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How input modality and visual experience affect the representation of categories in the brain

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“Nothing is in the intellect that was not first in the senses”

“Nella mente non c'è niente che non sia già stato nei sensi”

“Il n'est rien dans notre intelligence qui ne soit passé par nos sens.”

– Aristotle – *De Anima*

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Summary

The general aim of the present dissertation was to participate in the progress of our understanding of how sensory input and sensory experience impact on how the human brain implements categorical knowledge. The goal was twofold: (1) understand whether there are brain regions that encode information about different categories regardless of input modality and sensory experience (study 1); (2) deepen the investigation of the mechanisms that drive cross-modal and intra-modal plasticity following early blindness and the way they express during the processing of different categories presented as real-world sounds (study 2).

To address these fundamental questions, we used fMRI to characterize the brain responses to different conceptual categories presented acoustically in sighted and early blind individuals, and visually in a separate sighted group.

In study 1, we observed that the right posterior middle temporal gyrus (rpMTG) is the region that most reliably decoded categories and selectively correlated with conceptual models of our stimuli space independently of input modality and visual experience. However, this region maintains separate the representational format from the different modalities, revealing a multimodal rather than an amodal nature. In addition, we observed that VOTC showed distinct functional profiles according to the hemispheric side. The left VOTC showed an involvement in the acoustical categorization processing at the same degree in sighted and in blind individuals. We propose that this involvement might reflect an engagement of the left VOTC in more semantic/linguistic processing of the stimuli potentially supported by its enhanced connection with the language system. However, paralleling our observation in rpMTG, the representations from different modalities are maintained segregated in VOTC, showing little evidence for sensory-abstraction. On the other side, the right VOTC emerged as a sensory-related visual region in sighted with the ability to rewires itself toward acoustical stimulation in case of early visual deprivation.

In study 2, we observed opposite effects of early visual deprivation on auditory decoding in occipital and temporal regions. While occipital regions contained more information about sound categories in the blind, the temporal cortex showed higher decoding in the sighted. This unbalance effect was stronger in the right hemisphere where we, also, observed a negative correlation between occipital and temporal decoding of sound categories in EB. These last results suggest that the intramodal and crossmodal reorganizations might be inter-connected. We therefore propose that the extension of non-visual functions in the occipital cortex of EB may trigger a network-level reorganization that reduce the computational load of the regions typically coding for the remaining senses due to the extension of such computation in occipital regions.

1

BACKGROUND

1.1 Functional tuning of occipital regions in early blind people

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"Forty years ago, [...] we had no idea of the plasticity of the brain. We thought that every part of the brain was predetermined genetically, and that was that. Now we know that enormous changes of function are possible. The miracle of plasticity and redeployment of the nervous system excites me very much."

- Oliver Sacks -

Discover (October 2010)

1.1.1 Crossmodal plasticity in early blindness

The quality of being plastic refers to the ability of being molded and changing in shape. In 1904, Cajal for the first time suggested that the brain could be a plastic system (Ramon, Y., & Cajal, S.,1904). About 60 years later, Hubel and Wiesel were the first to compellingly demonstrate it, showing that the development of the visual cortex in kittens can be modified by alterations in visual experience (Wiesel and Hubel, 1963). This was the first of many works about neuroplasticity.

The study of congenitally blind individuals represents one of the most exquisite models to investigate brain plasticity since the visual deprivation leads to dramatic functional and structural reorganization in the brain (Bock and Fine, 2014; Collignon et al., 2012; Kupers and Ptito, 2013; Merabet and Pascual-Leone, 2010). For years the occipital lobe of blind individuals had been thought to be unused since it does not receive any visual input. However, in the 90s, some innovative studies (Veraart et al., 1988, 1990; De Volder et al., 1997) observed a high neural activity in the occipital areas of blind individuals (see figure1.1).

