

The blind brain: How (lack of) vision shapes the morphological and functional architecture of the human brain

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Abstract

Since the early days, how we represent the world around us has been a matter of philosophical speculation. Over the last few decades, modern neuroscience, and specifically the development of methodologies for the structural and the functional exploration of the brain have made it possible to investigate old questions with an innovative approach. In this brief review, we discuss the main findings from a series of brain anatomical and functional studies conducted in sighted and congenitally blind individuals by our's and others' laboratories. Historically, research on the 'blind brain' has focused mainly on the cross-modal plastic changes that follow sensory deprivation. More recently, a novel line of research has been developed to determine to what extent visual experience is truly required to achieve a representation of the surrounding environment. Overall, the results of these studies indicate that most of the brain fine morphological and functional architecture is programmed to develop and function independently from any visual experience. Distinct cortical areas are able to process information in a supramodal fashion, that is, independently from the sensory modality that carries that information to the brain. These observations strongly support the hypothesis of a modality-independent, i.e. more abstract, cortical organization, and may contribute to explain how congenitally blind individuals may interact efficiently with an external world that they have never seen.

Keywords: Blindness, supramodality, cross-modal plasticity, brain imaging, brain functional architecture, mental representation

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Introduction

The information that we acquire through our eyes plays a central role in shaping the manner in which we represent and interact with the world around us. The ancient Greek term for the verb 'to know' was the past tense of the verb 'to see', indicating that knowledge was subordinated to prior visual experience (I saw and thus I know).

Though lack of visual experience may often delay childhood physiological development in blind individuals,^{1–3} modulate their cognitive strategies^{4–7} or affect to some extent their social functioning,^{1,2} congenitally blind individuals overall show perceptual, cognitive and social skills comparable to those of sighted individuals – see for instance, Cattaneo *et al.*,⁵ Pasqualotto *et al.*,^{7–9} Ricciardi *et al.*,^{10–13} Klinge *et al.*,¹⁴ Bedny *et al.*¹⁵ and Proulx *et al.*,¹⁶ among many other behavioural observations.

The fact that congenitally blind individuals show comparable-to-sighted performances, in spite of the relevance of the visual modality for human and non-human primates, raises some fundamental questions, including in the first

place to what extent is vision truly necessary for the human brain to develop and function, and which fate visual brain areas undergo in blind individuals.

While historically the latter question has been widely investigated both in humans as well as in animal models with congenital or acquired blindness, more recently researchers from distinct labs across the world, including our own, have developed innovative lines of research finalized to understand how much vision is a mandatory prerequisite for the brain morphological and functional development to occur.

Here we discuss general findings from brain structural and functional studies in congenitally blind individuals that have contributed to understand not only the cross-modal plastic modifications that do occur in the 'visual' regions as a consequence of the lack of visual input, but mainly the role of (lack of) visual experience on the development of the brain morphological and functional architecture in humans. Novel hypotheses, open questions and ill-defined aspects regarding the 'blind brain' are reviewed.^a

How does the brain reorganize when vision lacks since birth?

The structural and functional characterization of the brain in people who lack vision since birth and report no visual experience represents an unprecedented tool for understanding how cross-modal plasticity reorganizes sensory-deprived brain areas.^{12,13,17–19} Because sight has always been considered as the most important sense for humans to acquire knowledge of the surrounding world, researchers have been constantly interested in defining the fate of unisensory ‘visual’ brain areas in blind individuals.

Notably, a functional recruitment of ‘visual’ occipital areas in the ‘blind brain’ has been described both at rest (that is, in the absence of any sensory stimulation) and during various non-visual tasks since the earliest studies.^{20–22} Over the last 15 years the neural modifications subserving the processes through which ‘visual’ brain regions undergo a plastic cross-modal reorganization in sight-deprived individuals have been characterized to a greater detail. Nonetheless, several questions still remain to be addressed.

For instance, the functional specificity of these cross-modal adaptations within occipital areas is still under debate. As a matter of fact, occipital activations in blind individuals appear to play a fundamental role in sensory processing across a wide gamut of experimental tasks (e.g. lexical, verbal and phonological processing, object discrimination, selective attention, verbal and episodic memory, sound localization).^{19,23–26} In addition, their recruitment relates to the individual behavioural outcome and is transitorily disrupted by transcranial magnetic stimulation (TMS).^{19,27} However, the lack of a precise anatomical and functional characterization of these cross-modal responses leaves still open the question whether occipital regions in blind individuals reorganize in a task-specific and performance-correlated manner, or whether this sensory-deprived cortex may just respond to non-visual inputs irrespectively from their perceptual content.^{28–32}

