects, compared to both voice and scrambled objects sounds, elicit robust and selective crossmodal responses within occipital regions in early blind but not sighted individuals (Figure 4). Importantly, these responses (Figure 4 (b) and (c)) partially overlapped with bilateral LOC (localized visually) in the absence of any shape-related information. Together, these findings suggest that at least portions of LOC in early blind individuals contain representations of object sounds that are not related to shape and that these regions develop because of a lack of developmental vision, since they are not observed in sighted individuals.

What may be the nature of these representations? In vision, LOC is thought to support hierarchically intermediate processing stages for analyzing coarse object-like features, such as shape, by the assimilation of inputs from lower visual regions in the hierarchy (Malach et al., 1995). This may contribute to the segmentation of a distinct object present within a complex visual scene (MacEvoy & Epstein, 2011). While sounds of objects, unlike vision, typically convey no information about the size or shape of these objects, they provide different sensory cues that allow for their identification (e.g. frequency spectrum, pitch, envelope, harmonicity). In fact, in the absence of vision, these sensory cues are likely to become particularly important in order to identify objects that are outside of peri-personal space and can thus not be recognized by touch. Environemental sounds that are perceived as "object-like", such as those produced by automated machinery and man-made objects (as in the present study), share common acoustical features which may serve as low-level cues for their rapid identification in a complex acoustic environment (Lewis et al., 2012). In the present study, sounds of objects elicited selective responses in bilateral LOC compared to another category of sounds with high harmonicity (voices) and compared to non-harmonic unrecognizable sounds matched in overall energy and frequency spectrum. Hence, it is possible that crossmodal plasticity associated to early visual deprivation drives the occipital cortex, including LOC, to rely on the extraction of such low-level auditory features in order to gain auditory object recognition.

Selective responses to sounds of objects in the deprived occipital cortex of EB were not limited to bilateral LOC but extended medially and posteriorly towards the middle occipital gyrus, particularly in the left hemisphere. Interestingly, these activations are in the vicinity of regions previously reported as displaying semantic effects when early blind subjects (compared to sighted subjects) process lexical information (sentences and word lists compared to non-words sentences and non-word lists) (Bedny et al., 2011), generate semantically related verb to heard nouns (Burton et al., 2003), and perform semantic decisions on heard nouns (Noppeney et al., 2003). Since all sounds of objects used in the present study were highly recognizable, a possibility is that these activations are related to the automatic processing of object meaning (i.e. what the object is) when listening to these sounds. Supporting this assumption, both EB and SI displayed common selective responses to object sounds (relative to voices and scrambled objects) in the inferior frontal cortex as well as in lateral and ventral portions of the posterior temporal cortex in the left hemisphere (Supplemental Figure 1, Supplemental Table 2), regions that have been consistently associated to conceptual and semantic processing across a number of tasks requiring meaning-based processing, especially regarding concrete objects (Gold et al., 2006; Gough, Nobre, & Devlin, 2005; Sharp, Scott, & Wise, 2004; Wheatley, Weisberg, Beauchamp, & Martin, 2005; for a review see Martin, 2007).

Future studies should investigate how the reorganized occipital regions of the early blind integrates the hierarchical processing flow allowing the extraction of specific acoustic features leading to auditory object-selective response.

Contrary to our expectations, we did not observe any selective responses to voices when contrasted to object sounds in the VOTC of EB (or SI) subjects. Nevertheless, activations in the bilateral fusiform gyri were observed in EB (relative to SI) when contrasting voices to their scrambled controls only (Figure 5, Supplemental Table 5), in line with a recent study that reported a voice congruency effect in congenitally blind (relative to sighted controls) in the right anterior fusiform gyrus (Hölig et al., 2014). The lack of category selective responses in VOTC of EB individuals contrasts with another fMRI study that identified selective responses to vocal over non-vocal sounds in the fusiform, lingual and inferior occipital gyri of five congenitally blind individuals (compared to sighted subjects) when passively listening to these sounds (Gougoux et al., 2009). In this study however, unlike ours, there was not attempt to control for low-level acoustic features of the stimuli from the vocal and non-vocal categories. Hence, any differential response could be putatively related to differences in the constituent acoustic features. Moreover, vocal stimuli in that study involved many different human vocalizations varying in prosody, emotional content, speech etc. In the present study, we chose to use neutral vowels in order to target more specifically the intrinsic neural coding of voice information. In turn, it is possible that these vocal stimuli lacked saliency compared to the object sounds used and may have prevented the observation of crossmodal category-specific effects for voices in the VOTC of EB.

However, the observation of selective activation for voice information in bilateral superior temporal sulcus (e.g. the temporal voice area) suggests that the absence of functional preference for voices in the occipito-temporal cortex of EB is unlikely to be solely related to a lack of sensitivity of our paradigm. These findings may suggest that different regions within the VOTC cortex are not equally susceptible to reorganize in a functional specific manner following visual deprivation since early life. For instance, regions that are face-selective in the sighted brain may not transfer their function to the recognition of human voices (over other categorical information such as sounds of objects) in case of early blindness. Because face recognition is an evolutionary ancient cognitive ability with potential survival advantage, it has been argued that this skill may be under high genetic control (Kanwisher, 2010). This assumption is supported by studies on families with hereditary prosopagnosia (Duchaine, Germine, & Nakayama, 2007; Grüter, Grüter, & Carbon, 2008; Schmalzl, Palermo, & Coltheart, 2008) and performance of monozigotic relative to dizigotic twins in a face memory task (Wilmer et al., 2010). In the same vein, Polk and collaborators (2007) found that genetics may play a larger role on neural activity patterns evoked by faces (and places) (Polk, Park, Smith, & Park, 2007) compared to the ones evoked by written peuso-words, the latter being more dependent on experience (Park, Park, & Polk, 2012; Polk et al., 2007; but see Pinel et al., 2014). Hence, different functional areas in the cortex may result from different neurodevelopmental factors (Kanwisher, 2010). For example, while the visual word form area selectivity for word strings may emerge through pure learning-dependent mechanisms (Dehaene et al., 2010; He, Liu, Jiang, Chen, & Gong, 2009), face selectivity in the FFA may arise because "the specific instructions for constructing the critical circuits for face perception are in the genome" (Kanwisher, 2010). These different developmental mechanisms for the emergence of functional areas might interact with sensory deprivation and therefore influence and constrain the process of crossmodal plasticity.

In summary, these findings demonstrate that object sound processing in the blind triggers preferential activity in the occipital cortex, including LOC, independently of shape processing. However, the absence of voice-selective crossmodal responses in the VOTC of early blind individuals suggests that the anatomo-functional correspondence observed between sighted and blind individuals may not be a general principle of the reorganized "visual" cortex following early visual deprivation. Rather, the maintenance of a functional specialization in crossmodal plasticity may depend on the neural systems investigated and on the neurodevelopmental mechanisms based on which these systems emerge.

5. Supplemental Material

Subject	Age	Gender	Hand	Light perception	Onset	Etiology	Educational Level	Musical Experience
EB1	48	M	R	No	1y	Glaucoma	University	Yes
EB2	44	M	R	Diffuse light	0	Leber’s congenital amaurosis	University	No
EB3	60	F	R	No	0	Retinopathy of prematurity	High school	Yes
EB4	43	M	R	No	0	Retinopathy of prematurity	High school	Yes
EB5	36	F	R	No	10m (OS) / 3.5y (OD)	Retinoblastoma	Cegep	No
EB6	31	M	R	No	0	Leber’s congenital amaurosis	University	Yes
EB7	55	M	R	No	2m	Electrical burn of optic nerves	High School	No
EB8	51	M	R	No	0	Glaucoma	University	Yes
EB9	45	M	R	No	0	Retinopathy of prematurity	University	Yes
EB10	31	F	A(R)	No	0	Retinopathy of prematurity	High School	No
EB11	51	M	A(R)	No	0	Major eye infection (Thalidomide's victim)	University	Yes
EB12	62	M	R	Diffuse light	0	Congenital cataracts	Cegep	Yes
EB13	23	M	R	Diffuse light	0	Glaucoma and microphtalmia	University	Yes
EB14	28	M	R	No	0	Retinopathy of prematurity	University	Yes
EB15	57	F	R	No	0	Chorioretinal atrophy associated to Toxoplasmosis	Cegep	Yes
EB16	58	F	R	No	0	Retinopathy of prematurity	Cegep	Yes

Supplemental Table 1. Characteristics of the blind participants. *Handedness was evaluated using an adapted version of the Edinburgh inventory. EB and SI participants were classified as musicians if they had practiced a musical instrument or vocal for at least 2 years on a regular basis (at least 2 h a week). M: male, F: female, m: months, y: years, OS: left eye, OD: right eye.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
(1) Between-groups conjunction for object-selective responses					
L Planum Temporale	-50	-28	12	4.80	0.017***
L Transverse Temporal G	-40	-34	18	4.64	0.033***
L Transverse Temporal Sulcus (A1)	-42	-22	-2	4.80	0.017***
L posterior Middle Temporal Gyrus	-54	-60	0	4.63	0.034***
L Inferior Temporal Gyrus	-48	-56	-6	4.24	0.002*
L Inferior Temporal Sulcus	-60	-48	-12	3.17	0.045*
R Heschl's G (A1)	48	-24	8	4.56	0.044***
R Planum Temporale	62	-36	16	3.82	0.007*
L Inferior Frontal G (Orbital part)	-34	32	-8	4.47	0.062***
L Inferior Frontal Sulcus	-46	38	12	4.11	0.003*
L Intraparietal Sulcus	-32	-72	36	3.76	0.01*
R Intraparietal Sulcus	32	-70	50	3.94	0.005*
L Collateral Sulcus (Fusiform G)	-26	-38	-18	4.17	0.002*
L Fusiform G	-36	-26	-20	3.51	0.018*
(2) Between-groups conjunction for voice-selective responses					
R Superior Temporal Sulcus	62	-24	0	3.04	$0.065^{\#}$
L Superior Temporal Sulcus	-62	-28	0	3.03	$0.068^{\#}$

Supplemental Table 2. *Summary of the functional results obtained for the between-group conjunctions (common activations between EB and SI) testing for specific responses to (1) object sounds (compared to both voices and scrambled objects) and (2) voices (compared to both object sounds and scrambled voices). Coordinates significant (*p_{corr} *< 0.05 FWE) after correction (*) over small spherical volumes (SVC, 15 mm radius) or (***) over the whole brain. (#) Coordinates marginally significant after correction over small spherical volumes (SVC, 15 mm radius).*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
[Blind > Sighted] X [Objects + Voices + ScrO + ScrV]					
L Middle Occipito-Temporal Gyrus	-48	-72	6	5.01	0.007***
R Inferior Occipito-Temporal Gyrus	46	-64	-4	4.57	0.042***
R Lateral Occipito-Temporal Sulcus	48	-44	-16	4.56	0.045***
R Middle Occipital Gyrus	34	-84	10	3.82	0.008*
L Lateral Occipito-Temporal Sulcus	-46	-46	-14	3.56	0.016*
L Superior Occipital Gyrus	-20	-82	36	3.33	0.03*

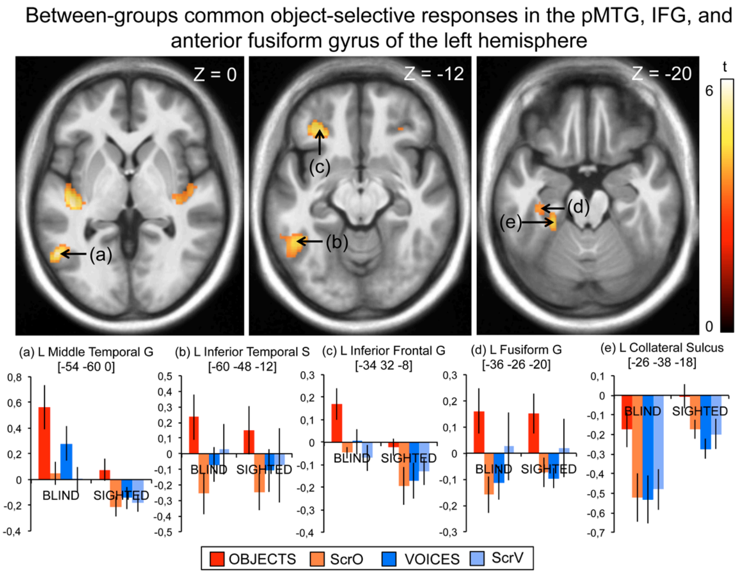
Supplemental Table 3. *Summary of the functional results obtained for the main effect of group (Blind > Sighted) independently of condition. Coordinates are significant ($p_{corr} < 0.05$ FWE) after correction over (*) small spherical volumes (SVC, 15 mm radius) or over (***) the whole brain.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
(1) [Blind > Sighted] X [Objects > ScrO]					
L Middle/Inferior Occipital G	-36	-80	-2	5.64	0.000***
L Inferior Occipital Gyrus	-22	-92	-6	5.58	0.001***
L Fusiform Gyrus	-38	-68	-14	5.43	0.001***
R Inferior Occipito-Temporal Gyrus	40	-64	-4	5.46	0.001***
R Fusiform Sulcus	36	-42	-18	5.33	0.002***
R posterior Middle Temporal Gyrus	50	-68	10	5.03	0.007***
(2) [Blind > Sighted] X [Objects > Voices]					
R Inferior Occipito-Temporal Gyrus	40	-66	-6	5.56	0.001***
R Fusiform Gyrus	32	-76	-2	4.96	0.011***
R Lateral Occipital Sulcus	34	-84	6	4.83	0.019***
L Middle/Inferior Occipital Gyrus	-36	-78	-4	5.54	0.001***
L Lateral Occipital Sulcus	-34	-80	8	5.47	0.001***
L Middle Occipital Gyrus	-26	-90	8	5.38	0.002***
R Superior Occipital Gyrus	22	-74	22	4.93	0.013***
L Cuneus	-10	-90	34	4.80	0.022***
R Cuneus/Superior Occipital Gyrus	16	-94	24	4.77	0.025***
R Superior Occipital Gyrus	22	-78	36	4.60	0.048***
(3) Conjunction of (1) and (2)					
L Middle/Inferior Occipital G	-36	-78	-4	5.50	0.001***
L Middle Occipital Gyrus	-26	-90	8	5.36	0.002***
L Fusiform Gyrus	-32	-56	-12	4.79	0.018***
R Inferior Occipito-Temporal Gyrus	40	-64	-4	5.46	0.001***
R Inferior Occipital Gyrus	32	-80	-2	4.62	0.035***
R Middle Occipital Gyrus	36	-84	10	4.75	0.022***

Supplemental Table 4. *Summary of the functional results obtained for the Group by Task interaction analyses testing for (1) larger responses to Object sounds relative to ScrO in EB relative to SI, (2) larger responses to Object sounds relative to Voices in EB relative to SI, (3) Conjunction of (1) and (2). (***) Coordinates are significant ($p_{corr} < 0.05$ FWE) after correction over the whole brain.*

Area	X (mm)	Y (mm)	Z (mm)	Z	p
[Blind > Sighted] X [Voices > ScrV]					
R Fusiform G	32	-60	-18	3.59	0.015*
R Fusiform G	42	-46	-8	3.32	0.032*
L Fusiform G	-36	-46	-22	3.63	0.014*
L Lateral Occipito-Temporal Sulcus	-40	-50	-10	3.47	0.022*

Supplemental Table 5. *Summary of the functional results obtained for the Group by Task interaction analyses testing for larger responses to Voices relative to ScrV in EB relative to SI. There were no significant activations for the contrast testing for larger responses to Voices relative to Object sounds in EB relative to SI. (*) Coordinates are significant ($p_{corr} < 0.05$ FWE) after correction over small spherical volumes (SVC, 15 mm radius).*



Between-groups common object-selective responses in the pMTG, IFG, and anterior fusiform gyrus of the left hemisphere

(a) L Middle Temporal G [-54 -60 0]

(b) L Inferior Temporal S [-60 -48 -12]

(c) L Inferior Frontal G [-34 32 -8]

(d) L Fusiform G [-36 -26 -20]

(e) L Collateral Sulcus [-26 -38 -18]

Supplementary Figure 1. *Common Task-related brain activity for object sounds (relative to both Voices and Scrambled Objects) common to blind and sighted participants are displayed at* $p_{uncorr} < 0.001$ *over transversal slices of the mean structural image of all subjects normalized to the same stereotaxic space. Color bar represents t-values. Mean activity estimates (arbitrary units ± SEM) in the blind and the sighted.*

Chapter 4.