This revolutionary finding led to a conspicuous body of studies, which showed occipital activation in blind individuals during tactile (Büchel et al., 1998a; Burton et al., 2002a; Pietrini et al., 2004; Sadato et al., 1996), auditory (Röder et al., 2013; Weeks et al., 2000), memory (Amedi et al., 2003) and language-related (Burton et al., 2002a; Röder et al., 2000) tasks. Interestingly the recruitment of the occipital regions has been shown to be related to the superior non-visual skills often observed in blind individuals (Amedi et al., 2003; Gougoux et al., 2005; Théoret et al., 2004). The evidence for this functional relevance comes from a series of studies showing a bond between the occipital recruitment and the behavioural performance in early blind subjects. In 2003, Amedi and colleagues reported a correlation between the magnitude of the activity in the primary visual cortex and the blind individual's performances during a verbal-memory task (Amedi et al., 2003). Gougoux and collaborators found a similar effect for a sound localization task: they reported that the degree of activation of the occipital cortex was strongly correlated with sound localization accuracy across the entire group of blind subjects (Gougoux et al., 2005).

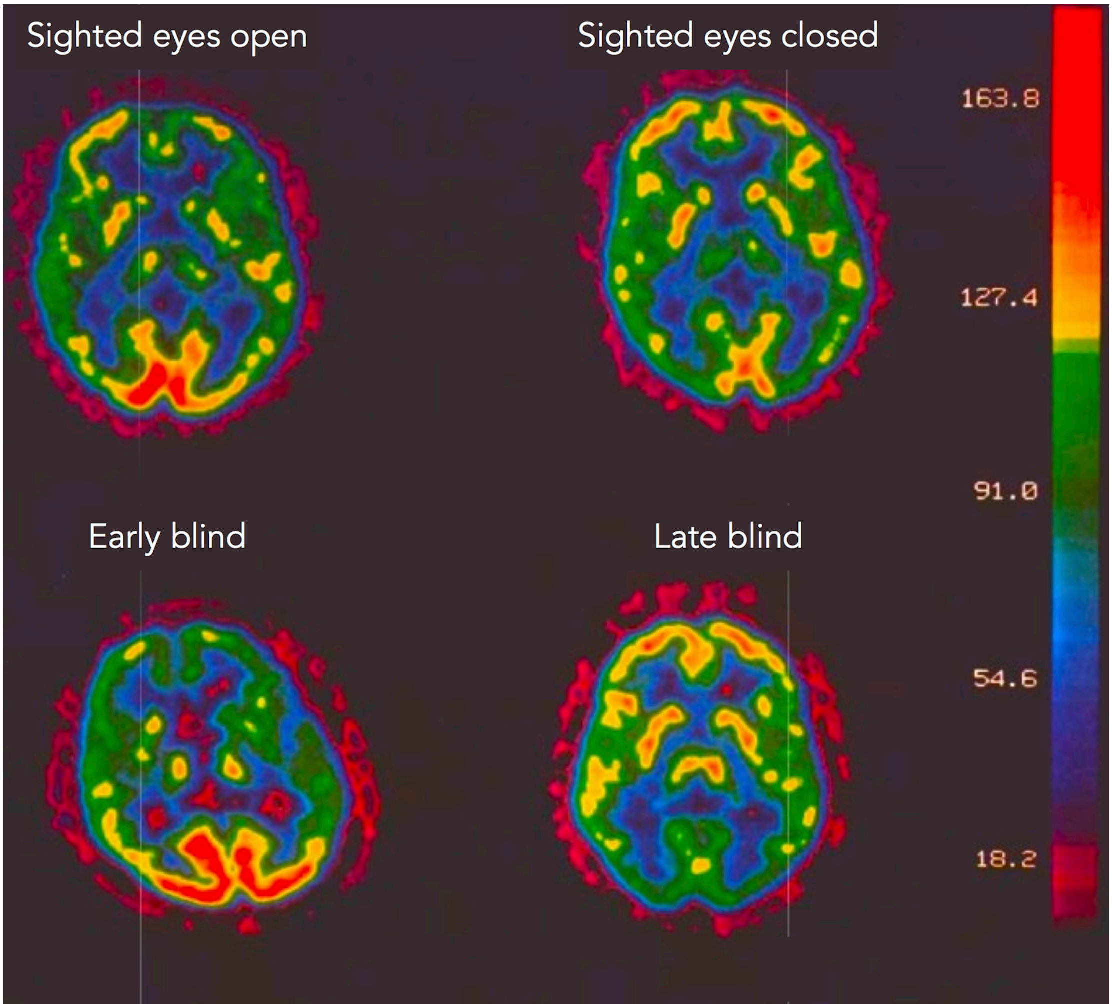


Figure 1.1: Glucose metabolism at rest in sighted and blind individuals. The mean glucose utilization maps are displayed in a sighted subject with eyes open (top-left); in a sighted subject with eyes closed (top-right); in an early blind subject (bottom-left) and in a late blind subject (bottom-right). Early blind subject show an increased glucose metabolism in the occipital cortex compared to sighted subjects with eyes closed and to late blind subjects. *Adapted from Veraart et al. 1990.*

Moreover, the use of transcranial magnetic stimulation (TMS) allowed to show that the transient disruption of the occipital cortex in early blind individuals impairs their behavioral performance in different kind of tasks such as braille reading (Cohen et al., 1997; Kupers et al., 2007), auditory spatial localization (Collignon et al., 2007) and verb generation (Amedi et al., 2004). In addition, from the neuropsychological perspective, this functional relevance is supported by a single case study of a congenitally blind patient that developed Braille alexia after bilateral occipital stroke (Hamilton et al., 2000). Taken together these results show that in case of early blindness the occipital cortex is able to change its functional profile and to rewire itself toward the processing of inputs from non-visual sensory modalities.