This issue tightly relates to another still-open key question regarding the ‘blind brain’: how does non-visual information reach ‘visual’ occipital cortical regions? After sensory deprivation, the human visual cortex rewires and accommodates non-visual sensory inputs.^{18,33} The loss of a specific sense allows the deprived cortical area to be invaded by inputs originating from other primary cortical regions, as early sensory areas physiologically show direct, heteromodal connections.^{34,35} In addition, two other anatomical pathways should be taken into account. First, non-visual information reaches the occipital cortex through cortico-cortical connections. In particular, the parieto-occipital pathway^{18,19} becomes stronger after vision loss^{18,33,36–38} and conveys information from somatosensory and multisensory parietal areas to the reorganized occipital cortex.^{39–42} Second, a concomitant reorganization of thalamic-cortical connections occurring after vision loss in early life may contribute to reorganize sense-specific links among distinct sensory cortical areas,^{43,44} including afferences to

the occipital cortex. Nevertheless, it is yet to be fully understood how these different pathways convey the information to the occipital cortex in blind individuals.

A possible modality-specific, but task-independent localization of cross-modal responses in different portions of the occipital cortex in blind individuals has been recently proposed.^b Using a meta-analytic approach, an enhanced recruitment of the dorsal occipital and parietal cortex was found specifically across tactile-prompted tasks in blind as compared to sighted individuals. This tactile-induced recruitment in blind subjects suggests that tactile information may be primarily conveyed from sensorimotor areas to parietal-occipital regions through a potentiation of the existing cortico-cortical connections.^{39–42} On the contrary, an enhanced recruitment of more medial and ventral occipital and inferior temporal areas was found specifically across auditory-prompted tasks in blind. Consequently, auditory information may be directly brought to occipito-temporal areas via direct heteromodal or subcortical connections.^{35,45} As the different modalities, such hearing and touch, convey sensory inputs with peculiar spatio-temporal and organizational features (e.g. global *vs.* analytic; simultaneous *vs.* sequential) and distinctively link to the occipital clusters,⁴⁶ the cross-modal adaptation in blind people is likely to be affected by the sensory channel variable^{a,47}

A final consideration relative to neural adjustments occurring after sensory deprivation regards the modulation of cross-modal phenomena due to the age of blindness onset or the cause of sensory loss. The examination of different subpopulations of sensory-deprived individuals is actually offering novel and surprising suggestions in the comprehension of cross-modal plasticity in blindness.

For instance, the degree of plastic compensatory changes is influenced by the age at which sight loss occurs, and is reflected by the extent of cross-modal phenomena in ‘visual’ occipital areas. Typically, late blind individuals show a limited activation in occipital areas and a reduced connectivity between occipital and stimulus-processing areas.^{40,42} Nonetheless, late blind individuals provide a fundamental comparison to fully characterize the behavioural and neural changes that occur in people who have had no visual experience, and thus exploit the potentiality of sensory-substitution or prosthetic devices in sighted individuals who lost vision later in life.⁴⁸

Similarly, anophthalmic and monocular patients represent unique models to study the effects of sensory deprivation, as compared to other causes of blindness. In anophthalmia, retinal input to the visual system is absent due to the congenital lack of eye development, and therefore it is possible to investigate the structural and functional cerebral reorganization that results from truly absolute peripheral blindness with no central nervous system involvement.^{49–51} On the other hand, the study of monocular individuals is useful to understand behavioural and neural compensatory processes associated with receiving images through one eye only.⁵

How does the brain organize independently from visual experience?

As previously discussed, most of the research in blind individuals typically has focused on the compensatory plastic rearrangements that follow sensory deprivation. However, the loss of sight represents a powerful tool also to understand to what extent the brain morphological and functional architecture is programmed to develop independently from any visual experience.

Vision is indeed considered crucial to provide the main sensory inputs to explore the world around us. Visual stimuli are received and hierarchically processed in the human brain along segregated, though integrated, pathways that process distinct, simpler elements into more complex, unified percepts.⁵² As a matter of fact, from a neuroanatomical perspective, the 'visual brain' is parcelated into distinct, hierarchical connected functional areas that extends from striate and peristriate occipital regions, to temporal, parietal and even frontal cortex.⁵³

While we know that early visual-processing areas in occipital cortex undergo adaptative cross-modal modifications, the question is what takes place in the other areas of the "visual" brain in congenitally blind individuals. As a matter of fact, most of the functional elements along the visual pathways have been shown to be able to process external information regardless of the sensory modality through which such an information has been acquired.

Behavioural protocols have shown that several perceptual, cognitive and social skills are substantially comparable between congenitally blind and sighted individuals.^{12,54} More recently, brain functional studies have demonstrated that during perceptual tasks congenitally blind people rely on patterns of neural response that overlap to those in sighted individuals.¹² For instance, in both sighted and blind individuals, visual and non-visual recognition of object form activates the inferior temporal and ventral occipital cortex,^{55–58} visual, tactile and auditory motion discrimination activates the middle temporal areas,^{59,60} and spatial representation, either processed through vision, tactile exploration or sound localization, relies on parietal networks.^{29,61,62} If a given 'visual' area is recruited for visual and non-visual tasks in sighted individuals, as well as in congenitally blind individuals for non-visual tasks, then this activation indicates a more abstract, supramodal representation of a specific content of information, and cannot be simply ascribed to a plastic rearrangement due to the lack of vision.^{12,13,33} Thus, a supramodal brain region shares a specific, more abstract representation of the perceived stimuli, which does not depend uniquely on the input from a specific sensory modality.