Tracking the evolution of crossmodal plasticity and visual recovery before and after sight-restoration[10]

Abstract

Visual deprivation leads to massive reorganization in both the structure and function of the occipital cortex, inevitably raising crucial challenges for sight-restoration. We tracked the behavioral, structural and neurofunctional changes occurring in an early and severely visually impaired patient before as well as 1.5 and 7 months after sight restoration using magnetic resonance imaging. Robust pre-surgical auditory responses were found in occipital cortex despite residual preoperative vision. In primary visual cortex, crossmodal auditory responses overlapped with visual responses and remained elevated even 7 months post-surgery. However, these responses decreased in extrastriate occipital regions after surgery, together with improved behavioral vision and with increases in grey matter density and neural activation in low-level visual regions. Visual selective responses in high-level visual regions involved in motion and face processing were present even pre-surgery and did not evolve after surgery. Altogether, these findings demonstrate that structural and functional reorganization of occipital regions are present in an individual with a longstanding history of severe visual impairment, and that such reorganizations can be partially reversed by visual restoration in adulthood.

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[10] This chapter is a slightly modified version of a manuscript with the same title by authors Dormal, Lepore, Harissi-Dagher, Albouy, Bertone, Rossion, & Collignon that is currently under review.

Tracking the evolution of crossmodal plasticity and visual recovery before and after sight-restoration

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1. Introduction

One of the most striking examples of experience-dependent brain plasticity originates from studies of blind individuals, whose cortical areas normally devoted to vision reorganize to support non-visual functions (Bavelier & Neville, 2002; Noppeney, 2007). This crossmodal plasticity inevitably raises important challenges for individuals undergoing surgical procedures to recover vision, as the deprived and reorganized occipital cortex may not provide the necessary cortical resources for adequate visual analysis of the restored optical input (Collignon, Champoux, Voss, & Lepore, 2011a; Merabet & Pascual-Leone, 2009). Support for this assumption comes from research conducted on deaf individuals demonstrating that the success of cochlear implants is inversely related to the amount of visual activity measured in the auditory cortex (Lee et al., 2007; Sandmann et al., 2012; Strelnikov et al., 2013). Empirical investigations of this question in visually-deprived individuals are very scarce. Historical cases of sight-recovery in adulthood after longstanding blindness typically encounter severe visual deficits even years following the intervention (Ackroyd et al., 1974; Carlson et al., 1986; Fine et al., 2003; Gregory & Wallace, 1974). Only one functional Magnetic Resonance Imaging (fMRI) study to date jointly investigated occipital visual and crossmodal responses in two early blind patients whose vision was partially restored in adulthood and demonstrated robust and specific crossmodal auditory motion responses coexisting with regained visual motion responses in area MT+/V5 (Saenz et al., 2008). However, since this study was carried out several years after sight restoration, no observations were reported about the evolution of the occipital cortex functional tuning before and after sight was regained.

In addition, neuroimaging studies exploring the impact of longstanding visual deprivation on sight-recovery were carried out in individuals experiencing total blindness since early infancy (i.e. diffuse light perception at most) (Fine et al., 2003; Röder et al., 2013; Saenz et al., 2008). However, most cases of vision loss occur gradually and individuals often maintain some degree of residual sensory function (Merabet & Pascual-Leone, 2009). Surprisingly, the question of whether crossmodal plasticity may be observed even in cases where the sensory deprivation is not total remains largely unexplored. This is an issue of particular relevance considering these individuals are the main targets of new advances in surgical procedures to restore vision (Aldave, Kamal, Vo, & Yu, 2009; Robert & Harissi-Dagher, 2011).

In the present study, we provide the first extensive longitudinal investigation of a case of sight-recovery after a life-long history of severe visual impairment. We performed both pre- and post-surgery measurements and combined behavioral, neurostructural (MRI) and neurofunctional (fMRI) methods in order to test the presence of crossmodal plasticity prior to surgery despite residual visual functions and investigate its evolution together with visual recovery within face and motion processing systems.

2. Materials and Methods

2.1. Case Description

KL is a right-handed female, born in 1965 in Meteghan, Nova Scotia in a family with low socio-economical status. Her visual impairment history was assessed by obtaining access to her medical records, by discussing the case with the ophthalmologist who carried out the ophthalmic procedure (MHD in the authorship), and by carrying out detailed anamneses with her and with her 9 years older brother. KL's vision has been highly altered since very early in life. At 10 months of age, her parents and older brothers noticed a lack of visually guided behavior and an inability to avoid obstacles around her. She was diagnosed with dense bilateral cataracts between 2 and 3 years of age, which were surgically removed at that time by extraction of the crystalline lens bilaterally. The surgery was not successful in restoring functional vision since she has only experienced residual patterned, color and motion information in the right eye but none in the left. The left eye was deemed amblyopic. During infancy and adolescence, she attended school in specific classes for children with learning disabilities. At that time, she would always sit a few feet away from the black board and was capable of reading in books with large letters from a distance of about 5 inches. She had to stop attending school in grade 8 (first year of high school), as there were no more adapted classes and her vision was too altered to allow her to attend regular classes. At home she would rather listen to music than watching television and when she did it was from about 3 inches from the screen. She never played any sports involving a ball as she was unable to see it on time in order to catch it. KL and her older brother recall it was never possible for her to recognize anyone familiar solely based on their face.

KL got married and moved from Nova Scotia to Quebec in 1984. In 1996, rhegmatogenous retinal detachment occurred in her right eye for which she underwent surgical repair by pars plana vitrectomy. In 2000, a rhegmatogenous retinal detachment occurred again in the same eye, which was also repaired by pars plana vitrectomy. She worked as a dishwasher in a restaurant between 1995 and 2005 and as a nurse aid from 2005 to 2007, until her vision decreased even more to a point were she stopped working completely. A corneal graft was attempted in her right eye in December 2008 and an anterior chamber lens was implanted to correct the refractive power. The corneal graft was rejected in September 2010. A second corneal graft was attempted in October 2010 and was rejected again 3 months later. At that point, visual acuity in her medical records was reported to be 20/300 and KL resorted to using a white cane. A Boston Keratoprosthesis was implanted in her right eye in April 2012. A soft contact lens with optical correction of -0.5 diopters was placed to protect the eye. KL was tested with this correction at Post 1.5m. In August 2012, the optical correction of the lens was increased to -6 diopters to improve distance vision, and KL was prescribed glasses with optical correction of +2 diopters for near vision. KL was tested with this correction at Post 7m.

2.2. General experimental design and control participants

KL was tested in 3 separate sessions involving identical behavioral, MRI and fMRI procedures. The first session, referred to as *Pre*, took place 3 weeks (18 days) prior to surgery. The two other sessions, referred to as *Post 1.5m* and *Post 7m*, took place 1.5 months (48 days) and 7 months (218 days) following visual restoration with Boston Keratoprosthesis (Khan, Harissi-Dagher, Khan, & Dohlman, 2007). Behavioral tasks consisted of computerized tests evaluating visual acuity, contrast sensitivity, global motion detection, face/non-face categorization and individual face discrimination. Each neuroimaging session comprised four functional runs followed by the acquisition of a high-resolution anatomical image in order to investigate structural changes across time. Functional runs consisted of a motion localizer, a face localizer, and two auditory experiments. Visual runs aimed at testing residual visual functions within key neural systems of the dorsal and of the ventral visual pathways. The two auditory experiments tested the presence of crossmodal recruitment of occipital regions by sounds, as a result of longstanding visual impairment. Three normally sighted (SI) right-handed females with corrected-to-normal vision and aged 55, 40 and 52, were tested in the behavioral experiments and served as control participants. For MRI measures, we used previously acquired anatomical images from 9 normally sighted subjects (3 females) who were scanned on two occasions separated by a delay ranging between 35 days and 3.5 years (mean delay ± SD = 1.45 ± 1.32 years ; mean age at Scan 1 ± SD = 35 ± 10 years ; mean age at Scan 2 ± SD = 36 ± 10 years). For fMRI experiments, we used previously acquired data with identical paradigms from 12 sighted controls (SI) with normal or corrected-to-normal vision for the motion localizer, the face localizer and the auditory experiment 1 (4 females, mean age ± SD = 29 ± 4,3 years), and from 17 sighted (SI) with normal or corrected-to-normal vision (9 females, mean age ± SD = 40 ± 14 years), 12 early blind (4 females, mean age ± SD = 41 ± 11 years), and 10 late blind individuals (8 females, mean age ± SD = 48 ± 11 years) for the auditory experiment 2 (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). All participants gave their written informed consent to take part in the study, which was approved by the research ethic and scientific boards of the Quebec Bio-Imaging Network (QBIN), the Notre-Dame hospital (CHUM) and the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR).

2.3. Behavioral experiments

Behavioral tasks consisted of computerized tests evaluating distance visual acuity, contrast sensitivity function, global motion detection thresholds, face/non-face categorization and face individuation abilities. They were administered in a dimly lighted room and presented on a Viewsonic (PT775) CRT monitor (330 mm x 245 mm). Stimulus generation, presentation and data collection for tests of distance visual acuity, contrast sensitivity and global motion detection were controlled by a Macintosh Pro 2.8 GHz Quad-Core Intel Xeon using DataPixx (www.vpixx.com) graphic program and visual stimulator (16-bit video digital-to-analogue converter (DAC)). The mean luminance of the display was 50.0 cd/m^2 (x = 0.2783, y = 0.3210 in CIE (Commission Internationale de l'Eclairage) u' v' color space) where L_{min} and L_{max} were 0.5 and 99.50 cd/m^2, respectively. Screen resolution was 1280 x 1024 pixels and refresh rate was 85 Hz. Stimulus presentation and data collection for the face/non-face categorization and the face individuation tasks were controlled with an HP Compaq dc5850 Microtower PC using E-prime2 (Psychology Software Tools). Screen resolution was 1024 x 768 pixels and refresh rate was 60 Hz.

Measures of distance visual acuity, contrast sensitivity and global motion detection were performed with MLPEST algorithm (Harvey, 1997) implementing the maximum-likelihood adaptive staircase method for estimating sensory thresholds. The staircase fitted a new psychometric function to the data after each trial and ended after a 90% confidence level that the detection threshold estimate fell within ±0,1 log units of the true threshold measure. In all of these tasks, responses were given verbally by the participants and were encoded by the experimenter. Luminance readings and gamma correction were verified using a Minolta CS-100 Chroma Meter colorimeter on a regular basis.

2.3.1. Distance Visual Acuity. Distance visual acuity was measured binocularly and monocularly using a Landolt-C paradigm at a distance of 285 cm from the computer screen (with the exception of KL at Pre who was tested at 100 cm because of her impossibility to carry out the task at the same distance). Stimuli corresponded to high contrast white optotypes ($L_{optotype}$ = 99.5 cd/m^2) on a black background ($L_{background}$ = 0.5 cd/m^2). Participants were asked to identify the orientation (up, down, left or right) of the gap opening of the optotype using a four alternative forced-choice paradigm. Far visual acuity was defined by Snellen decimal acuity, the reciprocal of the smallest resolvable visual angle of the optotype gap in arc minutes needed to correctly identify its orientation.

2.3.2. Contrast Sensitivity. Contrast sensitivity function (CSF) was assessed binocularly at a distance of 57 cm from the computer screen, by measuring contrast detection thresholds to luminance-defined vertically-oriented sine-wave gratings with smoothed edges (in gaussian envelope) of different spatial frequencies. Gratings size was 20° x 20° when viewed from 57 cm. The mean luminance of the remainder of the display was 50 cd/m^2. Detection thresholds were measured separately for gratings of 0.25, 0.5, 1, 2, 4, 6 and 8 cycles per degree (cpd). In each trial, the target grating appeared in either one of two successively presented frames of 1 s duration each and separated by a 200 ms interval. A sound was emitted concomitantly to each frame presentation. Participants were instructed to indicate verbally in which presentation, the first or the second, the target grating was present. The non-target presentation consisted of a uniform gray screen. The contrast sensitivity function was calculated for each participant using the inverse of the contrast detection threshold measured for each spatial frequency.

2.3.3. Global Motion Detection. Global motion detection thresholds were measured separately for radial and vertical trajectories at a distance of 57 cm from the computer screen. Stimuli consisted of limited lifetime random-dot kinematogram displays (RDKs) (Newsome & Paré, 1988). A hundred white dots (0.75° diameter, $L_{dots} = 99.5$ cd/m^2) were presented against a 23° x 23° black background square ($L_{background} = 0.5$ cd/m^2) and moved at a speed of 12°/sec. A subset of randomly chosen (signal) dots moved in the same direction whereas the remaining (noise) dots in the display moved in random directions. Signal strength was manipulated by varying the percentage of signal dots in the display. The dots had a limited lifetime of 250 ms to ensure that the global direction of motion could not be simply detected based on local motion information. In the radial task, signal dots moved toward (contracting) or away from (expanding) the center of the screen. In the vertical task, signal dots moved upward or downward. In line with previous studies that have used comparable radial RDKs stimuli (Burr & Santoro, 2001), the magnitude of the dot displacement in the radial task was always constant across space so that it did not differ from the vertical task in terms of local speed. We measured a coherence threshold for each of the 2 tasks (minimum percentage of signal dots required to accurately detect the overall direction of motion). Participants were instructed to identify the direction of the dots that were coherently moving towards the same direction. Each trial lasted for maximum of 5 seconds, or until participants responded.

KL's distance visual acuity for binocular and monocular vision (in Snellen decimal acuity), contrast detection thresholds at each spatial frequency (in percentage), global motion detection thresholds (in percentage) measured at Pre, Post 1.5m and Post 7m were compared to the controls by means of the modified t-test of Crawford et al. (Crawford, Garthwaite, & Porter, 2010), specifically designed for comparing an individual's test score against norms derived from small samples. Here we used a p-value 0.05 within the framework of a unilateral hypothesis. Consequently, KL's thresholds associated with a one-tailed p-value below 0.05 were considered as reflecting a significant difference relative to the controls. Analyses were conducted using a computerized version of the method (SINGLIMS_ES.exe).

2.3.4. Face/Non-face Categorization. Face categorization was assessed using a sequential two alternative forced choice delayed matching task (2AFC). A total of 48 greyscale pictures of full front faces (half male) and full front cars were used in this task. Pictures measured 300 pixels in height (about 9.5° on the screen) with a width ranging between 200 and 250 pixels for faces (about 7.5° on the screen), and between 350 and 400 pixels for cars (about 12° on the screen). All pictures were equalized for luminance using the SHINEtoolbox (Willenbockel et al., 2010) implemented in MATLAB (Mathworks). Each trial consisted of the presentation of either a face or a car at the centre of the screen during 360 ms and followed, after a 1000 ms delay, by the central presentation of two objects (one of each category) arranged the one on top of the other, which remained on the screen until a response was given. The task was to determine which object, the face or the car, had been presented at encoding. Participants were instructed to respond as accurately and as fast as possible. Forty-eight trials were administered in total, in half of the trials the encoding item was a face, in the other half the encoding item was a car.

Both accuracy rates and correct response times (RTs) were considered for analyses. A chi-square test for independence was performed on KL's accuracy (1 versus 0 at each trial) in order to test for any significant change in accuracy across time. Only correct response times that were below 2000 ms were considered for analyses and were ln-transformed in order to meet criterion of normal distribution for the use of parametric tests. Ln-transformed correct RTs that were below or above 3 standard deviations from the mean of each session were excluded. To compare KL's response speed across time, a one-way repeated-measure ANOVA and post-hoc t-tests were conducted on ln-transformed correct RTs with Session (Pre, Post 1.5m, Post 7m) as a within-subject factor. Finally, KL's performance in each session (overall accuracy and ln-transformed correct RTs) was compared to the controls' by means of the modified t-test of Crawford et al. (2010) using a p-value 0.05 within the framework of a unilateral hypothesis.

2.3.5. Face Individuation. Face individuation for full front faces and depth-rotated (¾ profile) faces were assessed using two separate tasks. Both tasks consisted of a sequential two alternative forced choice delayed matching paradigm (2AFC). Stimuli consisted of 100 pictures of full front faces (half male) and of 96 pictures of depth rotated (¾ profile) faces (identical identity). They all measured 300 pixels in height (about 9.5° on the screen) with a width ranging between 200 and 265 pixels (about 7° on the screen). All faces were greyscale, cropped for external features, and equalized for luminance using SHINEtoolbox (Willenbockel et al., 2010) implemented in MATLAB (Mathworks). Each trial consisted of the presentation of a face for 500 ms and followed, after a 1000 ms delay, by the central presentation of two faces arranged the one on top of the other, which remained on the screen until response was given. The exact same faces were presented at upright and inverted (vertically flipped) orientations in four separate blocks (upright – inverted – inverted – upright) within each task. Tasks consisted of identifying within each trial, which face was presented at encoding. Participants were instructed to respond as accurately and as fast as possible. In the first task, the target face and the subsequent faces were all presented full front. In the second task, the target face was presented full front whereas the subsequent faces were depth-rotated (3/4 profile). A hundred trials (half upright) were administered in the first task, and 96 trials (half upright) were administered in the second task.