1.1.2 Crossmodal plasticity is not a stochastic process

As a consequence of the discovery of the occipital involvement in early blind individuals during non-visual tasks, a new question emerged: does the crossmodal reorganization in blindness follow some specific organizational principles?

In sighted individuals, the processing of visual information in the occipital cortex is hierarchically organized. It begins in the primary occipital cortex (V1) for the physical properties of the stimuli such as orientation, spatial frequencies and contours (Grill-Spector, 2003; Wiesel and Hubel, 1963) and it gradually flows toward the extrastriate cortex till the dorsal occipito-parietal and the ventral occipito-temporal streams, where information about object location and object recognition are respectively processed with a gradually disengagement from the low-level properties of the stimuli (Goodale et al., 1992; Ungerleider and Mishkin, 1982). In 1982, Ungerleider and Mishkin were the first to suggest the two-streams hypothesis according to which the visual information exits the occipital pole and follows two main pathways: the dorsal stream and the ventral stream. The first one, also called "where pathway" arrives to the parietal lobe and it is involved in processing the spatial position of the stimulus, while the ventral stream or "what pathway" travels to the temporal lobe and it is involved in object recognition. A basic property of these areas, in the occipital cortex of sighted individuals, is domain specialization (Zeki, 1991) emerging as a subdivision into several functional areas, each one specialized in the processing of a specific visual aspect (Martin, 2007).

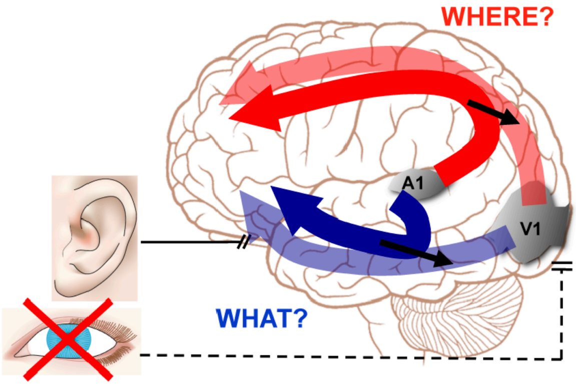


Figure 1.2: Schematic representation of functional reorganization following early visual deprivation. Several lines of evidence suggest that the dual stream structure that characterizes both visual and auditory cortex is preserved in the rewired sensory cortices of blind individuals.

Interestingly, several studies about crossmodal plasticity in blindness showed that the reorganization of these brain regions seems to follow similar principles of functional specificity (see figure 1.2). In other words, even if these regions are rewired toward non-visual processing, they still maintain their selective functional preference (Dormal et al., 2012).