For the most part, the supramodal nature of neural representation of sensory stimuli has been primarily assessed within the well-known functional organization of the visual system. As briefly stated above, highly specialized regions subserving object form recognition (lateral occipital clusters), motion processing (middle temporal complex), spatial layout coding (parahippocampal cortex) and spatial localization (dorsal occipito-parietal pathway) have been the most explored 'visual' brain areas through visual and

non-visual stimulation paradigms, in both sighted and congenitally blind individuals (e.g. Pietrini *et al.*,⁵⁷ Ricciardi *et al.*,⁶⁰ Bonino *et al.*,⁶¹ Weeks *et al.*,⁶² De Volder *et al.*,⁶³ Peelen *et al.*⁶⁴ and Kupers *et al.*⁶⁵). These initial studies not only assessed the overlapping patterns of neural responses in both sighted and blind individuals, but also determined that supramodal brain areas share overlapping connectivity maps in sighted and blind individuals,^{40,41} yield to task-specific, modality-independent behavioural impairments when functionally-inhibited via TMS,^{66,67} and even respond when a specific information is conveyed by visual-to-auditory or visual-to-tactile sensory substitution devices.^{48,68} Altogether, these observations from imaging studies indicate that the brain functional organization of 'visual' pathways is able to process information in a supramodal fashion, does not strictly depend on the contribution of a specific sensory modality to function and is to a large extent independent from visual experience, or from visually-based mental imagery, to form and to develop.

More recently, as reported in details by Ricciardi *et al.*, the description of supramodal responses rapidly moved from the 'simpler' perceptual contents within the visual pathways to more complex semantic representations – such as tool use or action recognition,^{11,69} – and in the direction of affective functioning – such as representations of others' emotions and mental states.^{15,70} The concept of supramodality appears to be not limited to functionally specialized cortical clusters but rather extends to distributed brain networks. Thus, at different levels of stimulus processing, the human brain may rely on a broader 'supramodal mechanism', which advances sensory information towards a more abstract, possibly 'conceptual', representation. While this mechanism may result clearer when dealing with semantic knowledge, it remains to be defined at which processing level the information content of stimuli separates from sensory input features and becomes supramodal.^{12,13,71}

This theoretical framework tightly relates to still uncertain aspects of supramodality. Do the overlapping activations in a particular brain region elicited by distinct sensory modalities reflect an identical recruitment of individual supramodal neurons, or rather a selective recruitment of distinct unimodal subpopulations within the same cortical areas? In other words, at which level (e.g. single neuron, cluster or cortical network) does the supramodal representation of information occur? Are similarities in the functional patterns between sighted and blind individuals limited to the topographic localization of the recruited cortical areas (i.e. simple overlapping of brain activations), or conversely involve the content of the neural responses (i.e., rely on the same neural representation)?

While several protocols have been developed in animals for investigating cross-modal plasticity (recently reviewed by Kupers *et al.*¹⁸ and Kupers and Ptito⁵⁴), very few studies have been conducted to assess the neuronal correlates of supramodality. For instance, in monkeys, more abstract representations of grating orientation have been found in occipital area V4,⁷² and in neurons in the ventral premotor cortex for specific finalized motor acts.⁷³ Interestingly, these studies suggest that supramodal properties may be

restricted to only a part of the whole neuronal populations within the different brain areas, whereas the majority of neurons show unimodal responses, and concern representations of different perceptual complexity (e.g. stimulus orientations *vs.* action goals).

Recent brain functional studies in humans have used pattern-classification algorithms and multivariate analysis to decode the information that is represented in a spatially distributed pattern of neural activity, and to identify those brain regions that may contribute significantly to the discrimination of different mental states.^{74–76} Consequently, pattern recognition approaches may be employed to describe overlapping neural responses across experimental samples (e.g. congenitally blind and sighted) and/or sensory modalities. As compared to the ‘more classical’ univariate approach in imaging studies, the homologies in the functional representation obtained with multivariate approaches are not limited only to a mere overlap in the topographical localization of neural activations, but do involve the intrinsic content of the neural responses.