Both accuracy rates and correct response times (RTs) were considered for analyses. A binomial test was conducted on KL's accuracy scores (1 versus 0 at each trial) within each session, separately for upright and inverted orientations in order to test whether performance significantly differed from chance. As KL performed at chance pre-surgery in both tasks and with both orientations, we conducted subsequent analyses only on post-surgery data. Chi-square tests for independence were performed on KL's accuracy scores (1 versus 0 at each trial) in order to test for any significant between-session change in performance separately for upright and inverted orientations and in order to test for a face inversion effect within each post-surgery session. The same test was conducted on each of the controls' accuracy scores (1 versus 0 at each trial) in order to test for the presence of a face inversion effect at the individual level. Only correct response times that were below 5000 ms were considered for analyses and were ln-transformed in order to meet criterion of normal distribution for the use of parametric tests. Ln-transformed correct RTs that were below or above 3 standard deviations from the mean of each session were excluded. A two-way between-groups ANOVA and post-hoc t-tests were conducted on KL's ln-transformed correct RTs to explore the impact of Orientation (upright vs. inverted) and Session (Post 1.5m, Post 7m) on response speed. To test the presence of a face inversion effect in each of the controls separately, independent t-tests were conducted on ln-transformed correct RTs. Finally, KL's performance within each task (overall accuracy and ln-transformed correct RTs) at each orientations in each of the post-surgery sessions was compared to the controls' by means of the modified t-test of Crawford et al. (2010) for single-case studies using a p-value 0.05 within the framework of a unilateral hypothesis.

2.4. fMRI experiments

KL was scanned in three separate fMRI sessions lasting about 1.5 hour each, and consisting of four different experiments (one functional run for each experiment) followed by the acquisition of a high-resolution anatomical image. Functional runs were block designs consisting of a motion localizer, a face localizer, and two auditory experiments. Before each fMRI acquisition, KL and controls underwent a 45 minutes training session in a mock scanner. Recorded scanner noise played in the bore of the simulator while practicing the tasks in order to familiarize them with the fMRI environment. In the scanner, visual stimuli were projected onto a mirror (127 mm x 102 mm) that was mounted at a distance of about 12 cm from the eyes of the participants. Auditory stimuli were delivered by means of circumaural, fMRI-compatible headphones (Mr Confon, Magdeburg, Germany).

2.4.1. Motion Localizer. The motion localizer run lasted 9 min and consisted of radially moving dots and static images of the same dots alternating in a block design with 18 s blocks that were each repeated 10 times. Stimuli in both conditions consisted of large white dots (about 1.5° in the scanner) on a black background (about 45° x 45° in the scanner), randomly placed at a minimum radius (about 3° in the scanner) from a central white fixation cross (about 2° x 2° in the scanner). Blocks were separated by a baseline (white fixation cross on a black background) lasting 7, 9 or 11 s (9 s on average). In the Motion blocks, 6 consecutive radially moving stimuli each lasting 3 seconds (1.5 s of expansion and 1.5 s of contraction) were presented (no ISI) (dots lifetime: 250 ms, velocity: about 15°/s in scanner). In the static blocks, 6 consecutive frames were presented in random order for 3 seconds each (no ISI). Occasionally, the background of the display turned from black to grey for 500 ms. Within each condition, there were 3 blocks with one such target, 3 blocks with 2 such targets and 4 blocks with no targets at all. The task consisted of detecting that color change and press a response key with the right index finger.

2.4.2. Face Localizer. The face localizer run lasted 15 minutes and consisted of 8 repetitions of each of 4 conditions, alternating in blocks of 19.35 s. Each condition consisted of a different category: faces, cars and their phase-scrambled version (Rossion et al., 2012). Pictures measured 210 x 184 (about 20° width x 25° height in the scanner). The Face category consisted of full front pictures of 43 (22 females) different faces that were cropped for external features and embedded in a grey rectangle. Similarly, the Car category consisted of full front pictures of 43 different cars inserted in a grey rectangle.

Pictures of faces and cars were equalized for luminance and presented in color. The phase-scrambled pictures were used in order to control spatial frequencies and pixel intensity in each color channel (RGB) in the Face and in the Car categories. They were created using a Fourier phase randomization procedure by replacing the phase of each original image by the phase of a uniform noise allowing for amplitude to be conserved in each frequency band (Sadr & Sinha, 2004). Blocks were separated by a baseline condition (white fixation cross of about 2° x 2° on a black background) lasting 7, 9 or 11 s (9 s on average). In each block, 43 images were presented on a black background for 380 ms with a 70 ms ISI. Occasionally, a picture was replaced by a uniform gray rectangle (380 ms) that the participant had to detect by pressing a key with the right index finger. Within each condition, there were 3 blocks with one such target, 2 blocks with 2 such targets and 3 blocks with no targets at all.

2.4.3. Auditory Experiment 1: Voices versus horizontally moving sounds. Participants were instructed to keep their eyes closed during this run. The run lasted about 13 minutes and consisted of 2 conditions alternating in blocks of 16.8 s with 15 repetitions for each condition. The 2 conditions consisted of human voices and horizontally moving sounds which were matched for low-level properties. Human voices were vowels ‘a’, ‘e’, ‘i’, ‘o’, ‘u’, pronounced by 12 different francophone speakers (half male) recorded in the lab. They were cut at 700 ms (695ms + 5ms silence) and normalized for overall RMS using MATLAB) (Mathworks). Target vowels consisted of a longer vowel lasting 1400 ms. Original and target vowels were then concatenated (no ISI) into 10 blocks of 16.8 s, such that 5 blocks contained 1 target (23 stimuli total), 5 blocks contained 2 targets (22 stimuli total) and 5 blocks contained 3 targets (21 stimuli total). Blocks of horizontally moving sounds were created based on the frequency-scrambled version of the vocal blocks. Firstly, the vocal blocks were Fourier fast transformed and cut into frequency windows of 150 Hz. Scrambling was then performed by randomly intermixing the amplitude and frequency of each Fourier component (Belin et al., 2000) within each of these frequency windows separately. The inverse Fourier transform was then applied on the resulting signal. The output was a sound of the same length of the original vocal block with similar energy within each frequency band. Secondly, an envelope was created and applied on each scrambled block. This envelope consisted of 21 (3 targets blocks), 22 (2 targets blocks) or 23 (1 target blocks) linear ramps going from 0 to maximal intensity and from maximal intensity to 0 every 700 ms (or 1400 ms when position in the scrambled block corresponded to a target in the original vocal block). This envelope was applied separately for the left and the right ear resulting in a stereo sound where intensity would increase in one ear, and decrease simultaneously in the other ear, creating the vivid perception of a sound moving from one ear to the other in the azimuth every 700 ms (or 1400 ms for target moving sounds). Blocks were separated by rest periods of 7, 9 or 11 s (9 s on average). Occasionally, a stimulus (either a vowel or a moving sound) lasted longer (1400 ms). The task was to detect that target and press a response key with the right index finger. Stimuli and task were modeled after those used in previous studies of crossmodal verbal/voice responses (Gougoux et al., 2009) and motion responses (Poirier et al., 2006; Saenz et al., 2008) in blind subjects.

2.4.4. Auditory Experiment 2: Spatial versus pitch discrimination. Stimuli and paradigm were identical to the ones used in previous studies of our group (see (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b) for a full description of the procedure). Participants that were tested in these studies were blindfolded at that time. However, because KL in the present study had to perform visual experiments within the same scanning session, she was simply instructed to keep her eyes closed during this run. During both auditory runs, the scanning room was put in complete darkness by shutting down the light of the room and of the projector, resulting in complete obscurity, and ensuring that no light was perceived even through the closed eyelids.

2.5. MRI/fMRI data acquisition

The fMRI series were acquired using a 3T TRIO TIM system (Siemens) equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (time to repetition (TR) 2200 ms; echo time (ET) 30 ms; flip angle (FA) 90°; 35 transverse slices; 3.2 mm slice thickness; 0.8 mm (25%) inter-slices gap; field of view 192 x 192 mm^2; matrix size 64 x 64 x 35; voxel size 3 x 3 x 3.2 mm^3). The 3 (in all runs except auditory experiment 2) or 4 (in auditory experiment 2) initial scans were discarded to allow for steady-state magnetization. A structural T1-weigthed 3D magnetization prepared rapid gradient echo sequence (voxel size 1 x 1 x 1.2 mm^3; matrix size 240 x 256; TR 2300 ms; ET 2.91 ms; TI 900 ms; FoV 256; 160 slices) was also acquired in each session. Functional volumes were preprocessed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/; Welcome Department of

Imaging Neuroscience, London), implemented in MATLAB (Mathworks). Preprocessing included the realignment of functional time series, the coregistration of functional and anatomical data, a spatial normalization to an echo planar imaging template conforming to the Montreal Neurological Institute space, and a spatial smoothing (8 mm Full Width at Half Maximum (FWHM) isotropic Gaussian kernel).

2.6. MRI data analysis: Voxel Based Morphometry (VBM)

Anatomical images acquired in the Pre, Post 1.5m and Post 7m session were preprocessed using the vbm8 toolbox of SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/, London, UK). The 'Process Longitudinal Data' module, taking into account the characteristics of intra-subject analysis, was used to perform these analyses. Following an initial realignment of the anatomical images from the 3 sessions, the mean image was calculated and was used as a reference image for a subsequent realignment. Realigned anatomical images were then corrected for signal inhomogeneity with regard to the reference (mean) image. Bias-corrected realigned images from each session were segmented into grey matter, white matter and cerebrospinal fluid. This procedure resulted in a set of nine images (3 tissue probability maps for each session of the 3 sessions) in the same space as the original T1-weighted image, in which each voxel was assigned a probability of being grey matter, white matter, and cerebrospinal fluid, respectively. These images were spatially smoothed with an 8 mm (FWHM) isotropic Gaussian kernel.

In order to estimate the variability of the measure (including error noise) that should be expected when comparing grey matter tissue probability maps (GM TPM) from anatomical images acquired on separate sessions, we performed identical analyses on the anatomical images of 9 normally sighted participants who were scanned on two separate occasions (Scan 1 and Scan 2).

Statistical analyses were computed as follows. Firstly, we calculated between-session differential images in KL and in each control subject using the ImCalc function implemented in SPM. This lead to 3 differential images in KL (*Post 7m - Pre*, *Post 1.5m - Pre*, *Post 7m - Post 1.5m*) (Figure 2A and 2B) and 1 differential image in each control subject (*Scan 2 - Scan 1*). Secondly, for each of these 13 differential images, we calculated the mean and standard deviation of the distribution of differential values obtained within each voxel across the brain (Figure 2A and 2B). As expected, mean absolute differences (increases or decreases) between Scan 1 and Scan 2 in controls were close to 0, with a change of 0.4% on average (range = min. 0.15% - max. 0.82%, SD = 0.25%). Similarly in KL, mean absolute between-session differences were 0.08% (within normal range) in the Post 7m - Post 1.5m differential image. In contrast, mean absolute between-session differences in KL in Post 1.5m and Post 7m relative to Pre were 1.32% and 1.22%, respectively, more than 3 SD above the mean of controls. Thus, only the latter differential images were considered for further analyses in KL. Across KL's brain, we defined voxels showing significant differences at Post 1.5m relative to Pre and at Post 7m relative to Pre, as the ones displaying the largest 1% increases or decreases within each differential image (± 3SD from the mean of the distribution of changes, see grey shaded areas in Figure 1A and 1B). Finally, to ensure reliability of the changes across sessions, we reported only those voxels that passed the statistical threshold in both Post 1.5m and Post 7m sessions relative to Pre (i.e. voxels showing significant gains/losses both in Post 1.5m (≥8.07%/≤-5.43%) and Post 7m (≥8.45%/≤-6.01%) relative to Pre) (Figure 1C).

2.7. fMRI Data Analysis

Analyses of fMRI data in KL (3 sessions) and in controls (1 session, see *General design and control participants* section) were performed based on a mixed effects model, and were conducted in a single step accounting for fixed effects. Changes in brain regional responses in KL were estimated by a general linear model including 6 regressors in the motion localizer (2 conditions x 3 sessions), 12 regressors in the face localizer (4 conditions x 3 sessions) and 6 regressors in each of the two auditory experiments (2 conditions x 3 sessions). In controls, changes in brain regional responses were estimated by a general linear model including 2 regressors in the motion localizer, 4 regressors in the face localizer and 2 regressors in each of the two auditory experiments. These regressors consisted of a boxcar function convolved with the canonical hemodynamic response function. For each session, the movement parameters derived from realignment of the functional volumes (translations in the x, y and z directions and rotations around the x, y and z axes) and a constant vector were included as covariates of no interest. In addition, for each session of the auditory experiment 2, the instructions preceding each block were further included as a covariate of no interest. High-pass filtering was implemented in sessions using a cut-off period of 128 s to remove slow drifts from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

In controls, contrasts of interest in each of the 4 experimental runs were performed as follows. In the motion localizer, the contrast [Motion > Static] identified motion-specific responses. In the face localizer, a conjunction analysis was performed in order to identify face-specific responses relative to both scrambled faces and to cars [Face > ScrFaces ∩ Face > ScrFaces] (Rossion et al., 2012). In auditory experiment 1, the contrast [Motion + Voice] tested the global processing of sounds, and the contrasts [Motion > Voice] and [Voice > Motion] tested specific processing of motion and voices. Finally, in auditory experiment 2, the contrast [Spatial + Pitch] tested the global processing of sounds, and the contrasts [Spatial > Pitch] and [Pitch > Spatial] tested specific processing of spatial and pitch attributes of sounds (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b).

In KL, for each of the 4 experimental run separately, analyses were performed in two steps. Firstly, a conjunction (AND) analyses between sessions [Pre ∩ Post 1.5m ∩ Post 7m] was performed on contrasts of interest in order to identify regions that were consistently activated in a given contrast across sessions (motion Localizer: motion-specific responses across sessions [Motion > Static Pre ∩ Post 1.5m ∩ Post 7m]; auditory experiment 1: global processing of sounds across sessions [Motion + Voice Pre ∩ Post 1.5m ∩ Post 7m], specific processing of moving sounds across sessions [Motion > Voice Pre ∩ Post 1.5m ∩ Post 7m] and specific processing of voices across sessions [Voice > Motion Pre ∩ Post 1.5m ∩ Post 7m]; auditory experiment 2: global processing of sounds across sessions [Spatial + Pitch Pre ∩ Post 1.5m ∩ Post 7m], spatial processing of sounds across sessions [Spatial > Pitch Pre ∩ Post 1.5m ∩ Post 7m] and pitch processing across sessions [Pitch > Spatial Pre ∩ Post 1.5m ∩ Post 7m]). In the face localizer, the conjunction was performed across sessions [Pre + Post 1.5m + Post 7m] in order to identify face-specific responses relative to both scrambled faces and to cars when considering all sessions [Face all sessions > ScrFaces all sessions ∩ Face all sessions > ScrFaces all sessions] (Rossion et al., 2012). Secondly, between-session comparisons were performed using linear contrasts testing for significant between-session brain responses between conditions of interest (motion localizer: linear contrasts testing the effect of session on motion-specific responses ([Motion > Static X Post 1.5m > Pre]; [Motion > Static X Post 7m > Pre], [Motion > Static X Post 7m > Post 1.5m]); face localizer: conjunctions between linear contrasts testing the effect of session on face-specific responses relative to both scrambled faces and cars ([Faces > ScrFaces ∩ Faces > Cars X Post 1.5m > Pre]; [Faces > ScrFaces ∩ Faces > Cars X Post 7m > Pre], [Faces > ScrFaces ∩ Faces > Cars X Post 7m > Post 1.5m]); auditory experiment 1: linear contrasts testing the effect of session for general auditory processing [Motion + Voice X Pre > Post 1.5m], [Motion + Voice X Pre > Post 7m], [Motion + Voice X Post 1.5m > Post 7m], for specific processing of moving sounds [Motion > Voice X Pre > Post 1.5m], [Motion > Voice X Pre > Post2], [Motion > Voice X Post 1.5m > Post 7m] and for specific processing of voices [Voice > Motion X Pre > Post 1.5m], [Voice > Motion X Pre > Post 7m], [Voice > Motion X Post 1.5m > Post 7m]; auditory experiment 2: linear contrasts testing the effect of session for general auditory processing [Pitch + Spatial X Pre > Post 1.5m], [Pitch + Spatial X Pre > Post 7m], [Pitch + Spatial X Post 1.5m > Post 7m]), for the spatial processing of sounds [Spatial > Pitch X Pre > Post 1.5m], [Spatial > Pitch X Pre > Post 7m], [Spatial > Pitch X Post 1.5m > Post 7m], and for pitch processing [Pitch > Spatial X Pre > Post 1.5m], [Pitch > Spatial X Pre > Post 7m], [Pitch > Spatial X Post 1.5m > Post 7m]).