In the dorsal stream the hMT+/V5 complex and the area V3/V3A are regions known to be involved in motion perception in the visual modality in sighted (Haxby et al., 1991; Sunaert et al., 1999; Watson et al., 1993). Interestingly, several studies in early blind individuals reported an increased involvement of these regions for auditory (Bedny et al., 2010; Dormal et al., 2016; Poirier et al., 2005, 2006) and tactile (Matteau et al., 2010; Ricciardi et al., 2007) motion processing. Moreover, Wolbers and colleagues reported that the activation in response to auditory motion in the homolog of area hMT+/V5 in blind individuals reflects the direction of perceived moving sounds (Wolbers et al., 2011a), a feature that emerged in the same region in sighted for visually moving stimuli (Born and Bradley, 2005). The recruitment of the dorsal pathway in blind individuals has been shown also for audio-spatial tasks. Two PET studies demonstrated that both binaural (Weeks et al., 2000) and monaural (Gougoux et al., 2005; Voss et al., 2008) sound localization tasks activate dorsal occipital regions of blind subjects. Moreover, Collignon and collaborators reported an increased activity of the regions V3/V3A and hMT+/V5 in early blind compared to sighted subjects during a spatial localization task relative to a pitch discrimination task (Collignon et al., 2011). Finally, TMS studies are in support of a functional role of the occipital dorsal stream for auditory spatial processing in early blind (Collignon et al., 2007, 2009a).

As mentioned before, the ventral pathway is mostly involved in object recognition processing and it is considered as the neural substrate of the visual categorization system. Indeed, several areas have been isolated in the ventral pathway of sighted subjects based on their stronger response to stimuli from a specific category as compared to stimuli from other categories (for a review see Grill-Spector and Weiner, 2014). These clustered areas are selective for specific categories of visual stimuli such as the visual word form areas (VWFA) for written words (McCandliss et al., 2003), the lateral occipital complex (LOC) for manipulable objects and tools (Grill-Spector et al., 1998; Malach et al., 1995), the parahippocampal place area (PPA) for scenes and big objects (Epstein and Kanwisher, 1998), the extrastriate body area (EBA), for body parts (Downing et al., 2001) and the fusiform face area (FFA) for faces (Kanwisher et al., 1997; Tong et al., 2000). Similarly to the dorsal stream, there is evidence of a recruitment of the ventral visual pathway for auditory and tactile stimuli in blind individuals. Also in this case these regions seem to maintain a functional specialization similar to the one observed in sighted.

The recruitment of VWFA in blind subjects has been shown for braille reading words (Bedny, 2017; Reich et al., 2011; Sadato et al., 1998). Moreover, occipital activity has been reported also for embossed letters, excluding the possibility that this effect could be driven by the enhanced skills acquired by blind people in braille reading (Burton et al., 2006; But see Bedny, 2017).

Selective activation of LOC in early blind was reported during tactile exploration of objects (Amedi et al., 2010) during shape imagery task triggered by objects's sounds (De Volder et al., 2001) and for the processing of object's shape using visual-to-audition sensory substitution device (SSD, Amedi et al., 2007; Merabet et al., 2008). Moreover, LOC also activates in early blinds in response to auditory words of manipulable objects (Peelen et al., 2013a).

The activity of PPA in early blind people emerged during the listening of auditory words of big non-manipulable objects (He et al., 2013a) and for haptic exploration of 3D spatial configuration compare to 3D objects (Wolbers et al., 2011b). Striem-amit & Amedi were also able to isolate EBA in the ventral stream of blind individuals for silhouette of body parts using a visual-to-auditory SSD (Striem-Amit and Amedi, 2014).

Going beyond the functional reorganization of the discrete regions, a recent study investigated the macroscopic functional organization of VOTC during categorical processing of auditory and visual stimuli in sighted and in blinds individuals (Hurk et al., 2017). They found that it is possible to predict the global pattern of activity generated by different categories presented visually in sighted using the global pattern of activity generated by the same categories presented acoustically in early blind.