Multi-voxel pattern analyses have revealed a more abstract representation in congenitally blind and sighted individuals across visual and/or non-visual presentation of motion direction in middle temporal areas,⁷⁷ and for hand-made actions in the bilateral, though left-prevalent, action–observation network.⁷⁸ Similarly to what has been reported in animal studies and in line with early imaging studies in humans, pattern recognition approaches have shown that supramodal properties are restricted to only a part of the whole neuronal populations within the different brain areas – suffice to mention the LOTv cluster within the broader lateral occipital cortex,^{55,57} the anterior portion of human middle temporal complex,^{59,60} or the more limited ventral premotor and inferior parietal clusters within the more extended action observation network (see Figure 3 of Ricciardi *et al.*⁷⁸) – and concerned representations of different perceptual complexity (e.g. motion discrimination *vs.* action goals).

The comprehension of how unisensory information is processed and integrated into a supramodal representation represents a major challenge for research in the neuroscience of the ‘blind brain’. To date, interesting hints have been prompted from recent studies that investigate the relationship between sensory modality and conceptual knowledge.

Theories on the organization of conceptual knowledge proposed two types of neural representation models in relation to perceptual processing: modality-specificity and domain-specificity.⁷⁹ The modality-specificity theories postulate that conceptual knowledge is organized by the sensory modality (e.g. visual, motor, tactile) enrolled during the acquisition or the processing of concepts, while according to the domain-specificity theories this organization is based on a more abstract, semantic categorization regardless of the sensory modality that conveys the information to the brain.⁸⁰ On this topic, neuropsychological evidence appears to support a domain-specific organization in the human brain. Specifically, selected patients with brain lesions may develop category-specific and category-selective semantic deficits (i.e. for animals or fruit/vegetables), that are usually not associated with impairments in

perception (for a review by Gainotti⁸¹). Conversely, impairments within sensory modalities are not inevitably associated with category specific semantic deficits: for instance, neuropsychological observations showed that perception of colour is represented autonomously from object colour knowledge.⁸²

The entangle between sensory modality and conceptual knowledge can be also evaluated from a linguistic point of view. Even if they acquire conceptual knowledge through auditory or haptic inputs, congenitally blind individuals show globally a high similarity in language properties as compared to sighted ones, including when processing knowledge directly related to visual experience (i.e. colour terms, verbs of vision).⁸³ Moreover, even when restricting to semantic categorial features in language production, only few differences are found between blind and sighted individuals, especially in categories in which vision is salient (i.e. fruits and vegetables).^{84,85}

The neuropsychological and linguistic approaches did not fully clarify to which extent conceptual knowledge is grounded into the sensory modalities. Novel approaches in functional neuroimaging studies are indicating that ‘concepts’ are characterized by a more complicated and distributed organization within the human brain.^{58,86} Further studies should look for potential functional similarities between congenitally blind and sighted individuals and assess whether these are dependent on sensory modalities and sensory experiences, particularly when dealing with conceptual knowledge across several semantic categories.

Final considerations

Over the last two decades, functional brain studies in blind individuals have offered a unique opportunity to examine the role of visual experience in forming a representation of the external world, as well as to understand to what extent visual experience is a mandatory prerequisite for the human brain to develop and function. Individuals who lack sight since birth have provided inspiring ideas on many questions regarding both the cross-modal plastic rearrangements that take place when vision is absent, and the development of the morphological and functional organization of the sighted brain itself. The demonstration of the modality independent, more abstract nature of the functional cortical organization, and consequently of information representation, may contribute to explain how congenitally blind individuals are able to acquire knowledge and interact with an external world that they have never seen. This proficient mental representation would not only explain the perceptual, cognitive and social performances comparable to those in sighted individuals,^{5,12,18,19} but mainly indicate that the blind brain is not ‘disable’, but rather ‘differentially abled’.^{12,13,33,87}

Nevertheless, blind individuals certainly experience important sensorial limitations, including the inability to perceive features that are strictly ‘visual’ (e.g. colours, perspective, shadows, etc.), and to have immediate simultaneous synoptic representation (as touch and hearing only allow for a sequential processing of information). These

differences may result in the adoption of distinct mental strategies to perform a given task, as well as in impaired behavioural responses, as in the case of spatial representations that involve complex mental abilities, including angle discrimination or three-dimensional spatial imagery tasks (e.g. Noordzij *et al.*,⁴ Cattaneo *et al.*,⁵ Pasqualotto *et al.*,⁷ Pasqualotto and Proulx⁸⁸ and Gori *et al.*⁸⁹).

Interestingly, from a neurofunctional perspective, the demonstration of a similar supramodal brain organization in normally sighted people and in individuals deprived of sight since birth indicates that visual experience is not necessary for the brain to develop its morphological and functional architecture. Thus, this supramodal cortical functional development appears to be to some extent hard-wired in our genetic code,¹² though vision and the other unimodal sensory inputs certainly play an important role in the shaping of the perceptual processing system.