Statistical inferences on the t-statistics maps resulting from contrasts of interest were performed at a threshold of $p<0.05$ after correction for multiple comparisons over the whole brain (Family Wise Error method) or over small spherical volumes (15mm radius) located in regions of interest (SVC). Significant clusters extended to at least 10 contiguous voxels - unless localized in regions of interest - and were anatomically labelled using structural neuroanatomy information provided by the Anatomical Automated Labelling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) and Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). Automatic labelling was systematically and carefully checked. In order to ensure reliability of the changes across sessions in KL, between-session comparisons of brain responses in Pre vs. Post 1.5m session and in Post 1.5m vs. Post 7m session were masked inclusively ($p_{uncorr} < 0.001$) by the between-session contrast comparing brain responses in Pre vs. Post 7m session. Doing so, we only included regions showing between-session changes that were consistent over time (e.g. regions showing a differential effect when comparing Pre vs. Post 1.5m for a given contrast but no differential effect when comparing Pre vs. Post 7m for the same contrast would not be included).

In order to illustrate brain responses to sounds within KL's primary visual cortex, 13 spheres of 6 mm radius were traced along the calcarine sulcus including its lower and upper banks, in steps of 3 mm along the y axis, from the most caudal part (y = -96) to the most rostral part (y = -60). The coordinates of these 13 ROIs were: [0, -60, 15], [0, -63, 15], [0, -66, 14], [0, -69, 12], [0, -72, 9], [0, -75, 5], [0, -78, 0], [0, -81, -1], [0, -84, -2], [0, -87, -2], [0, -90, -2], [0, -93, -2], [0, -96, -2]. Using Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002), we extracted the t-values in each of these ROIs (see Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009a for similar analyses). Finally, in order to illustrate the crossmodal recruitment of primary visual cortex during sound processing in KL within each session relative to early blind, late blind (auditory experiment 2) and sighted control participants (auditory experiments 1 and 2), we used an anatomical mask encompassing the primary visual cortex around the calcarine fissure (delivered by Marsbar toolbox (Brett et al., 2002)) and we extracted the estimated auditory activity in this mask using the Marsbar toolbox (Brett et al., 2002) for auditory experiment 1 and 2 separately, in KL (3 sessions separately) and in sighted, early blind and late blind participants (1 session).

Spherical small volume correction (SVC, 15 mm sphere) were used only in the Face Localizer in order to identify face-selective regions. These SVCs were performed on coordinates reported in Rossion et al. (2012) who used identical stimuli and analyses as in the present study. As coordinates in that paper were reported in Talairach space, we first transformed them in MNI space using Matthew Brett's bilinear transformation (http://imaging.mrc-cbu.cam.ac.uk/imaging/MNITalairach) before performing the SVCs. Standard stereotactic coordinates were as follows: the right fusiform gyrus (37, -48, -15) and the right inferior Occipital Gyrus (OFA) (38, -72, -11).

3. Results

3.1. Behavioral Results

Far Visual Acuity. At Pre, KL's best corrected distance visual acuity expressed in Snellen decimal acuity was 0.04 in the right (operated) eye (Figure 1A). The success of the surgery was witnessed by improvements in visual acuity as soon as 1.5 months after surgery. Acuity in the right eye increased to 0.2 at Post 1.5m, and to 0.7 at Post 7m. At all times, distance visual acuity in left eye was too low to be tested. In fact, distance visual acuity for binocular vision (OU) was identical to the one measured in the right (operated) eye (OD). Even at Post 7m, KL's acuity remained significantly below normal range (OU: $t=-3.3$, OD: $t=-2.9$, $ps<0.05$).

Contrast Sensitivity Function. KL’s contrast sensitivity function (CSF) pre-surgery was essentially flat, with a resolution limit of 6 cycles per degree (cpd) (Figure 1B). A substantial and selective improvement for low spatial frequencies was observed at Post 1.5m and Post 7m. Between 1.5 and 7 months post-surgery, contrast sensitivity did not improve further for spatial frequencies up to 0.5 cpd, but there were improvements for spatial frequencies from 1 to 4 cpd at Post 7m relative to Post 1.5m. KL’s contrast sensitivity at all spatial frequency ranges was well below normal range in all sessions (all ps < 0.00001) except for 0.25 cpd at Post 7m (0.25 cpd, t=2.798, p=0.053).

Global Motion. KL’s coherence thresholds were stable across the 3 sessions in both the radial and the vertical conditions (Figure 1C). In the radial condition, thresholds measured in each session (Pre=22.6%, Post 1.5m=23.9%, Post 7m=27.4%) were comparable to normal controls’ thresholds (30%, all p>0.3), whereas in the vertical condition thresholds were higher (worse performance) for KL (Pre=37.8%, Post 1.5m=37.2%, Post 7m=35.9%) compared to controls (19.8%, all ps < 0.02).

Face categorization and individuation. KL performed well in the face vs. car categorization task in all sessions (Pre=90%, Post 1.5m=96%, Post 7m=100%), with accuracy being significantly below controls’ only at Pre (t=-7.432, p=0.009; other ps > 0.06; no differences in correct RTs: all ps > 0.3) (Figure 1D). The effect of Session did not reach significance neither in accuracy rates (χ^2 (2, n=140)=5.706, p=0.06) nor in ln-transformed correct RTs (F(2,80)=2.913, p=0.06).

In the front-to-front (FF) and the front-to-profile (FP) individual face discrimination task, KL performed at chance prior to surgery in both orientations and in both tasks (all ps > 0.12). Post-surgery, she performed significantly above chance (all ps < 0.01) except in the FP task at Post 1.5m, where performance with inverted faces was still not significantly different than chance (p=0.11) (Figure 1E and 1F).

There was no significant change in performance between Post 1.5m and Post 7m neither for upright faces (FF: χ^2 (1, n=100)=0.61, p=0.44 ; FP: χ^2 (1, n=96)=0.865, p=0.35) nor for inverted faces (FF: χ^2 (1, n=100)=0.203, p=0.65 ; FP: χ^2 (1, n=96)=1.212, p=0.27). In the FF task, KL was faster overall at Post 7m compared to Post 1.5m (main effect of Session FF : F(1,150)=6.89, p=0.01), but slower at Post 7m relative to Post 1.5m in the FP task (main effect of Session FP : F(1,132)=20.77, p<0.001). Performance with upright faces remained significantly below normal range in both tasks post-surgery (all ps<0.035) whereas performance with inverted faces was below normal range at Post 1.5m (FF: t=-3.468, p=0.037 ; FP: t=-5.489, p=0.015) but not at Post 7m (FF : t=-2.22, p=0.07 ; FP : t=-2.081, p=0.086). KL was as fast as the controls in both tasks at Post 1.5m and Post 7m (all ps > 0.13).

Some controls showed an inversion effect – a lower performance for upright than inverted faces (Rossion, 2008) - in accuracy (FF task : Ctrl2: χ^2 (1, n=100)=4.43, p=0.035; FP task : Ctrl1: χ^2 (1, n=96)=4.41, p=0.036; Ctrl2: χ^2 (1, n=96)=5.55, p=0.019), and all showed an inversion effect in correct RTs in both tasks ((FF task: Ctrl1: t(61.7)=-4.07, p<0.001; Ctrl2: t(91)=-5.44, p<0.001; Ctrl3: t(86)=-7.44, p<0.001; FP task: Ctrl1: t(83.3)=-7.13, p<0.001; Ctrl2: t(86)=-3.85, p<0.001; Ctrl3: t(80)=-5.269, p<0.001). Importantly, KL did not show any significant inversion effect post-surgery in accuracy in any task (all ps > 0.09). In the FP task, she showed no inversion effect in correct response times (main effect of Orientation and interaction not significant, ps > 0.25). In the FF task, the interaction between Session and Orientation was significant (F(1,150)=9.613, p=0.002), due to faster response times for upright than for inverted faces at Post 1.5m (t(76)=2.27, p= 0.026) and faster response times for inverted than for upright faces at Post 7m (t(74)=-2.13, p= 0.036).

In summary, individual face discrimination was at chance prior to surgery and was significantly above chance level for both upright and inverted faces 7 moths post-surgery. However, performance remained quantitatively below (for upright faces at least) and qualitatively different from normal controls, as there was no consistent evidence of a face inversion effect in KL.

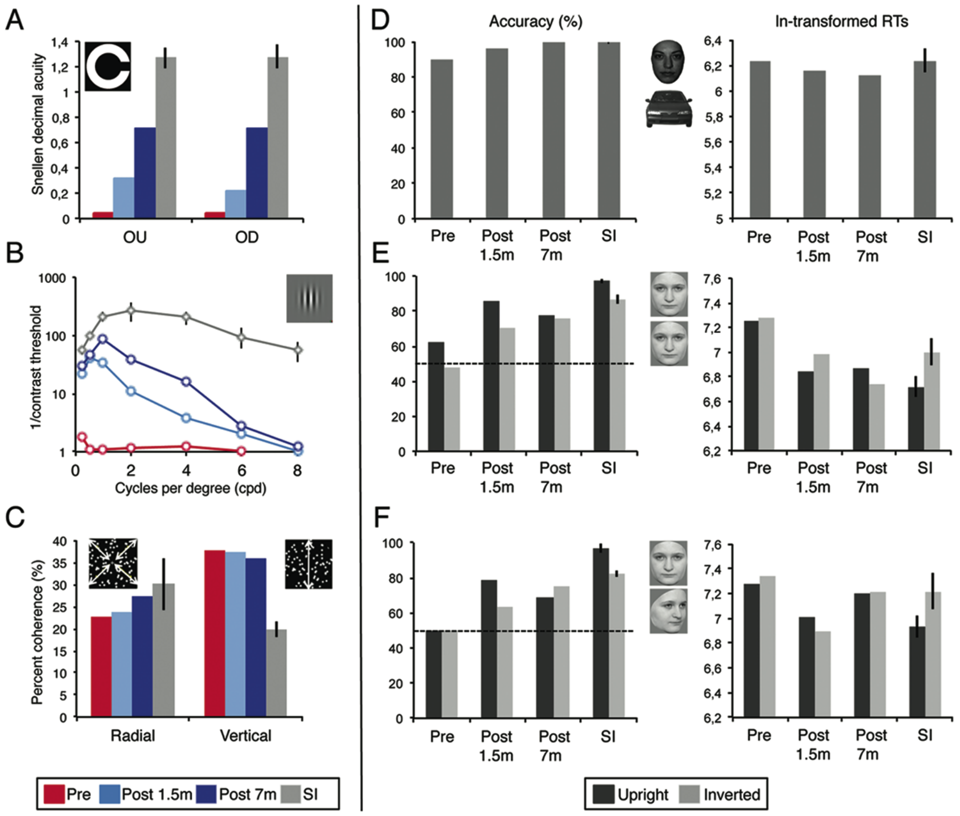

Figure 1. Behavioral performance in KL (at Pre, Post 1.5m and Post 7m) and in sighted controls (SI). *(A) Distance visual acuity measures expressed in Snellen Decimal acuity obtained in the Landolt-C paradigm for binocular (OU) and right (operated) eye (OD). (B) Contrast sensitivity function (CSF). (C) Percentage coherence thresholds for radial and vertical global motion detection. Percent accuracy and In-transformed correct response times in (D) the face categorization task, (E) the front-to-front and (F) the front-to-profile face individuation tasks, separately for upright and inverted faces. Bars represent standard error from the mean.*

3.2. Voxel-Based Morphometry Results

Because of the well-known impact of perceptual experience on brain structure and the close relationship existing between brain structure and brain function (Zatorre, Fields, & Johansen-Berg, 2012), we investigated potential morphological changes associated with sight restoration using voxel-based morphometry. Grey matter density increases were consistently observed at Post 1.5m and Post 7m relative to Pre in several occipital regions including bilateral peri-calcarine cortex and lingual gyri, left inferior occipital gyrus and right cuneus (Figure 2C, Supplemental Table 1).

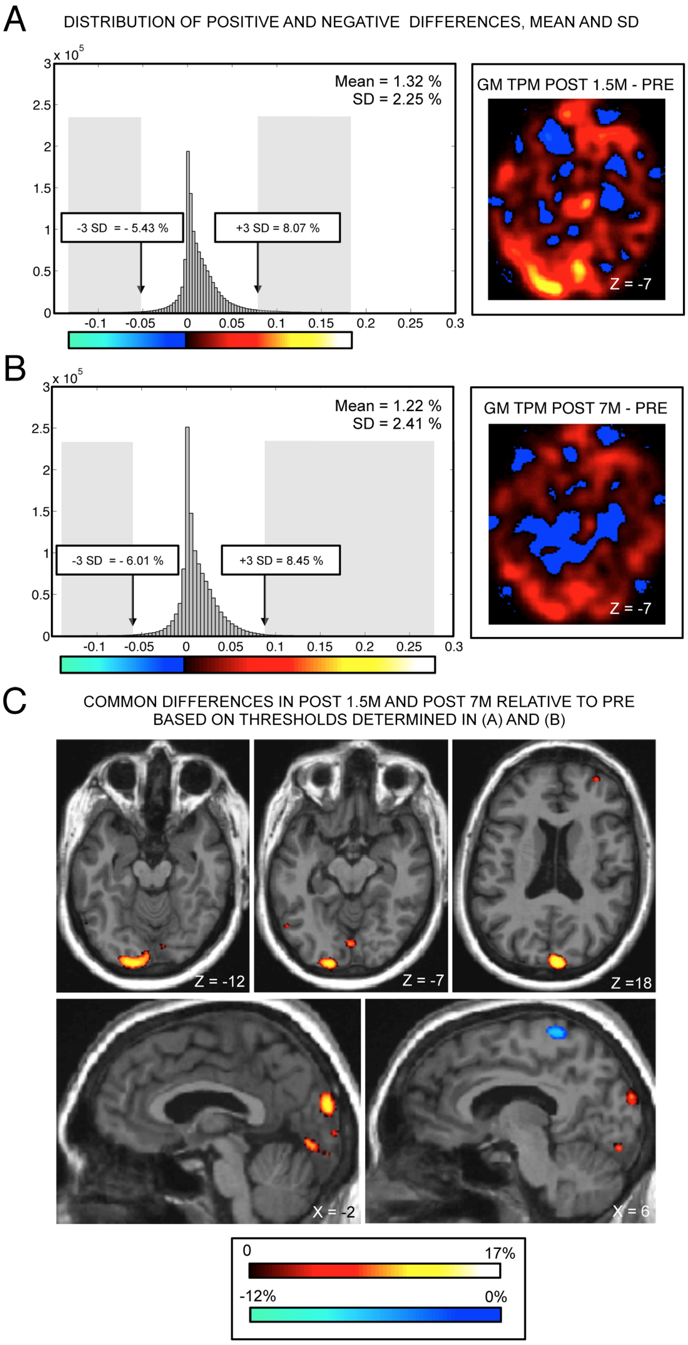

Figure 2. Voxel-based morphometry analyses and results. *VBM analyses in KL are illustrated in (A) and (B). The smoothed grey matter tissue probability map (GM TPM) obtained at Pre was subtracted from the smoothed GM TPM obtained at Post 1.5m (A) and*

at Post 7m (B). Thresholds for significant differences were established based on the mean and standard deviations of the distribution of positive and negative differences observed in the differential image obtained in (A) and (B). Only voxels showing common between-session differences above or below 3 standard deviations from the mean of the distribution in (A) and (B) were reported in (C), by overlapping the thresholded differential image on KL's native anatomical image.