Taken together, these findings suggest that the dual-stream organization might be preserved in the rewired sensory cortices of early blind individuals (Dormal and Collignon, 2011). Hence, the crossmodal plasticity seems to manifest in these regions rewiring them toward non-visual sensory modalities but maintaining the category-selective structure similar to the one existing in sighted individuals for visual processing.

However, not all the regions in VOTC seem to be affected at the same extent by the crossmodal plasticity reorganization. An exception is, indeed, represented by the fusiform cortex, selectively recruited, in the visual domain by face stimuli. A recent line of research investigated the neural format of VOTC and the impact of visual experience in shaping the functional architecture of the occipital cortex in sighted. They showed that visual experience had a salient effect on the connectivity and functional profile of the posterior lateral fusiform gyrus in contrast with the anterior medial and posterior lateral parts of the ventral visual cortex that showed a more multimodal profile (Bi et al., 2016; Wang et al., 2015). The authors defined this effect a "domain–by–modality interaction" suggesting that intrinsic characteristics of objects belonging to different categories might drive this difference. For example, in the case of inanimate objects, motor and function representations are constrained by the shape, whereas this is not the case for animate stimuli. Therefore, the representational format of the fusiform regions might be more strictly visual compared to the rest of the ventral occipito-temporal stream

(Bi et al., 2016).

The involvement of the face visual network in non-visual processing of human stimuli in early blind individuals is, indeed, controversial. On one hand, some studies failed to display a crossmodal reorganization of the face processing system in early blind subjects during tactile face exploration (Goyal et al., 2006; Pietrini et al., 2004). This result is not really unexpected since touch is probably not the main sensory modality on which blind subjects rely to extract social information, such as the speaker's identity and emotional state. Conversely, to perform these tasks blind individuals rely mostly on voice perception, therefore we could expect that human voice would be remapped in FFA. This hypothesis it is supported by the evidence of direct functional and structural links (Blank et al., 2011) between FFA and the temporal voice area (TVA), the voice-selective region in the auditory cortex (Belin et al., 2000). Recent findings in congenitally deaf individuals also demonstrated the presence of face-selective responses in this population within regions of the temporal cortex that are typically tuned to voices in hearing participants (Benetti et al., 2017). However, in EB the remap of human voice in FFA is not so straightforward. A study reported larger voice priming effects in congenitally blind individuals compared to sighted subjects (Hölig et al., 2014), a recent study including a small number of blind participants (n=7) reported a remap of emotional, mostly linguistic, voice stimuli in their fusiform gyrus (Fairhall et al., 2017), another study reported a trend in stronger responses to human voices relative to object sounds (Gougoux et al., 2009) however, the effect was not statistically significant; and a recent study failed in showing a stronger activity for sounds of voices when contrasted with non-living sounds and scrambled sounds (Dormal et al., 2017). More in general, the attempt to show selectivity for animate (i.e. animal) non-visual stimuli relative to other objects in the fusiform gyrus was unsuccessful using both auditory words (He et al., 2013) and mental imagery (Lambert et al., 2004). These contrasting findings let the possibility of a crossmodal reorganization of FFA from visual faces to non-visual human stimuli still under debate.

1.2 What the "blind brain" can tell about the conceptual-categorical system

"What we do see depends mainly on what we look for. […] In the same field the farmer will notice the crop, the geologists the fossils, botanists the flowers, artists the colouring, sportmen the cover for the game. Though we may all look at the same things, it does not all follow that we should see them."

– Jhon Lubbock –

The beauties of nature and the wonders of the world we live in

1.2.1 Changing point of view

Approximately a decade after the appearance of the first studies describing that the occipital cortex of early blind people reacts to non-visual inputs, some researchers started to look at these data in a wider framework. They realized that the case of early visual deprivation could represent an exquisitely informative model not only to investigate the crossmodal plasticity phenomenon but also to better understand the development of the functional organization of the brain in general. In the light of this new perspective, a new wave of studies on blindness paved the way for important debates about the sensory nature of several brain regions, the format of the conceptual system, and the implementation of semantics in the brain. As we will see below, the study of congenitally blind individuals have provided novel and stimulating insights not only on the cross-modal reorganization that inevitably occurs when vision is absent since birth, but, most importantly on how sensory experience shape the functional development and organization of the brain (Ricciardi et al., 2014).