Of note, recent exceptional reports in congenitally blind individuals, who recovered sight in their adulthood after eye surgery, indicate that these subjects do not exhibit an immediate transfer of their tactile knowledge to the visual domain during an object form detection task.^{90,91} Nonetheless, these abilities were acquired after a very short time, thus suggesting a rapid learning process for establishing relationships across sensory modalities.^{90,91} This observation may induce to hypothesize that the rapidity of the cross-modal mapping may be facilitated by a shared, supramodal representation of object form. The newly acquired sensory experience, however, appears to require some extra time to gain access to such a representation, suggesting that some functional reorganization may anyway be needed.

In conclusion, the blind brain is a fascinating model to investigate the molecular and neurobiological underpinnings of how the brain develops its marvellous morphological and functional architecture. We believe that step forwards in the comprehension of both cross-modal adaptive plastic responses and supramodal functional cortical organization will expand our understanding of the nature *versus* nurture role in the shaping of the human brain and will improve our ability to significantly develop novel educational/rehabilitative programs and sensory-substitution devices for sensory-deprived individuals.⁴⁸

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NOTES

- a. Researchers who work on the effects of blindness on the brain by using neuroimaging and molecular methodologies, recently gathered together to discuss the state-of-the-art and future perspectives on what we can learn from studying the blind brain ('The Blind Brain Workshop: How Blindness Can Open Our Eyes', San Giuliano Terme, Pisa, Italy, 16–18 October 2013, <http://www.theblindworkshop.com>). Cortical development, cross-modal plasticity, supramodal organization, multisensory integration and sensory-substitution devices were the major topics discussed in the two-day workshop.
- b. Ricciardi E, Tozzi L, Leo A, Pietrini P. Modality dependent cross-modal functional reorganization following congenital visual deprivation within occipital areas: a meta-analysis of tactile and auditory studies. Submitted for publication.

REFERENCES

1. Fraiberg S. *Insights from the blind: comparative studies of blind and sighted infants*. New York, NY: Basic Books, 1997
2. Peterson CC, Peterson JL, Webb J. Factors influencing the development of a theory of mind in blind children. *Br J Dev Psychol* 2000;**18**:431–47
3. Tobin MJ. Is blindness a handicap? *Br J Spec Educ* 1998;**25**:107–13
4. Noordzij ML, Zuidhoek S, Postma A. The influence of visual experience on visual and spatial imagery. *Perception* 2007;**36**:101–12
5. Cattaneo Z, Vecchi T, Cornoldi C, Mammarella I, Bonino D, Ricciardi E, Pietrini P. Imagery and spatial processes in blindness and visual impairment. *Neurosci Biobehav Rev* 2008;**32**:1346–60
6. Pasqualotto A, Spiller MJ, Jansari AS, Proulx MJ. Visual experience facilitates allocentric spatial representation. *Behav Brain Res* 2013;**236**:175–9
7. Pasqualotto A, Taya S, Proulx MJ. Sensory deprivation: visual experience alters the mental number line. *Behav Brain Res* 2014;**261**:110–3
8. Pasqualotto A, Finucane CM, Newell FN. Ambient visual information confers a context-specific, long-term benefit on memory for haptic scenes. *Cognition* 2013;**128**:363–79
9. Pasqualotto A, Lam JS, Proulx MJ. Congenital blindness improves semantic and episodic memory. *Behav Brain Res* 2013;**244**:162–5
10. Ricciardi E, Renzi C, Bonino D, Kupers R, Pietrini P. Space representation in the absence of sight in the human brain. In: *Space in language – proceedings of the pisa international conference* (eds G Marotta, A Lenci, L Meini, F Rovai), Pisa, Italy: Edizioni ETS, 2010, pp.95–122
11. Ricciardi E, Bonino D, Sani L, Vecchi T, Guazzelli M, Haxby JV, Fadiga L, Pietrini P. Do we really need vision? How blind people “see” the actions of others. *J Neurosci* 2009;**29**:9719–24
12. Ricciardi E, Bonino D, Pellegrini S, Pietrini P. Mind the blind brain to understand the sighted one! Is there a supramodal cortical functional architecture? *Neurosci Biobehav Rev* 2014;**41**:64–77
13. Ricciardi E, Pietrini P. New light from the dark: what blindness can teach us about brain function. *Curr Opin Neurol* 2011;**24**:357–63
14. Klinge C, Eippert F, Roder B, Büchel C. Corticocortical connections mediate primary visual cortex responses to auditory stimulation in the blind. *J Neurosci* 2010;**30**:12798–805
15. Bedny M, Pascual-Leone A, Saxe RR. Growing up blind does not change the neural bases of theory of mind. *Proc Natl Acad Sci U S A* 2009;**106**:11312–7
16. Proulx MJ, Brown DJ, Pasqualotto A, Meijer P. Multisensory perceptual learning and sensory substitution. *Neurosci Biobehav Rev* 2014;**41**:16–25
17. Frasnelli J, Collignon O, Voss P, Lepore F. Crossmodal plasticity in sensory loss. *Prog Brain Res* 2011;**191**:233–49
18. Kupers R, Pietrini P, Ricciardi E, Ptito M. The nature of consciousness in the visually deprived brain. *Front Psychol* 2011;**2**:1–14
19. Noppeney U. The effects of visual deprivation on functional and structural organization of the human brain. *Neurosci Biobehav Rev* 2007;**31**:1169–80

20. Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, Hallett M. Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* 1996;**380**:526–8
21. Wanet-Defalque MC, Veraart C, De Volder A, Metz R, Michel C, Doms G, Goffinet A. High metabolic activity in the visual cortex of early blind human subjects. *Brain Res* 1988;**446**:369–73
22. Veraart C, De Volder AG, Wanet-Defalque MC, Bol A, Michel C, Goffinet AM. Glucose utilization in human visual cortex is abnormally elevated in blindness of early onset but decreased in blindness of late onset. *Brain Res* 1990;**510**:115–21
23. Amedi A, Stern WM, Campardon JA, Bermpohl F, Merabet L, Rotman S, Hemond C, Meijer P, Pascual-Leone A. Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. *Nat Neurosci* 2007;**10**:687–9
24. Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Català MD, Hallett M. Functional relevance of cross-modal plasticity in blind humans. *Nature* 1997;**389**:180–3
25. Kupers R, Pappens M, de Noordhout AM, Schoenen J, Ptito M, Fumal A. rTMS of the occipital cortex abolishes Braille reading and repetition priming in blind subjects. *Neurology* 2007;**68**:691–3
26. Zangaladze A, Epstein CM, Grafton ST, Sathian K. Involvement of visual cortex in tactile discrimination of orientation. *Nature* 1999;**401**:587–90
27. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol* 2000;**10**:232–7
28. Amedi A, Raz N, Pianka P, Malach R, Zohary E. Early ‘visual’ cortex activation correlates with superior verbal memory performance in the blind. *Nat Neurosci* 2003;**6**:758–66
29. Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F. A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. *PLoS Biol* 2005;**3**:e27
30. Noppeney U, Friston KJ, Price CJ. Effects of visual deprivation on the organization of the semantic system. *Brain* 2003;**126**:1620–7
31. Raz N, Amedi A, Zohary E. V1 activation in congenitally blind humans is associated with episodic retrieval. *Cereb Cortex* 2005;**15**:1459–68
32. Renier LA, Anurova I, De Volder AG, Carlson S, VanMeter J, Rauschecker JP. Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. *Neuron* 2010;**68**:138–48
33. Pietrini P, Kupers R, Ptito M. Blindness and consciousness: new lights from the dark. In: Tononi G, Laureys S (eds). *The neurology of consciousness*. New York, NY: Academic Press, 2009, pp. 360–74
34. Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci* 2010;**11**:44–52
35. Ptito M, Desgent S. Sensory input-based adaptation and brain architecture. In: Baltes P, Reuter-Lorenz P, Rösler F (eds). *Lifespan development and the brain*. Cambridge: Cambridge University Press, 2006, pp. 111–23
36. Kupers R, Fumal A, de Noordhout AM, Gjedde A, Schoenen J, Ptito M. Transcranial magnetic stimulation of the visual cortex induces somatotopically organized qualia in blind subjects. *Proc Natl Acad Sci U S A* 2006;**103**:13256–60
37. Ptito M, Fumal A, de Noordhout AM, Schoenen J, Gjedde A, Kupers R. TMS of the occipital cortex induces tactile sensations in the fingers of blind Braille readers. *Exp Brain Res* 2008;**184**:193–200
38. Wittenberg GF, Werhahn KJ, Wassermann EM, Herscovitch P, Cohen LG. Functional connectivity between somatosensory and visual cortex in early blind humans. *Eur J Neurosci* 2004;**20**:1923–7
39. Leo A, Bernardi G, Handjaras G, Bonino D, Ricciardi E, Pietrini P. Increased BOLD variability in the parietal cortex and enhanced parieto-occipital connectivity during tactile perception in congenitally blind individuals. *Neural Plast* 2012;**2012**:720278
40. Fujii T, Tanabe HC, Kochiyama T, Sadato N. An investigation of cross-modal plasticity of effective connectivity in the blind by dynamic causal modeling of functional MRI data. *Neurosci Res* 2009;**65**:175–86
41. Sani L, Ricciardi E, Gentili C, Vanello N, Haxby JV, Pietrini P. Effects of visual experience on the human MT+ functional connectivity networks: an fMRI study of motion perception in sighted and congenitally blind individuals. *Front Sys Neurosci* 2010;**4**:159