3.3. fMRI Results

3.3.1. Behavioral performance in the scanner. Visual detection performance (hits versus misses) in the Motion (i.e. detect change in background color) and in the Face (i.e. detect a gray rectangle) localizers was close to ceiling in all sessions with no difference between sessions (Hits in Face Localizer at Pre, Post 1.5m, Post 7m: 26, 27, 22 (out of 28 targets), χ^2 (2, n=84)=5.227, p=0.073 - Hits in Motion Localizer at Pre, Post 1.5m, Post 7m: 18, 17, 17 (out of 18 targets), χ^2 (2, n=54)=1.038, p=0.59). In auditory experiment 1 (i.e. repetition detection in the Voice condition vs. speed change detection in the Motion condition), performance was higher in the Voice condition relative to the Motion condition at Pre (Hits in Voice vs. Motion conditions at Pre : 28, 18 (out of 30 targets), χ^2 (1, n=60)=7.547, p=0.006) but not at Post 1.5m (Hits in Voice vs. Motion conditions at Post 1.5m : 24, 18 (out of 30 targets), χ^2 (1, n=60)=1.984, p=0.159) nor at Post 7m (Hits in Voice vs. Motion conditions at Post 7m : 27, 26 (out of 30 targets), χ^2 (1, n=60)=0, p=1). There was a significant association between Session and performance only in the Motion condition (χ^2 (2, n=90)=6.636, p=0.036) due to higher performance at Post 7m relative to both Pre and Post 1.5m sessions in that condition (χ^2 (1, n=60)=4.176, p=0.041). Performance in the Voice condition remained stable across time (χ^2 (2, n=90)=2.693, p=0.26). In auditory experiment 2 (i.e. discrimination of Pitch vs. Spatial attributes of sounds), there was a main effect of Condition (F(1,14)=220.59, p<0.001) indicating that KL was more accurate in the Spatial than in the Pitch condition and a main effect of Session (F(2,28)=6.083, p=0.006) due to the overall better performance at Post 7m (74%) relative to Pre (63%, p=0.037) and Post 1.5m (64%, p=0.04) sessions. The interaction between the 2 factors was also significant (F(2,28)=4.752, p=0.017) as performance significantly improved over time only in the Pitch condition when comparing performance at Post 7m relative to Pre (t(14)=3.544, p=0.003) and Post 1.5m (t(14)=3.371, p=0.005).

3.3.2. Visual Motion Localizer. A conjunction (AND) analysis identified a large set of regions which consistently responded to radially moving relative to static dots across the 3 sessions ([Motion > Static Pre ∩ Post 1.5m ∩ Post 7m])

(Figure 3A, Supplemental Table 2). In line with previous studies investigating visual-motion selectivity (Sunaert et al., 1999; Tootell et al., 1995), these regions included the middle temporal cortex (MT+/V5), the superior occipital gyrus (V3/V3A), and the superior temporal gyrus bilaterally as well as the left middle occipital gyrus (LOS/KO). Similar activation maps were observed in our control participants scanned with the same protocol (Supplemental Figure 1A). In KL, between-session increases in motion-selective activity were observed at Post 7m relative to Pre ([Motion > Static X Post 7m > Pre]) in bilateral extrastriate cortices along the motion pathway localized posteriorly to MT+/V5: the middle occipital gyri bilaterally extending medially to the superior occipital gyri/cuneus (V2/V3/V3A) [Motion > Static Post 7m > Pre] (Figure 3B, Supplemental Table 2). No such changes were observed in bilateral MT+/V5 (Figure 3B).

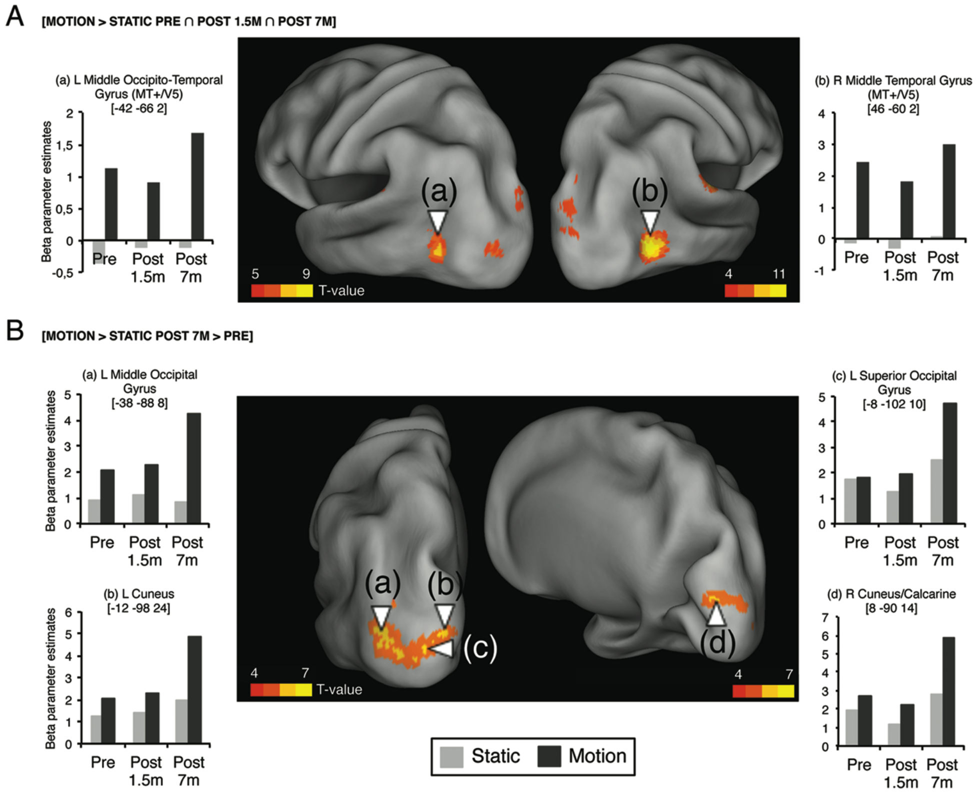

Figure 3. fMRI activation maps of visual motion processing*. (A) Between-session conjunction analysis highlighting regions showing consistent motion-specific responses [Motion>Static] across the 3 sessions in KL, and associated beta parameter estimates in bilateral MT+/V5. (B) Brain regions showing larger motion-specific visual responses [Motion>Static] at Post 7m relative to Pre and associated beta parameter estimates.*

Results are displayed at a threshold of p<0.05 FWE corrected over the whole brain on a 3D render of the brain.

<u>3.3.3. Face Localizer.</u> Before surgery, regions in fusiform and inferior occipital gyri showed a preference for faces over cars and scrambled faces ([Faces Pre > ScrFaces Pre ∩ Faces Pre > Cars Pre]) (Supplemental Figure 1B) with no significant changes across time (Supplemental Table 3). Hence, a conjunction (AND) analysis was performed across sessions [Faces all sessions > ScrFaces all sessions ∩ Faces all sessions > Cars all sessions] (Rossion et al., 2012) and disclosed face selectivity in bilateral inferior occipital gyrus ("Occipital Face Area" or "OFA") and in the right fusiform gyrus ("Fusiform Face Area" or "FFA") (Figure 4, Supplemental Table 3), in accordance with previous neuroimaging studies of face perception (Haxby, Hoffman, & Gobbini, 2000) and with activation maps observed in our sighted control participants scanned with the same protocol (Supplemental Figure 1B).

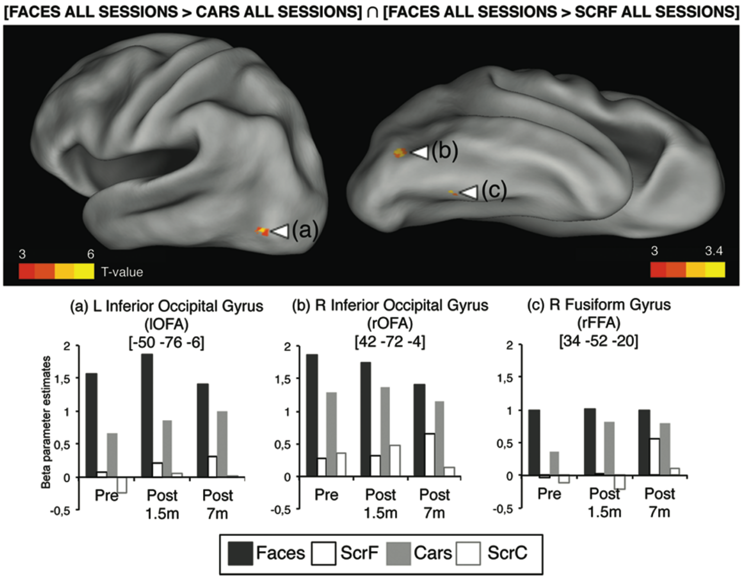

Figure 4. fMRI activation maps of face processing. *Brain regions responding more to Faces relative to both Cars and Scrambled Faces in all sessions in KL, and associated beta parameter estimates. Results are displayed at a threshold of p<0.001 uncorrected on a 3D render of the brain.*

<u>3.3.4. Auditory Experiments.</u> In both auditory experiments, several occipital regions were consistently recruited during the processing of auditory information across the 3 sessions in KL ([Motion + Voice Pre ∩ Post 1.5m ∩ Post 7m] ; [Spatial + Pitch Pre ∩ Post 1.5m ∩ Post 7m]) (Figure 5A and 5B, Supplemental Tables 4, 5). These regions were essentially localized along the calcarine sulcus

extending medially to the cuneus and to the lingual gyrus (Figure 5A and 5B, Supplemental Tables 4, 5). In both auditory experiments, peaks of activation to global auditory processing in KL's primary visual cortex were located in the caudal part of the calcarine sulcus and t-values steadily decreased along the calcarine sulcus when sliding to its most rostral part (Figure 5A and 5B). Importantly, significant auditory responses in peri-calcarine regions were also observed in early- and late-blind participants (tested with the same protocol as in auditory experiment 2 (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b)), but not in normally sighted participants (tested with the same protocols as in auditory experiments 1 and 2) (Figure 5C, Supplemental Figure 1C and 1D).

Despite the fact that auditory activity was still massively present 7 months post-surgery in striate cortex (Figure 5A to C), the recruitment of occipital cortex for auditory processing steadily decreased relative to pre-surgery ([Motion + Voice X Pre > Post 7m] ; [Spatial + Pitch X Pre > Post 7m]), especially in extrastriate regions, including the bilateral middle occipital gyri in both auditory experiments as well as the bilateral superior occipital gyri and lingual gyri in auditory experiment 2 (Figure 5D and 5E, Supplemental Tables 4, 5). Beta parameter estimates in these regions highlight a progressive reduction of activation in response to auditory stimulation with time, some of these regions even showing sound-related deactivation at Post 7m (Figure 5D, 5E).

No consistent functional specialization (selective auditory activity for a specific task) was found in KL's occipital cortex in either of the two auditory experiments across sessions (i.e., contrast between Motion and Voice conditions in auditory experiment 1 and between Spatial and Pitch conditions in auditory experiment 2 (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b)).

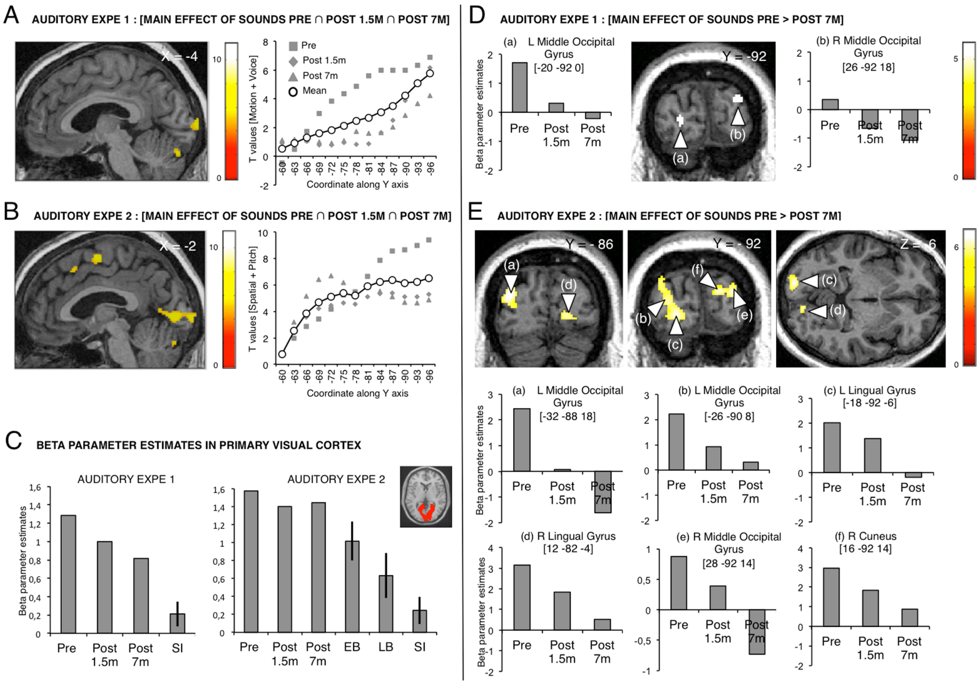

Figure 5. fMRI activation maps of auditory processing. *(A-B) Between-session conjunction analysis highlighting brain regions that are consistently activated during auditory stimulation across the 3 sessions in KL in (A) auditory experiment 1 [Motion + Voice Pre ∩ Post 1.5m ∩ Post 7m] and (B) auditory experiment 2 [Spatial + Pitch Pre ∩ Post 1.5m ∩ Post 7m]. Corresponding t-values are plotted along the calcarine sulcus from the most rostral pole (-60 in the Y axis) to the most caudal pole (-96 along the Y axis) for each session separately (Pre, Post 1.5m and Post 7m) in grey and for the average of all sessions in black. (C) Beta parameter estimates are plotted for the main effect of sounds in an anatomical mask encompassing the peri-calcarine region (primary visual cortex) in auditory experiment 1 for KL (at Pre, Post 1.5m and Post 7m) and sighted controls (SI) and in auditory experiment 2 for KL (at Pre, Post 1.5m and Post 7m), early blind (EB), late blind (LB) and sighted controls (SI). Bars represent standard error from the mean. (D-E) Brain regions showing larger recruitment during auditory stimulation at Pre relative to Post 7m in KL and associated beta parameter estimates in (D) auditory experiment 1 [Motion + Voice X Pre > Post 7m] and (E) auditory experiment 2 [Spatial + Pitch X Pre > Post 7m]. Results are displayed at a threshold of $p < 0.05$ FWE corrected over the whole brain on sagittal, coronal and tranversal slices of KL's structural image normalized to the MNI space.*

4. Discussion

In the present study, we provide a comprehensive overview of the changes occurring in perceptual visual abilities as well as in brain structure and function in an early and severely visually impaired patient, KL, before and after sight restoration. KL was tested on 3 separate sessions taking place before, as well as 1.5 and 7 months following surgery with identical behavioral, MRI and fMRI protocols. The extent of KL's preoperative visual impairments was evidenced by extremely reduced visual acuity (0.04) and CSF pre-surgery. However, presurgical perceptual global motion detection (radial patterns) and face/non-face categorization abilities were accurate (Figure 1C and 1D) and sufficient to elicit specific functional responses within high-level visual areas involved in motion and face processing (Figure 3A, 4, Supplemental Figure 1A and 1B). Despite these residual visual functions, robust crossmodal auditory responses were observed within KL's occipital cortex pre-surgery, similar to those typically observed in totally blind individuals (Figure 5C and Supplemental Figure 1D). In peri-calcarine cortex, crossmodal responses overlapped with visual responses (Figure 6) and remained elevated even 7 months post-surgery (Figure 5A to C).

The success of the surgery was evidenced by behavioral improvements in visual acuity, sensitivity to low-spatial frequencies and face individuation (Figure 1A, 1B, 1E and 1F), as well as by significant increases in neural responses to radially moving patterns in low-level visual regions (Figure 3B). Crucially, crossmodal auditory responses progressively decreased in extrastriate occipital regions post-surgery relative to pre (Figure 5D and 5E). Moreover, significant increases in grey matter density were observed in low-level visual cortex as soon as 1.5 months post-surgery.