1.2.2 Terminology

Before entering the core of the debate, it might be useful to have a brief excursus on the different terms that have been employed in the literature related to this topic. As it often happens in long-lasting debates, a rich, and not always coherent, lexicon has been used. In order to avoid the possibility of misunderstandings and lack of clarity it is important as a first step to define the key-terms of the debate and to clarify the meaning that I assigned to them during the entire dissertation.

Unimodal regions. The prefix *uni*- comes from the latin *unus* and means *one*. These are brain areas that receive and process sensory information from one specific sensory modality (see figure 1.3A and 1.3B).

Amodal/Supramodal/Metamodal regions. Looking at the etymology of these three terms we find that they have a similar meaning even if the structure of the words reveals a different meaning's shade. *Amodal* is characterized by the presence of the "α" privative, a letter that in the ancient Greek was placed in front of a word to reverse its meaning. In this case, where *-modal* means *related to a specific sensory modality*, the introduction of the *a-* transforms this word into its contrary, which is *unrelated to any sensory modality.* In the second term, the prefix *supra-* comes from the Latin *super-* which means *above*, in this case above any sensory modality. Finally, the prefix *meta-* derives from the Greek "μετα-", with the meaning of *beyond;* placed before a word is referring to an abstraction from it, in this case an abstraction from the sensory modalities. In this dissertation, these three words will be used in an interchangeable way referring to brain regions that are abstracted from sensory modalities; in other words to the areas involved in the conceptual analysis of the stimuli regardless of the modality in which the stimuli are presented (see figure 1.3D).

Multimodal regions. With this term, I refer to brain regions that participate to the processing of stimuli from multiple sensory modalities. These areas are not abstracted from the sensory modalities but at the same time they are not exclusively involved in the analysis of stimuli coming from only one modality (see figure 1.3C).

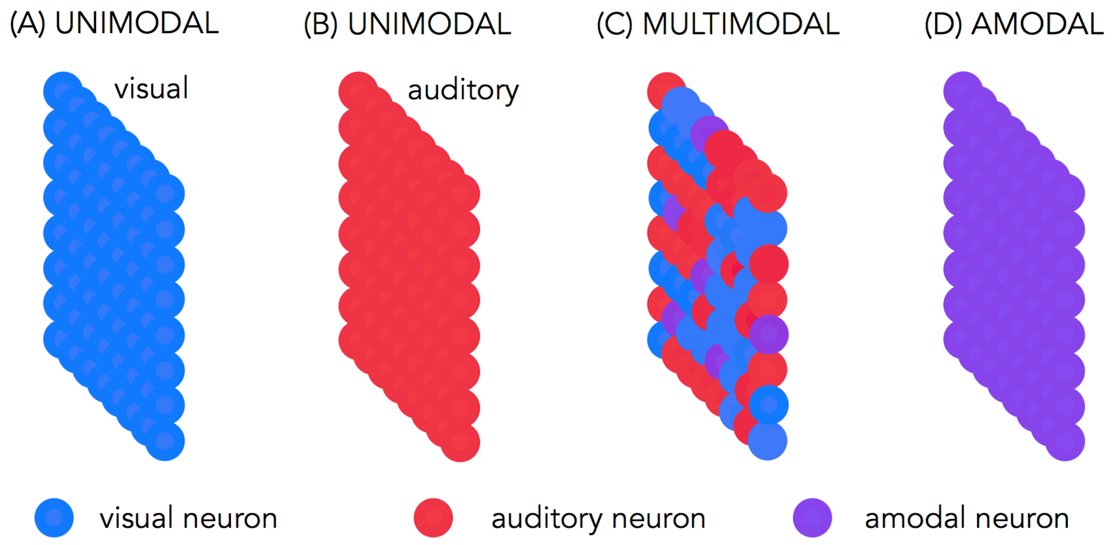


Figure 1.3: Models of several neuronal populations characterizing different brain areas. (A) Unimodal visual area; (B) Unimodal auditory area; (C) Multimodal audio-visual area; (D) Amodal area.