42. Collignon O, Dormal G, Albouy G, Vandewalle G, Voss P, Phillips C, Lepore F. Impact of blindness onset on the functional organization and the connectivity of the occipital cortex. *Brain* 2013;**136**:2769–83
43. Cowey A. Visual system: how does blindsight arise? *Curr Biol* 2010;**20**:R702–4
44. Schmid MC, Mrowka SW, Turchi J, Saunders RC, Wilke M, Peters AJ, Ye FQ, Leopold DA. Blindsight depends on the lateral geniculate nucleus. *Nature* 2010;**466**:373–7
45. Ptito M, Kupers R, Lomber S, Pietrini P. Sensory deprivation and brain plasticity. *Neural Plast* 2012;**2012**:810370
46. Klemen J, Chambers CD. Current perspectives and methods in studying neural mechanisms of multisensory interactions. *Neurosci Biobehav Rev* 2012;**36**:111–33
47. Bridge H, Thomas O, Jbabdi S, Cowey A. Changes in connectivity after visual cortical brain damage underlie altered visual function. *Brain* 2008;**131**:1433–44
48. Maidenbaum S, Abboud S, Amedi A. Sensory substitution: closing the gap between basic research and widespread practical visual rehabilitation. *Neurosci Biobehav Rev* 2014;**41**:3–15
49. Bridge H, Cowey A, Ragge N, Watkins K. Imaging studies in congenital anophthalmia reveal preservation of brain architecture in ‘visual’ cortex. *Brain* 2009;**132**:3467–80
50. Millington RS, Ajina S, Bridge H. Novel brain imaging approaches to understand acquired and congenital neuro-ophthalmological conditions. *Curr Opin Neurol* 2014;**27**:92–7
51. Bridge H, Thomas OM, Minini L, Cavina-Pratesi C, Milner AD, Parker AJ. Structural and functional changes across the visual cortex of a patient with visual form agnosia. *J Neurosci* 2013;**33**:12779–91
52. Ungerleider LG, Haxby JV. ‘What’ and ‘where’ in the human brain. *Curr Opin Neurobiol* 1994;**4**:157–65
53. Bourne JA. Unravelling the development of the visual cortex: implications for plasticity and repair. *J Anat* 2010;**217**:449–68
54. Kupers R, Ptito M. Compensatory plasticity and cross-modal reorganization following early visual deprivation. *Neurosci Biobehav Rev* 2014;**41**:36–52
55. Amedi A, Malach R, Hendler T, Peled S, Zohary E. Visuo-haptic object-related activation in the ventral visual pathway. *Nat Neurosci* 2001;**4**:324–30
56. Mahon BZ, Anzellotti S, Schwarzbach J, Zampini M, Caramazza A. Category-specific organization in the human brain does not require visual experience. *Neuron* 2009;**63**:397–405
57. Pietrini P, Furey ML, Ricciardi E, Gobbi MI, Wu WH, Cohen L, Guazzelli M, Haxby JV. Beyond sensory images: object-based representation in the human ventral pathway. *Proc Natl Acad Sci U S A* 2004;**101**:5658–63
58. Peelen MV, He C, Han Z, Caramazza A, Bi Y. Nonvisual and visual object shape representations in occipitotemporal cortex: evidence from congenitally blind and sighted adults. *J Neurosci* 2014;**34**:163–70
59. Poirier C, Collignon O, Scheiber C, Renier L, Vanlierde A, Tranduy D, Veraart C, De Volder AG. Auditory motion perception activates visual motion areas in early blind subjects. *Neuroimage* 2006;**31**:279–85
60. Ricciardi E, Vanello N, Sani L, Gentili C, Scilingo EP, Landini L, Guazzelli M, Bicchieri A, Haxby JV, Pietrini P. The effect of visual experience on the development of functional architecture in hMT+. *Cereb Cortex* 2007;**17**:2933–9
61. Bonino D, Ricciardi E, Sani L, Gentili C, Vanello N, Guazzelli M, Vecchi T, Pietrini P. Tactile spatial working memory activates the dorsal extrastriate cortical pathway in congenitally blind individuals. *Arch Ital Biol* 2008;**146**:133–46
62. Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, Hallett M, Rauschecker JP. A positron emission tomographic study of auditory localization in the congenitally blind. *J Neurosci* 2000;**20**:2664–72
63. De Volder AG, Toyama H, Kimura Y, Kiyosawa M, Nakano H, Vanlierde A, Wanet-Defalque MC, Mishina M, Oda K, Ishiwata K, Senda M. Auditory triggered mental imagery of shape involves visual association areas in early blind humans. *Neuroimage* 2001;**14**:129–39
64. Peelen MV, Atkinson AP, Vuilleumier P. Supramodal representations of perceived emotions in the human brain. *J Neurosci* 2010;**30**:10127–34