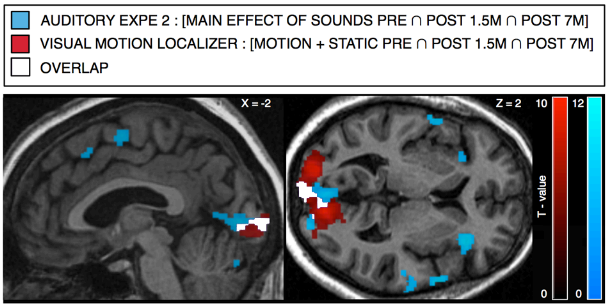

Figure 6. Overlap between auditory and visual responses in KL's primary visual cortex in all sessions*. Shown in blue is the between-session conjunction of the main effect of auditory conditions in auditory experiment 2 [Spatial + Pitch Pre ∩ Post 1.5m ∩ Post 7m]. Shown in red is the between-session conjunction of the main effect of visual conditions in the Motion localizer [Motion + Static Pre ∩ Post 1.5m ∩ Post 7m]. Shown in blue-grey is the overlap. Results are displayed at a threshold of $p < 0.05$ FWE corrected over the whole brain on sagittal and transversal slices of KL's structural image normalized to the MNI space.*

4.1. Presurgical visual selective responses in high-level visual cortex involved in motion and face processing

In accordance with the observation of normal presurgical performance in global motion detection thresholds for radially moving patterns and in face/non-face categorization, motion- and face-selective responses were found within well-documented regions of the dorsal and of the ventral visual pathway in KL pre-surgery and did not evolve post-surgery. These findings suggest that functionally specific responses have emerged in KL's high-level visual cortex during development despite a life-long history of severely degraded visual experience. In the case of motion-selective responses, this assumption is in good agreement with the fact that area MT+/V5 receives most of its input from the magnocellular pathway (Maunsell, Nealey, & DePriest, 1990) and may thus have tuned to visual motion despite a highly blurred optical input. In the case of face-selective responses, while a total absence of visual input since an early age seems to permanently alter the functional tuning of high level face-selective regions (Fine et al., 2003; Röder et al., 2013), residual visual information may be sufficient in tuning face-selective regions to categorical information of faces at least. Importantly, findings of face selective responses in OFA and FFA even prior to surgery (Figure 4 and Supplemental Figure 1B) do not necessarily imply that these regions are optimally tuned to individual faces discrimination. In fact, KL's individual face discrimination pre-surgery was at chance level (Figure 1E and 1F). In the same vein, the presence of face selective regions in the brain of acquired prosopagnosic patients is the neural signature of their ability to discriminate faces from non-face objects, despite profound deficits in individual face discrimination (Dricot, Sorger, Schiltz, Goebel, & Rossion, 2008; Rossion et al., 2003; Schiltz et al., 2006; Steeves et al., 2009). In these patients however, fMRI signal in these regions, despite being preferential for faces, does not show any evidence of sensitivity to the discrimination of individual faces (i.e. lack of release from adaptation with different compared to identical faces) (Dricot et al., 2008; Schiltz et al., 2006; Steeves et al., 2009). In KL, within face discrimination abilities increased after surgery (Figure 1E and 1F) but no changes in activation were observed in face-selective regions (Figure 4).

4.2. Presurgical crossmodal auditory responses in occipital cortex and overlap with visual responses

The finding of crossmodal responses in an individual with preoperative form vision (Figure 5A to C, Supplemental Figure 1C and 1D) suggests that this form of reorganization can be observed even when the visual loss is not total and despite the presence of visual functional specialization in high-level visual cortex. Similar evidence was previously reported in an adult man with severe visual impairment since childhood, who displayed crossmodal responses within the visual cortex during tactile pattern recognition tasks (Cheung, Fang, He, & Legge, 2009).

In the peri-calcarine cortex, crossmodal responses were robust and reliable across both auditory experiments and sessions and were comparable to the ones measured in totally blind subjects (Figure 5C and Supplemental Figure 1D). Interestingly, these responses in KL largely overlapped with visual responses in all sessions (Figure 6). Findings of coexisting crossmodal and visual responses were previously reported within high-level visual cortex in two sight-recovery subjects (Saenz et al., 2008) and in a case of severe visual impairment (Cheung et al., 2009). Our results thus extend these observations to the peri-calcarine cortex, demonstrating that this region, classically considered as purely unimodal, can respond to both visual and auditory modalities in cases with a life-long history of altered visual experience.

Across auditory experiments and sessions, estimated response amplitude during global sound processing steadily decreased from the most posterior part to the most anterior part of the calcarine sulcus (Figure 5A and 5B). In the sighted brain, the posterior part of the calcarine sulcus displays representations of the foveal and parafoveal visual field (Sereno et al., 1995) and contains neurons tuned to higher spatial frequencies (Singh, Smith, & Greenlee, 2000). In line with KL's poor sensitivity for high spatial frequencies (Figure 1B), we speculate that the reduced optical quality of her visual input since an early age prevented the normal development of populations of neurons in this region. In the same vein, retinotopic mapping in sight-recovery patient MM displayed a lack of foveal representation at the pole of the calcarine sulcus (Levin et al., 2010). In KL, the lack of optimal visual input to this region since early infancy may have yielded this area to process auditory information, as previously suggested in the case documented by Cheung and colleagues (2009), in whom crossmodal tactile responses in primary visual cortex were mainly observed at the occipital pole. These findings raise the possibility that crossmodal responses may interfere on visual functioning, preventing optimal visual recovery (Lee et al., 2007; Sandmann et al., 2012).

The absence of consistent functional specialization in crossmodal responses across sessions (selective auditory activity for a specific task) within KL's visual cortex suggests that the nature of crossmodal reorganization taking place in subjects with residual visual abilities may differ from the one observed in early-onset totally blind subjects, and rather resemble the one observed in late-onset totally blind subjects (Collignon et al., 2013; Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). Indeed, as in the latter case, KL has developed visually specific responses in higher-level visual regions, which might in return prevent the development of functionally specific crossmodal responses to auditory information. For instance, MT+/V5 responds to moving sounds in early- but not late-blind participants (Bedny et al., 2010; Collignon et al., 2013), in accordance with the assumption that this region tunes to visual motion information early during development (Ellemberg et al., 2002; Fine et al., 2003; Saenz et al., 2008).

4.3. Postsurgical decrease in crossmodal auditory responses in extrastriate occipital cortex

In deep contrast to what was observed in peri-calcarine regions, some extrastriate occipital regions showed robust between-session decreases in crossmodal recruitment. Several regions showing robust auditory activation before surgery even showed sound-related deactivation 7 months after sight-restoration (Figure 5D, 5E), as typically observed in sighted individuals (Laurienti et al., 2002). Therefore the progressive appearance of sound-related deactivations in KL's extrastriate occipital cortex may parallel the regain of visual tuning observed within these regions (Figure 3B). Overall, our results suggest that the primary visual cortex maintains its involvement in the processing of non-visual information despite sight restoration, whereas presurgical auditory responses in extrastriate regions decrease following sight restoration. Altogether, these data compellingly demonstrate the existence of region-specific mechanisms in the way visual deprivation and restoration affect the modality-tuning of the occipital cortex.

4.4. Postsurgical increase in grey matter density in low-level visual cortex

As soon as 1.5 months post-surgery, significant increases in grey matter density were evidenced in several portions of the low-level visual cortex (Figure 2C). These observations are in good agreement with experience-dependent grey matter density increases reported in longitudinal studies involving training protocols (Ditye et al., 2013; Draganski et al., 2004; Ilg et al., 2008) and suggest that important structural changes may be induced far more quickly than previously expected (gains of more than 8% in grey matter density in occipital cortex after only 1.5 month) when significantly increasing the quality of a sensory input (here vision).

5. Conclusions

The occipital cortex has long served as a front-runner model to understand how brain regions develop, specialize and reorganize their tuning toward a specific input and function (Hubel, 1995). We provide the first longitudinal investigation of the way crossmodal plasticity interacts with restored vision in a sight-recovery subject. We show that structural and functional reorganization of occipital regions are present in an individual with a longstanding history of severe visual impairment, and that such reorganizations can be partially reversed by visual restoration in adulthood.

6. Supplemental Material

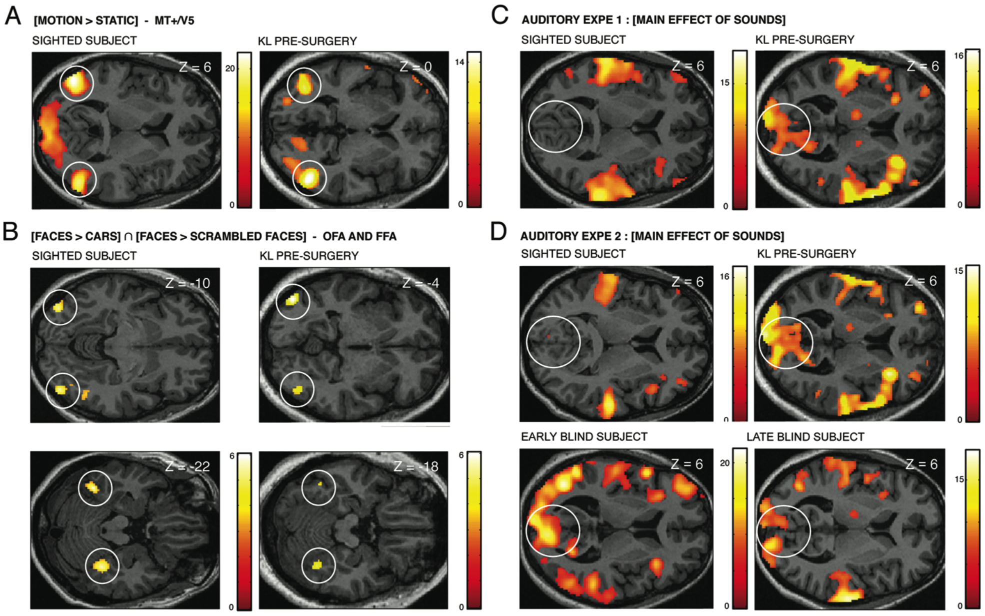

Figure 7. fMRI activation maps in control subjects. *Brain regions responding more to (A) Moving relative to Stationary dots and (B) Faces relative to both Cars and Scrambled Faces are shown in a representative subject from the sighted control group (right-handed female, 32 years old) and in KL before surgery. (C) Brain regions responding during global sound processing in auditory experiment 1 [Motion + Voice] are shown in a representative subject from the sighted control group (right-handed female, 32 years old) and KL pre-surgery. (D) Brain regions responding during global sound processing in auditory experiment 2 [Spatial + Pitch] are shown in a representative subject from the sighted control group (right-handed female, 48 years old), a representative subject from the early blind group (right-handed female, 56 years old), a representative subject from the late blind group (right-handed female, 46 years old) and KL pre-surgery. Results are displayed at a threshold $p<0.05$ corrected (FWE) corrected over the whole brain in (A), (C) and (D) and at a threshold of $p<0.001$ uncorrected in (B) on transversal slices of each subject's structural image normalized to the MNI space.*

	NATIVE SPACE					MNI SPACE		
Area	X (mm)	Y (mm)	Z (mm)	Change (%)	Cluster Size	X (mm)	Y (mm)	Z (mm)
Grey matter density increases in Post 1.5m and Post 7m relative to Pre								
R Cerebellum	27	-55	-35	17,47	3823	35	-62	-43
L Peri-calcarine cortex/ Inferior Occipital Gyrus	-16	-89	-8	12,17	1296	-16	-99	0
L Cerebellum	-27	-59	-32	13,07	1049	-30	-68	-37
R Cuneus	1	-83	17	15,15	590	6	-88	29
R Midd Frontal Gyrus	26	39	7	9,82	235	29	56	-14
L Fusiform Gyrus	-16	3	-29	11,07	169	-20	6	-45
R Putamen	23	-13	13	11,22	153	28	-7	9
L Peri-calcarine/Lingual Gyrus	-1	-73	-5	9,79	112	1	-79	-1
R Inf Temporal Gyrus	40	-20	-21	9,88	59	51	-18	-31
R Midd Frontal Gyrus	26	36	14	9,13	55	29	54	-4
L Inferior Occipital /Temporal Gyrus	-46	-62	-8	8,86	34	-53	-69	-4
L Sup Frontal Gyrus	-8	31	-3	9,04	29	-13	43	-24
L Midd Frontal Gyrus	-32	-6	51	9,17	22	-41	8	56
R Lingual Gyrus	6	-76	-10	8,95	18	10	-83	-8
L Peri-calcarine cortex	-3	-87	0	8,90	14	-1	-95	9
Grey matter density decreases in Post 1.5m and Post 7m relative to Pre								
L Cerebellum	-17	-46	-40	-12,92	1057	-18	-54	-50
R Postcentral Gyrus	7	-41	56	-7,73	354	13	-32	68
L Cerebellum	-40	-44	-33	-7,75	153	-46	-52	-41
R Postcentral Gyrus	23	-32	50	-7,19	74	34	-25	58
L Paracentral Lobule	-16	-41	53	-6,65	29	-16	-32	66
L Dorsolateral Superior Frontal Gyrus	-6	38	23	-5,73	7	-11	58	7

Supplemental Table 1. *Summary of the between-session grey matter changes obtained in the VBM analyses. Significant clusters are reported in KL's native space coordinates and in MNI space coordinates.*

Area	Cluster Size	X (mm)	Y (mm)	Z (mm)	z	p
Conjunction [Motion > Static Pre ∩ Post 1.5m ∩ Post 7m]						
R Middle Temporal Gyrus (MT+/V5)	404	46	-60	2	Inf	<0.001
R Superior Temporal Gyrus	129	62	-28	14	7.74	<0.001
L Middle Occipito-Temporal Gyrus (MT+/V5)	225	-42	-66	2	7.46	<0.001
R Middle/Superior Occipital Gyrus	314	34	-90	24	7.08	<0.001
L Middle Occipital Gyrus	79	-30	-86	6	6.72	<0.001
L Superior Occipital Gyrus	121	-16	-86	26	6.26	<0.001
L Superior Temporal Gyrus	18	-58	-42	18	5.62	0.001
R Superior Occipital Gyrus	21	30	-78	44	5.30	0.003
[Motion > Static Post 1.5m > Pre]						
no suprathrehold voxels						
[Motion > Static Post 7m > Pre]						
L Middle Occipital Gyrus	737	-38	-88	8	6.22	<0.001
R Cuneus	239	14	-96	28	5.84	<0.001
R Middle Occipital Gyrus	39	38	-88	14	5.27	0.004
[Motion > Static Post 7m > Post 1.5m]						
L Middle Occipital Gyrus	596	-40	-86	10	6.71	<0.001
R Cuneus	135	8	-86	20	6.61	<0.001
L Cuneus/Superior Occipital Gyrus	149	-10	-94	22	6.43	<0.001
R Middle Occipital Gyrus	177	36	-78	18	5.81	<0.001
L Inferior Occipital/Fusiform Gyrus	32	-42	-70	-14	5.81	<0.001
R Inferior Occipital Gyrus	21	52	-70	-2	5.53	0.001
R Inferior Occipital Gyrus	12	38	-82	-4	5.01	0.013

Supplemental Table 2. *Summary of the functional results obtained for the specific responses to visual motion relative to static dots (Motion > Static). All coordinates reported in this table are significant after correction over the entire brain (FWE p < 0.05).*

Area	Cluster Size	X (mm)	Y (mm)	Z (mm)	z	p
Conjunction [Faces > ScrF ∩ Faces > Cars all sessions]						
L Inferior Occipital Gyrus (OFA)	101	-50	-76	-6	6.50	<0.001
R Inferior Occipital Gyrus (OFA)*	20	42	-72	-4	3.93	0.011
R Fusiform Gyrus (FFA)*	7	34	-52	-20	3.31	0.074

Supplemental Table 3. *Summary of the functional results obtained for the specific responses to Faces relative to both Scrambled Faces and Cars. There were no significant activations in any of the between-session comparisons. Coordinates are significant after correction over the entire brain (FWE p < 0.05) or (*) over small spherical volumes (SVC, 15 mm radius).*

Area	Cluster Size	X (mm)	Y (mm)	Z (mm)	z	p
Conjunction [Motion + Voice Pre ∩ Post 1.5m ∩ Post 7m]						
L Superior Temporal Gyrus	1918	-64	-16	12	Inf	<0.001
R Middle Temporal Gyrus	2915	56	-22	-6	Inf	<0.001
R Middle Frontal Gyrus	342	42	38	30	7.41	<0.001
R Peri-calcarine Cortex	56	22	-94	-2	7.06	<0.001
L Cerebellum	95	-4	-82	-24	6.61	<0.001
R Inferior Frontal Gyrus	35	52	42	6	6.52	<0.001
R Superior Temporal Gyrus	16	68	-38	22	6.25	<0.001
L Peri-calcarine Cortex	104	-4	-102	6	6.10	<0.001
R Superior Temporal Gyrus	37	40	4	-18	5.82	<0.001
L Middle Frontal Gyrus	44	-38	52	10	5.77	<0.001
R Superior Frontal Gyrus	55	6	6	66	5.37	0.002
R Peri-calcarine Cortex	12	6	-92	12	5.34	0.003
L Thalamus	14	-12	-16	6	5.33	0.003
R Middle Temporal Gyrus	18	52	-48	8	5.22	0.005
L Cerebellum	17	-22	-66	-22	5.20	0.005
R Precentral Gyrus	31	42	4	36	5.11	0.008
R Supplementary Motor Area	16	8	16	50	5.09	0.009
[Motion + Voice Pre > Post 1.5m]						
no suprathreshold voxels						
[Motion + Voice Pre > Post 7m]						
R Middle/Superior Occipital Gyrus	18	26	-92	18	5.23	0.004
L Middle Occipital Gyrus	16	-20	-92	0	4.91	0.020
[Motion + Voice Post 1.5m > Post 7m]						
no suprathrehold voxels						