65. Kupers R, Chebat DR, Madsen KH, Paulson OB, Ptito M. Neural correlates of virtual route recognition in congenital blindness. *Proc Natl Acad Sci U S A* 2010;**107**:12716–21
66. Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nat Neurosci* 2004;**7**:1266–70
67. Ricciardi E, Basso D, Sani L, Bonino D, Vecchi T, Pietrini P, Miniussi C. Functional inhibition of the human middle temporal cortex affects non-visual motion perception: a repetitive transcranial magnetic stimulation study during tactile speed discrimination. *Exp Biol Med (Maywood)* 2011;**236**:138–44
68. Matteau I, Kupers R, Ricciardi E, Pietrini P, Ptito M. Beyond visual, aural and haptic movement perception: hMT+ is activated by electro-tactile motion stimulation of the tongue in sighted and in congenitally blind individuals. *Brain Res Bull* 2010;**82**:264–70
69. Mahon BZ, Schwarzbach J, Caramazza A. The representation of tools in left parietal cortex is independent of visual experience. *Psychol Sci* 2010;**21**:764–71
70. Klinge C, Roder B, Buchel C. Increased amygdala activation to emotional auditory stimuli in the blind. *Brain* 2010;**133**:1729–36
71. Mahon BZ, Caramazza A. What drives the organization of object knowledge in the brain? *Trends Cogn Sci* 2011;**15**:97–103
72. Haenny PE, Maunsell JH, Schiller PH. State dependent activity in monkey visual cortex. II. Retinal and extraretinal factors in V4. *Exp Brain Res* 1988;**69**:245–59
73. Keysers C, Kohler E, Umiltà MA, Nanetti L, Fogassi L, Gallese V. Audiovisual mirror neurons and action recognition. *Exp Brain Res* 2003;**153**:628–36
74. Pereira F, Mitchell T, Botvinick M. Machine learning classifiers and fMRI: a tutorial overview. *Neuroimage* 2009;**45**(1 Suppl): S199–209
75. Poldrack RA. Can cognitive processes be inferred from neuroimaging data? *Trends Cogn Sci* 2006;**10**:59–63
76. Poldrack RA, Halchenko YO, Hanson SJ. Decoding the large-scale structure of brain function by classifying mental states across individuals. *Psychol Sci* 2009;**20**:1364–72
77. Strnad L, Peelen MV, Bedny M, Caramazza A. Multivoxel pattern analysis reveals auditory motion information in MT+ of both congenitally blind and sighted individuals. *PLoS ONE* 2013;**8**:e63198
78. Ricciardi E, Handjaras G, Bonino D, Vecchi T, Fadiga L, Pietrini P. Beyond motor scheme: a supramodal distributed representation in the action-observation network. *PLoS ONE* 2013;**8**:e58632
79. Mahon BZ, Caramazza A. Concepts and categories: a cognitive neuropsychological perspective. *Ann Rev Psychol* 2009;**60**:27–51
80. Caramazza A, Shelton JR. Domain-specific knowledge systems in the brain the animate-inanimate distinction. *J Cogn Neurosci* 1998;**10**:1–34
81. Gainotti G. The influence of anatomical locus of lesion and of gender-related familiarity factors in category-specific semantic disorders for animals, fruits and vegetables: a review of single-case studies. *Cortex* 2010;**46**:1072–87
82. Miceli G, Fouch E, Capasso R, Shelton JR, Tomaiuolo F, Caramazza A. The dissociation of color from form and function knowledge. *Nat Neurosci* 2001;**4**:662–7
83. Zimler J, Keenan JM. Imagery in the congenitally blind: how visual are visual images? *J Exp Psychol Learn Mem Cogn* 1983;**9**:269–82
84. Connolly AC, Gleitman LR, Thompson-Schill SL. Effect of congenital blindness on the semantic representation of some everyday concepts. *Proc Natl Acad Sci U S A* 2007;**104**:8241–6
85. Lenci A, Baroni M, Cazzolli G, Marotta G. BLIND: a set of semantic feature norms from the congenitally blind. *Behav Res Methods* 2013;**45**:1218–33
86. Simanova I, Hagoort P, Oostenveld R, van Gerven MA. Modality-independent decoding of semantic information from the human brain. *Cereb Cortex* 2014;**24**:426–34
87. Kupers R, Pietrini P, Ricciardi E, Ptito M. The nature of consciousness in the visually deprived brain. *Front Psychol* 2011;**2**:19
88. Pasqualotto A, Proulx MJ. The role of visual experience for the neural basis of spatial cognition. *Neurosci Biobehav Rev* 2012;**36**:1179–87
89. Gori M, Sandini G, Martinoli C, Burr DC. Impairment of auditory spatial localization in congenitally blind human subjects. *Brain* 2014;**137**:288–93
90. Sinha P, Held R. Sight restoration. *F1000 Med Rep* 2012;**4**:17
91. Held R, Ostrovsky Y, de Gelder B, Gandhi T, Ganesh S, Mathur U, Sinha P. The newly sighted fail to match seen with felt. *Nat Neurosci* 2011;**14**:551–3