Supplemental Table 4. *Summary of the functional results obtained for the main effect of global sound processing in auditory experiment 1 [Motion + Voice]. All coordinates reported in this table are significant after correction over the entire brain (FWE p < 0.05).*

Area	Cluster Size	X (mm)	Y (mm)	Z (mm)	z	p
Conjunction [Spatial + Pitch Pre ∩ Post 1.5m ∩ Post 7m]						
L Postcentral Gyrus	912	-58	-18	14	Inf	<0.001
R Precentral Gyrus	719	44	6	32	Inf	<0.001
R Insula	260	32	22	6	Inf	<0.001
L Inferior Parietal Lobule	2393	-40	-44	42	Inf	<0.001
R Inferior Frontal Gyrus	920	56	12	10	Inf	<0.001
L Supplementary Motor Area	167	-8	-6	56	Inf	<0.001
R Supramarginal Gyrus	584	42	-40	36	Inf	<0.001
L Inferior Frontal Gyrus	330	-50	8	12	Inf	<0.001
R Superior Frontal Gyrus	329	8	20	44	7.43	<0.001
R Peri-calcarine	76	20	-96	0	7.16	<0.001
L Superior Occipital Gyrus	732	-10	-102	6	7.13	<0.001
L Cerebellum	118	-38	-60	-46	7.06	<0.001
R Middle Frontal Gyus	304	42	32	26	6.88	<0.001
R Middle Frontal Gyus		42	46	26	6.37	<0.001
L Middle Frontal Gyus	45	-34	52	12	6.71	<0.001
L Superior Parietal Gyrus	143	-22	-70	50	6.55	<0.001
R Superior Occipital Gyrus	17	16	-100	16	6.14	<0.001
L Superior Temporal Gyrus	24	-42	-20	0	5.86	<0.001
R Cerebellum	44	28	-50	-48	5.84	<0.001
L Cerebellum	28	-12	-70	-46	5.82	<0.001
L Insula	52	-34	22	-2	5.71	<0.001
L Middle Occipital Gyrus	23	-30	-96	10	5.66	0.001
L Inferior Frontal Gyrus	20	-34	34	14	5.59	0.001
L Cerebellum	33	0	-82	-24	5.51	0.001
L Lingual Gyrus	20	-12	-78	-14	5.41	0.002
R Cerebellum	20	16	-68	-46	5.41	0.002
L Temporal Pole	29	-56	14	-2	5.35	0.003
R Superior Frontal Gyrus	14	24	2	62	5.23	0.006
L Cerebellum	12	-18	-66	-24	5.22	0.006
[Spatial + Pitch Pre > Post 1.5m]						
no suprathreshold voxels						

[Spatial + Pitch Pre > Post 7m]

L Middle Occipital Gyrus	390	-32	-88	18	6.86	<0.001
R Lingual Gyrus	69	12	-82	-4	6.33	<0.001
R Superior Frontal Gyrus	18	20	0	70	6.19	<0.001
L Superior Temporal Sulcus	96	-48	-28	2	6.05	<0.001
R Middle/Sup Occipital Gyrus	95	28	-92	14	6.02	<0.001
R Cuneus/Middle Occipital Gyrus		16	-92	14	5.96	<0.001

[Spatial + Pitch Post 1.5m > Post 7m]

R Inferior Occipital Gyrus	84	46	-82	-4	6.35	<0.001
R Middle Occipital Gyrus	43	40	-76	4	5.49	0.001
R Middle Frontal Gyrus	28	4	36	-16	5.41	0.002
L Middle Temporal Gyrus	15	-54	-34	0	5.14	0.009

Supplemental Table 5. *Summary of the functional results obtained for the main effect of global sound processing in auditory experiment 2 [Spatial + Pitch]. All coordinates reported in this table are significant after correction over the entire brain (FWE* $p < 0.05$*).*

Chapter 5.

General Discussion

General discussion

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1. Functional selectivity in the occipito-temporal cortex of early blind individuals

Studies presented in chapter 2 and chapter 3 aimed at investigating the role of visual experience in shaping the modality- and functional specialization of neural systems typically associated with functions of the dorsal and of the ventral visual pathways, namely motion perception and object identification, respectively. In chapter 2, we investigated whether crossmodal selectivity for auditory motion processing is present in early blind individuals and whether specific reorganizations occur for in-depth auditory motion perception in particular (compared to lateral motion). In this chapter, we also attempted to clarify the extent to which cross-modal responses to auditory motion may be observed even in subjects with typical visual experience. Results of this experiment revealed that a region in the right middle temporal gyrus showed a very specific functional preference for both in-depth and laterally moving sounds in early blind but not in sighted subjects. An independent visual experiment in sighted controls confirmed that this region overlapped with the right visual hMT+/V5 area (Tootell et al., 1995; Watson et al., 1993). Moreover, in-depth moving sounds relative to laterally moving sounds elicited specific activity in bilateral ventral occipital cortex in early blind compared to sighted, a result that was also observed in the visual modality. Finally, despite the absence of auditory-driven activity in the right occipito-temporal cortex of sighted subjects, multivariate pattern analyses revealed that right hMT+/V5 contained information about auditory motion signals in both groups, although such information was more robust (higher decoding accuracy) in early blind compared to sighted participants.

In chapter 3, we investigated whether early visual deprivation leads to the existence of category-specific and topographically organized crossmodal responses to voices and object sounds in the ventral occipito-temporal cortex. Regarding object sounds more specifically, we tested whether sounds of objects that do not explicitly convey shape-related information may elicit selective responses within LOC in early blind individuals. Indeed, an influential theoretical account proposes that cross-modal involvement of LOC (e.g. tactile exploration of objects) underlies knowledge of shape independently of modality through which this information is conveyed and independently of visual experience (Amedi et al., 2010; Peelen et al., 2014). However, whether crossmodal responses in LOC during object identification are solely related to the processing of shape remains unknown. In line with previous studies and accounting for the notion that our task did not trigger mental imagery of shape (De Volder et al., 2001), sounds of objects did not elicit any activity in the shape-selective visual cortex of sighted subjects (or elsewhere in the occipital cortex) (Amedi et al., 2002; 2007b). In contrast, early blind subjects displayed robust and selective responses to sounds of objects (compared to both scrambled objects and voices) in the middle and inferior occipital gyri bilaterally. Finally, human voices did not elicit selective crossmodal responses (compared to both scrambled voices and object sounds) in either group of participants. An independent visual experiment conducted in the sighted showed that object-selective responses of early-blind participants partially overlapped with LOC bilaterally, and extended medially and posteriorly particularly in the left hemisphere. These findings demonstrate that the occipital cortex of early blind individuals disposes of specialized regions supporting the representation of auditory objects. We speculate that these regions may support the extraction of low-level auditory cues in order to allow auditory object identification and/or support higher-level semantic processes related to the automatic processing of the meaning of object sounds (i.e. what the object is).

Altogether, these findings demonstrate that the reorganized occipito-temporal cortex of early blind individuals is topographically organized so that distinct functional areas show preferential responses to different auditory stimuli (here conveying motion information on the one hand, and object-related information on the other) (Figure 1). Such a division of computational labor could ensure an efficient processing of different types of information provided by the preserved non-visual modalities (here audition) and, in this sense, may be considered as another argument accounting for the notion that cross-modal reorganization in early blindness is functionally-relevant.

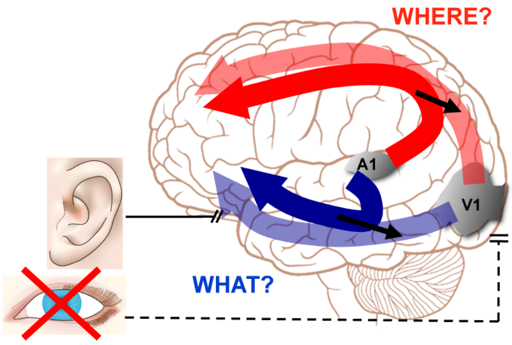

Figure 1. Schematic representation of functional specialization characterizing crossmodal plasticity in the early blind brain. *Several lines of evidence, including our empirical contribution presented in chapter 2 and chapter 3, suggest that crossmodal plasticity associated to early visual deprivation maintains a topographical organization similar to the one that characterizes the sighted occipital cortex, notably regarding its segregation into a dorsal "where" pathway involved in spatial/motion processing and a ventral "what" pathway involved in object identification. Adapted from Dormal & Collignon (2011).*

Importantly, no cross-modal responses to auditory motion or object sounds were observed in the visual cortex of sighted control participants (chapter 2 and chapter 3) unless using more fine-grained multivariate pattern analyses (chapter 2). Even then, decoding accuracy was significantly less robust in the sighted compared to the blind (chapter 2).

Independent visual experiments performed in sighted subjects confirmed that the anatomical localization of the reorganized occipito-temporal areas (e.g. right MTG for auditory motion, bilateral LOC for object-sounds) of early blind individuals closely matched the location of areas devoted to similar functions in the visual modality. Hence, these findings are in agreement with the notion that different areas of the occipital cortex may be inherently biased to subserve specific functions and that in case of early visual deprivation, these areas may still serve similar functions although shifting their modality-tuning from vision to audition (or touch) (Figure 1).

Nevertheless, findings from chapter 3 suggest that there are limits to this anatomo-functional correspondence. Human voices are a very specific category of sounds considered as the auditory counterpart of faces for person identification (Belin et al., 2004; Yovel & Belin, 2013). Based on recent findings (Föcker et al., 2012; Gougoux et al., 2009; Hölig et al., 2014), we expected to observe selective responses to voices in early blind individuals, in the vicinity of areas typically devoted to face processing (Kanwisher et al., 1997; Rossion et al., 2012). Despite the fact that we did find larger responses to voices relative to their scrambled control in the fusiform gyri bilaterally, no selectivity in these regions was observed when voices were contrasted to object sounds. A possible interpretation of this result is that different regions of the visual cortex may not be equipotential in their ability to transfer their function to another modality in case of early visual deprivation. For instance, it has been proposed that the development of face-selectivity in the human brain is under high genetic control (Kanwisher, 2010) and, as a consequence, may be more resistant to experience compared to other regions. Another possible explanation for the absence of crossmodal category-selective reponses to voices in our study may be a lack of sensitivity of the paradigm used. Indeed, it is possible that the vocal stimuli used in our study (i.e. vowels pronounced neutrally) lacked saliency compared to the sounds of objects and thus prevented the observation of crossmodal category-specific effects for voices in the blind. In light of recent evidence demonstrating that congenitally blind subjects show superior voice processing abilities and display voice identity priming effects in the anterior fusiform gyrus (Föcker et al., 2012; Hölig et al., 2014), it is important that future studies further investigate whether a category preference for voices exists, or not, in the reorganized occipital cortex of early blind individuals.

Even if we observed corresponding functional specialization in the sighted and in the blind, the modality tuning of these domain-selective regions differed radically between the two groups. Overall, the sighted individuals only showed marginal functional tuning towards auditory information in the occipital cortex (chapter 2). These findings do not support the influential view of the brain as a metamodal/supramodal structure segregated into operators acting independently of sensory modality and developing in the absence of visual experience (Pascual-Leone & Hamilton, 2001; Reich et al., 2012; Ricciardi & Pietrini, 2011). Beyond the fact that such a view appears theoretically implausible, several caveats challenge its validation.

Firstly, studies conducted on subjects who lost sight later in life suggest that crossmodal plasticity in these individuals is *not* functionally-specific (Bedny et al., 2012; Bedny et al., 2010; Collignon et al., 2013). These findings thus run counter to the predictions of the metamodal theory according to which any region should be able to perform its function irrespective of the input modality and irrespective of the presence or absence of previous visual experience.

Secondly, this theory relies on the misleading reasoning that co-localized activations observed in blind and sighted individuals during non-visual processing, and observed in sighted individuals during visual (e.g. picture viewing) and non-visual processing (e.g. haptic exploration of objects) *necessarily* imply that common ("metamodal/supramodal") representations are involved. Pushing this reasoning even further, many have argued that occipital activations during non-visual processing in the sighted *cannot* be solely related to visual imagery *if* similar crossmodal activations are observed in the blind (in whom visual imagery is absent) (Amedi et al., 2001; 2010; He et al., 2013; Peelen et al., 2014; Pietrini et al., 2004; Ricciardi et al., 2007). However, similar/overlapping activations in blind and sighted individuals during non-visual processing may be related to very different mechanisms in these two populations. For example, they may subtend non-visual sensory processing *per se* in the blind, whereas they may be associated to visual imagery in sighted subjects. This also applies to the observation of co-localized occipital responses to visual and non-visual information in the sighted, the latter being possibly related to visual imagery. We do not exclude the possibility that non-visual information might be present in the occipital cortex of the sighted aside of visual imagery. However, no study to date can compellingly reject the visual imagery hypothesis, challenging the empirical validation of the metamodal theory.

Even if not related to visual imagery, overlapping responses to visual and non-visual processing in the occipital cortex of the sighted could be associated with the involvement of different neuronal populations that are distinctly implemented on a scale that is below the standard resolution of fMRI. The question of whether similar or different neuronal populations in the occipital cortex are involved when processing a given type of stimulus (e.g. motion) in the auditory modality in the blind versus the same operation implemented in vision in the sighted remains almost entirely unexplored. For the reasons mentioned above, simple conjunction analyses carried out on smoothed functional data between the two groups are probably inappropriate for unraveling whether the same neural populations code for similar functions between groups and/or between sensory inputs. This question is crucial to address in order to state that a region is truly "supramodal" and therefore abstracted from its sensory input and/or sensory experience.

Future studies using techniques with enhanced spatial resolution and/or advanced modelisation of fMRI data (eg. crossmodal MVPA; hyperalignment) might prove to be useful to further address these questions. Indeed, identifying the format of the representations underlying the crossmodal occipital activations observed in blind and sighted subjects represents one of the most important challenges for future research in the field.

2. Putative mechanisms for cross-modal plasticity

The mechanisms underlying cross-modal reorganization of the visually-deprived occipital cortex remain largely elusive. The seminal observations of Veraart and collaborators (1990) were an early indication that the differential pattern of metabolic activity measured in the occipital cortex of early and late blind subjects at rest (see Figure 6 in chapter 1) might be related to the onset of deprivation occurring at radically different epochs during visual cortex development.

The human primary visual cortex undergoes dramatic changes in synaptic density across typical development from the prenatal period to late childhood (Huttenlocher, 1990; Huttenlocher & de Courten, 1987; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Zecevic, 1998). After a burst of synaptogenesis peaking between 2 to 4 months and ending approximately at the age of 8 months, about 40% of the synapses of the striate cortex are gradually pruned to achieve a stable synaptic density around the age of 11 years old (Huttenlocher, 1990; Huttenlocher et al., 1982; Huttenlocher & de Courten, 1987). Developmental changes in the human brain have also been examined by measuring brain glucose metabolism at rest using PET (Chugani, 1998; Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987; Kinnala et al., 1996). In the human occipital cortex, glucose metabolic rates at birth are about 30% below those measured in adults. These rates subsequently increase until about 4 years of age where they are twice as elevated as those observed in adults. These high metabolic rates are maintained until about 10 years of age and subsequently decline to reach adult levels by 16 to 18 years old (Chugani, 1998; Chugani & Phelps, 1986). While their interpretation at the cellular level is not straightforward, these PET studies nicely parallel the early postnatal overproduction of synapses and its subsequent decline reported in histological studies, suggesting that synaptic activity accounts for a large part of the glucose consumption measured in the cerebral cortex (Chugani, 1998; Chugani, Hovda, Villablanca, Phelps, & Xu, 1991).

Similar time courses of synaptogenesis and synaptic pruning have been reported within the striate cortex of the macaque monkey (Bourgeois & Rakic, 1993; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986) and of the cat (Chugani et al., 1991; Winfield, 1981). In the same vein, projections from somatosensory and auditory cortices to the visual cortices present in newborn kittens and macaque monkeys are gradually eliminated through cell death or retraction of exuberant collaterals during the synaptic pruning phase (Dehay, Kennedy, & Bullier, 1988; Innocenti & Clarke, 1984; Innocenti, Berbel, & Clarke, 1988; Kennedy, Bullier, & Dehay, 1989), and only a small fraction of these projections are maintained into adulthood (Falchier, Clavagnier, Barone, & Kennedy, 2002; Innocenti et al., 1988). While the first phase of synaptic proliferation appears to be relatively independent of retinal input (Bourgeois & Rakic, 1996; Bourgeois, Jastreboff, & Rakic, 1989; Winfield, 1981), synaptic revision is thought to be critically dependent on visual experience. Indeed, when animals are visually-deprived at birth, exuberant cortico-cortical and thalamo-cortical projections to the visual cortex fail to get pruned (Berman, 1991; Karlen, Kahn, & Krubitzer, 2006; Kingsbury, Lettman, & Finlay, 2002).

Based on the findings from animal studies, it is thus assumed that in the absence of a competitive visual input during the synaptic stabilization phase, a significant number of exuberant synapses and projections may persist and be reinforced in an activity-dependent manner (Hebbian-plasticity), and may be responsible for the recruitment of the occipital cortex for non-visual processing in early blind individuals[11].

In animals with typical visual experience, a small portion of the intermodal projections to the visual cortices present at birth survive the pruning period and stabilize (Innocenti et al., 1988). In fact, anatomical tracer studies in adult sighted monkeys have demonstrated the existence of direct projections from early auditory to early visual cortex (Falchier et al., 2002; Rockland & Ojima, 2003). Evidence for the existence of direct structural connections between primary auditory and visual cortices in sighted humans was recently provided in a diffusion tensor imaging (DTI) tractography study (Beer, Plank, & Greenlee, 2011). These connections are thought to contribute to multimodal integration at very early stages of the visual pathway in normally seeing subjects (for a review see Driver & Noesselt, 2008). As mentioned above, the absence of competitive visual input during the pruning period would lead to a larger maintenance of these ectopic connections and putatively support the recruitment of occipital

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[11] In contrast, in individuals losing sight later in life, exuberant synapses and projections would not escape the typical synaptic pruning due to the presence of stabilizing visual input.

regions for non-visual functions. In early blind humans, support for the assumption of reinforced intermodal connections comes notably from a PET study that visualized the effects of TMS application over the primary somatosensory cortex (S1) in early blind and sighted participants (Wittenberg, Werhahn, Wassermann, Herscovitch, & Cohen, 2004). The application of TMS over S1 induced significant activation of the peri-calcarine cortex in the absence of any thalamic activation in early blind individuals only, suggesting that V1 activation in this group was mediated by cortico-cortical connections, rather than subcortical connections. Interestingly, this activation did not reach significance in direct group comparisons. Hence, these findings are in line with the hypothesis of a re-inforcement, in early blind individuals, of cortico-cortical connections (here between S1 and V1) that are also potentially present in the sighted. More recently, a study by Klinge and collaborators (2010) used dynamic causal modeling[12] (DCM) to investigate how auditory information reaches V1 in congenitally blind and sighted individuals (Klinge, Eippert, Röder, & Büchel, 2010). In line with findings from Wittenberg et al. (2004), these authors were able to establish that cortico-cortical connections, rather than thalamo-cortical connections were more likely to convey auditory information from A1 to V1 in both groups of subjects and, furthermore, that this connectivity was significantly stronger in congenitally blind compared to sighted control subjects. According to another DCM study, cortico-cortical pathways conveying auditory information in V1 in congenitally blind individuals are likely to reflect direct long-range connections from A1 rather than indirect connections through polysensory (parietal) areas (Collignon et al., 2013).

In summary, the current theoretical account proposes that normally transient synapses and intermodal projections fail to get pruned during the synaptic revision period in early visually-deprived individuals, a phenomenon that may explain the observation of strong cross-modal responses to auditory stimuli in early blind but not sighted participants in our studies (chapter 2 and chapter 3).

Beyond the fact that this theoretical account needs further empirical support in humans, it also does not provide an explanation for the maintenance of a functional specialization in the visually-deprived occipital cortex. Indeed, functional specialization and stabilization of cortical networks during typical development are thought to occur *through* synaptic pruning. Hence, a *lack* of

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[12] DCM is a powerful hypothesis-driven tool that allows inferring the causal relationship existing between functional activity measured in different regions of the brain (Friston, Harrison, & Penny, 2003).

synaptic pruning would rather predict that the occipital cortex responds in an undifferentiated fashion to non-visual stimulation.

Alternative mechanisms driving the maintenance of functional specialization in the visually-deprived brain may be found in more recent theories of human brain development (Johnson, 2011; Mahon & Caramazza, 2011). According to these theoretical frameworks, the functional specialization or domain selectivity of individual regions in the human cortex is determined by the patterns of connectivity these regions have with larger functional networks serving a particular function (Johnson, 2011; Mahon & Caramazza, 2011). Mahon & Caramazza (2011) in particular proposed that domain selectivity for different object categories in the ventral stream may be constrained by the innate pattern of connectivity existing between these regions and higher-order (e.g. motor or affective) systems. According to these authors, it is an innate pattern of connectivity, rather than bottom-up sensory experience, that drives domain selectivity observed in the ventral pathway (Mahon & Caramazza, 2011). Transfering these theoretical frameworks to early visual deprivation, it could be that functional selectivity observed in specific occipital regions (e.g. hMT+/V5) for non-visual processing (e.g. auditory motion) arises from the intrinsic pattern of connectivity these regions share with a larger network devoted to a similar function (e.g. motion processing). This was notably supported by Collignon and colleagues (2011), who found that right extrastriate occipital regions devoted to auditory spatial processing in congenitally blind individuals were part of a larger network of fronto-parietal areas typically involved in spatial attention and awareness (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b). In the same vein, He et al. (2013) and Peelen et al. (2013) recently reported similar patterns of resting state activity in congenitally blind and sighted subjects between specific regions of the occipito-temporal cortex and larger brain networks (He et al., 2013; Peelen et al., 2013).

3. Crossmodal plasticity and visual recovery

The question of whether crossmodal plasticity may be observed even in cases where the sensory deprivation is not total remains largely unexplored. This is a crucial issue considering most cases of blindness occur gradually and individuals often maintain some degree of residual visual functions (Merabet & Pascual-Leone, 2009). In addition, these individuals are the main targets of current surgical procedures (Aldave et al., 2009; Robert & Harissi-Dagher, 2011), and crossmodal plasticity may interfere with the recovery of visual functions after surgery (Collignon, Champoux, Voss, & Lepore, 2011a; Merabet & Pascual-Leone, 2009). In chapter 4, we investigated a case of sight-recovery after a longstanding history of visual impairment. We performed both pre- and post-surgery measurements and combined behavioral, neurostructural (MRI) and neurofunctional (fMRI) methods. Our aim was to test the presence of crossmodal plasticity prior to surgery, despite residual visual functions, and investigate its evolution together with visual recovery within neural systems of the ventral (i.e. face) and of the dorsal (i.e. motion) processing systems.

Pre-surgery, robust auditory responses were found in occipital cortex despite residual preoperative form vision and despite visual functional specialization (for faces and visual motion) in high-level visual cortex. In the primary visual cortex, auditory responses largely overlapped with visual responses and remained elevated even 7 months post-surgery. Following surgery, behavioral improvements in both visual acuity and contrast sensitivity were accompanied by neural changes across time. Specifically, auditory responses decreased in extrastriate occipital regions, together with rapid increases in grey matter density and in neural activation in low-level visual regions.

These findings imply that crossmodal plasticity may be observed even in cases where visual loss is not total. Similar findings were previously reported in an adult man with severe visual impairment since the age of 6, who also displayed cross-modal tactile responses in the visual cortex (Cheung et al., 2009). Interestingly, a recent EEG study conducted on hearing impaired individuals reported the existence of crossmodal visual responses in the auditory cortex during the early stage of hearing loss (Campbell & Sharma, 2014). These findings and our own thus suggest that total sensory deprivation is not necessary for crossmodal plasticity to occur in sensory-deprived cortices.

Moreover, crossmodal changes associated to early visual impairment appear to be qualitatively different from the ones observed in early-onset and complete visual deprivation. Indeed, despite the fact that cross-modal auditory responses measured in the occipital cortex of KL were at least as high as the ones measured in early and totally blind individuals, they were largely unspecific. This pattern thus contrasts with the functional specialization that characterizes these responses in early blind individuals (see also chapter 2 and 3 in the present thesis), and with findings reported in patient MM (Saenz et al., 2008) who displayed cross-modal responses to moving sounds in hMT+/V5 when tested years after sight-recovery. The absence of functionally-specific responses in KL is unlikely to be related to the auditory stimuli used in our study, since at least those from auditory experiment 2 previously revealed functionally-specific crossmodal responses for auditory spatial processing in congenitally blind subjects compared to both sighted (Collignon, Vandewalle, Voss, Albouy, Charbonneau, et al., 2011b) and late blind subjects (Collignon et al., 2013). In KL, we were able to demonstrate that residual visual abilities in face categorization and global motion detection were associated with functionally-specific responses in relevant high-level visual regions (i.e. hMT+/V5 for visual motion > static dots, and FFA/OFA for faces > objects and scrambled objects). Hence, we hypothesize that this functional specialization to relevant visual information may have prevented the development of functionally-specific crossmodal responses in these regions. In the same vein, cortical visual areas such as hMT+/V5, do not display functionally-specific crossmodal responses in late onset blind individuals, presumably because developmental vision has tuned these regions to relevant visuo-spatial information before sight was lost (Bedny et al., 2010; Collignon et al., 2013). This assumption is in line with a general principle of human postnatal functional brain development ("interactive specialization") according to which the extent of plasticity observed within a given region following sensory deprivation is dependent on the degree of specialization already achieved by this region (Johnson, 2011). In other words, a region that is already well specialized, in the sense that it is confined to a limited amount of cortical tissue and that it responds selectively to a given class of stimuli relative to another, will be less susceptible to change (Johnson, 2011).

Importantly, crossmodal plasticity associated with severe visual impairment appears to be at least partially reversible following visual recovery. Indeed in KL, although auditory responses remained elevated in the primary visual cortex even 7 months after surgery, they progressively decreased in extrastriate visual areas when compared to pre-surgery. It is tempting to associate this decrease in crossmodal auditory responses with improvements observed in visual abilities at the behavioral level (e.g. visual acuity, contrast sensitivity, face individuation) and with occipital increases observed in grey matter density and in neural responses to visual motion. Similarly, it could be hypothesized that overlapping auditory and visual responses in the primary visual cortex before and after surgery may prevent vision from recovering to a larger extent. Indeed, as reviewed in chapter 1 (section 4.2.2), studies conducted in deaf cochlear implant users have provided clear evidence for the existence of an inverse relationship between the magnitude of cross-modal visual or resting activity in auditory cortices, and speech performance following cochlear implantation (Lee et al., 2001; Lee et al., 2007; Sandmann et al., 2012).

Since cases with residual vision are the main targets of current surgical interventions (Aldave et al., 2009; Robert & Harissi-Dagher, 2011), there is a necessity for future studies to characterize the nature of crossmodal plasticity occurring in such cases, to understand the factors that may influence it (e.g. onset, duration and severity of the visual impairment) and, most importantly, to clarify how this phenomenon is likely to modulate visual recovery. These studies are crucial in order to define pre-surgical predictors for the outcome of surgical interventions.

Future studies may also benefit from a finer investigation of different visual functions, such as motion and face processing, and of the integrity of the neural systems on which these functions rely. For instance, in KL, we found a dissociation at the behavioral level between global motion thresholds for radial motion (preserved) and global motion thresholds for vertical/translational motion (altered). This pattern of performance was observed before surgery and did not evolve after surgery. It is interesting to note that previous studies reported impaired sensitivity to translational (vertical) motion in patients born with dense bilateral cataracts that had been treated before the age of 8 months (Ellemberg et al., 2002; Hadad et al., 2012). Although radial motion was not tested in these studies, the same cohort of patients showed spared sensitivity to biological motion (Hadad et al., 2012). Together, these observations suggest that some types of motion processing (e.g. radial flow or biological motion) may be more resistant to severe visual impairment. Radial motion conveys motion-in-depth information, which is a crucial cue for many actions such as avoiding or reaching an object, heading, locomotion and posture. Accounting for the particular status of radial over translation motion, infants as young as 3 months of age preferentially look at radial over translational random-dots kinematograms (RDKs) (Shirai, Kanazawa, & Yamaguchi, 2008), and aging was reported to have a detrimental effect on translational motion but not on radial and biological motion (Billino, Bremmer, & Gegenfurtner, 2008). In KL, we only used radially moving patterns in the scanner as these are the most commonly used stimuli in neuroimaging studies of motion processing (Sunaert et al., 1999; Tootell et al., 1995). In line with KL's normal behavioral performance with radially moving patterns, these stimuli, compared to static patterns of dots, elicited strong selective responses in area hMT+/V5 in all sessions. Future studies in visually-impaired could thus further investigate whether dissociations may be observed both behaviorally and at the neurofunctional level for different types of motion. This is of particular interest in order to further develop adapted rehabilitation programs, since the perception of visual dynamic information in general is thought to be more resistant to visual deprivation compared to other visual abilities. Moreover, dynamic information is a cue on which sight-recovery subjects tend to rely heavily to compensate for their visual impairment (Fine et al., 2003; Gregory & Wallace, 1974; Ostrovsky et al., 2009).

Regarding face perception in KL, individual face discrimination was at chance prior to surgery and significantly improved for both upright and inverted faces 7 months post-surgery. In the scanner however, we only investigated face categorical responses (compared to objects and scrambled faces). In line with KL's accurate face categorization performance even prior to surgery, we found face-selective responses in FFA and OFA at that time. These responses did not evolve after surgery, despite the improvement in individual face discrimination observed at the behavioral level. Interestingly, acquired prosopagnosic patients also display face selective regions despite profound deficits in individual face discrimination (Dricot et al., 2008; Rossion et al., 2003; Schiltz et al., 2006; Steeves et al., 2009). However, adaptation paradigms have revealed that activity in these regions, despite being preferential for faces over non-face objects, is not sensitive to the discrimination of individual faces (Dricot et al., 2008; Schiltz et al., 2006; Steeves et al., 2009). Hence, future studies with sight-recovery individuals may therefore test sensitivity to faces in face-selective regions by means of adaptation paradigms in order to provide a finer investigation of neural responses to faces before and after surgery.

4. Conclusions

The study of crossmodal plasticity associated with visual deprivation has fascinated neuroscientists for nearly thirty years now, and has evolved considerably in the last decade. Research in this field has provided compelling evidence accounting for the crucial role played by sensory experience in the development of brain regions and of their functional role. Our studies in early and totally blind individuals (chapter 2 and 3) have notably shown the immense adaptability of the brain in response to visual deprivation occurring early in life. Moreover, the functional specialization we observe in crossmodal plasticity and its anatomo-functional correspondence with the organization of the visual cortex in sighted subjects, suggests that experience-independent mechanisms may be present early in life (maybe in the form of endogenous patterns of connectivity) and bias different cortical regions to process specific types of relevant information provided by the available sensory modalities.

However, there is a risk for an overemphasis of the similarity observed between the organization of the "visual" cortex in blind and sighted subjects (Fine, 2014). As pointed out in chapter 3, it may well be that this anatomo-functional correspondence is not a general principle of the reorganized occipital cortex following early visual deprivation. Moreover, the choice of the stimuli used and, even more dramatically, the choice of the regions where to look for "selective" crossmodal responses, are inevitably biased by our understanding of the way the visual cortex is organized in *sighted* individuals. As stressed in chapter 2, the use of whole-brain rather than region-of-interests analyses is, in our opinion, of primary importance in order to ascertain the existence of functional selectivity in the visually-deprived occipital cortex. Moreover, the possibility that sensory experience specific to one modality (e.g. tonotopy in audition, somatotopic mapping in touch) may be present in the occipital cortex of blind individuals with no direct correspondence in vision remains unexplored (Fine, 2014).

There is a crucial need for a larger understanding of the mechanisms underlying crossmodal reorganization in total blindness. The lack of synaptic pruning hypothesis is mainly based on animal work and necessitates further validation in humans. A better understanding of these mechanisms is crucial in order to propose adapted interventions to blind individuals, whether of the invasive or of the non-invasive type. Crossmodal plasticity in particular may be beneficial for the use of non-invasive sensory substitution devices but may be detrimental in cases of surgical interventions to restore vision, especially in cases where vision was lost early in life.

Our findings from chapter 4 indicate that robust crossmodal responses may be observed even in cases were visual deprivation is not total. In KL, these crossmodal responses remained elevated in primary visual cortex even months following surgery, a phenomenon that might potentially interfere with optimal visual recovery. However, auditory-driven responses decreased in extrastriate regions together with an increase in optical quality, suggesting that crossmodal plasticity may be modulated by a change in sensory experience even well into adulthood. Since low vision individuals are the main targets to current surgical interventions to restore visual input, there is a necessity of increasing this type of research in the future, in order to provide clear factors that may predict visual outcome and in order to develop adapted postsurgical rehabilitation interventions.

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