Crossmodal plasticity. This is a phenomenon of adaptive reorganization of a brain region following sensory deprivation. *Cross-* (from the Latin *crux)* means passing from one side to the other, in this case from one sensory modality to another. One specific case, as described above, is the reorganization of the occipital cortex of blind individuals: this region typically involved in visual processing starts to respond to non-visual stimulation in visually deprived people. Regions affected by crossmodal plasticity are sensory related areas (either unimodal or multimodal) that rewired themselves to a different modality from the one(s) they normally respond to.

1.2.3 The conceptual system: from sensory-based categorization to semantic knowledge

"All men by nature desire to know", wrote Aristotle in the IV century BC, and he also added that knowledge is based on order: he is the first author in the occidental culture introducing the concept of "category" (*κατηγορία*) as a system to organize the knowledge. It is indeed undeniable that we have an automatic and spontaneous impulse in categorization. Eleanor Rosch proposes two general principles that underlie categorization system: the first is to provide maximum information with the least cognitive effort and the second is to build a more structured perception of the world (Rosch et al., 1976). To work properly, this system should be able to generalize across exemplars of a category while maintaining specificity to distinguish among exemplars from different categories (Grill-Spector and Weiner, 2014).

It is well known that categorization is implemented at the sensory level for different modalities. In the visual domain, it requires a series of hierarchical stages from the primary occipital cortex (V1), passing through a succession of retinotopically organized visual areas (V2, V3, human V4) where the analysis of physical properties of the stimuli such as orientation, spatial frequencies and contours (Grill-Spector et al., 1998; Wiesel and Hubel, 1963) occurs, till the lateral-occipital cortex (LOC) and ventral occipito-temporal cortex (VOTC), where high level visual regions are located (Goodale et al., 1992; Ungerleider and Mishkin, 1982).

These high-level areas are mostly involved in process global shape, rather than local and low-level characteristics of the visual stimuli (Grill-Spector and Weiner, 2014). Moreover, clustered regions inside VOTC show a preference for particular categories of visual objects, such as faces (Kanwisher et al., 1997; Tong et al., 2000), scenes and big objects (Epstein and Kanwisher, 1998), bodies (Downing et al., 2001), written words (McCandliss et al., 2003) and manipulable objects and tools (Grill-Spector et al., 1998; Malach et al., 1995).

Similarly, in the auditory domain the processing starts with the physical analysis of the stimulus such as pitch, frequency and spectral centroid, in the core of the temporal cortex (A1) and becomes gradually more disengaged from the low-level aspects of the sound with the distance from A1, toward the belt and the parabelt regions (Giordano et al., 2013; Peelle et al., 2010), where information about the object categorization, such as human voices (Belin et al., 2004), instrumental sounds (Leaver and Rauschecker, 2010) and objects (Dormal et al., 2017; Lewis et al., 2011a) are processed.

Beyond this sensory related analysis of the stimuli, some regions in the brain might integrate the information into a more general concept. There is an extended literature about how different semantic categories are represented in the brain, however the principal theories can be included in three main groups: the modality-specific theory, the convergence zone(s) theories and the domain-specific theory.

The modality-specific theory

The modality-specific theory, also defined embodied-cognition theory, is based on the idea that concepts are grounded in perception and action (Allport, 1985; Martin and Chao, 2001; Pulvermuller, 2005) and that semantic knowledge is distributed inside sensory and motor regions (Martin, 2007). According to this approach, the same modal brain regions involved in the processing of sensory experiences are also activated by the knowledge retrieval (Barsalou, 2008). In other words, understanding a word requires the activation of sensorial (e.g. visual, auditory, tactile) and motor representations that are usually associated with the word's referent (Barsalou et al., 2003). For instance, understanding the word "grasp" will require the activation of the perceptual and motor system that is usually active when someone performs the action of grasping. As Allport describes in one of the first structured description of the theory: *"this model is, of course, in radical opposition to the view, apparently held by many psychologists, that 'semantic memory' is represented in some abstract, modality-independent, 'conceptual' domain remote from the mechanisms of perception and motor organization"* (Allport, 1985).

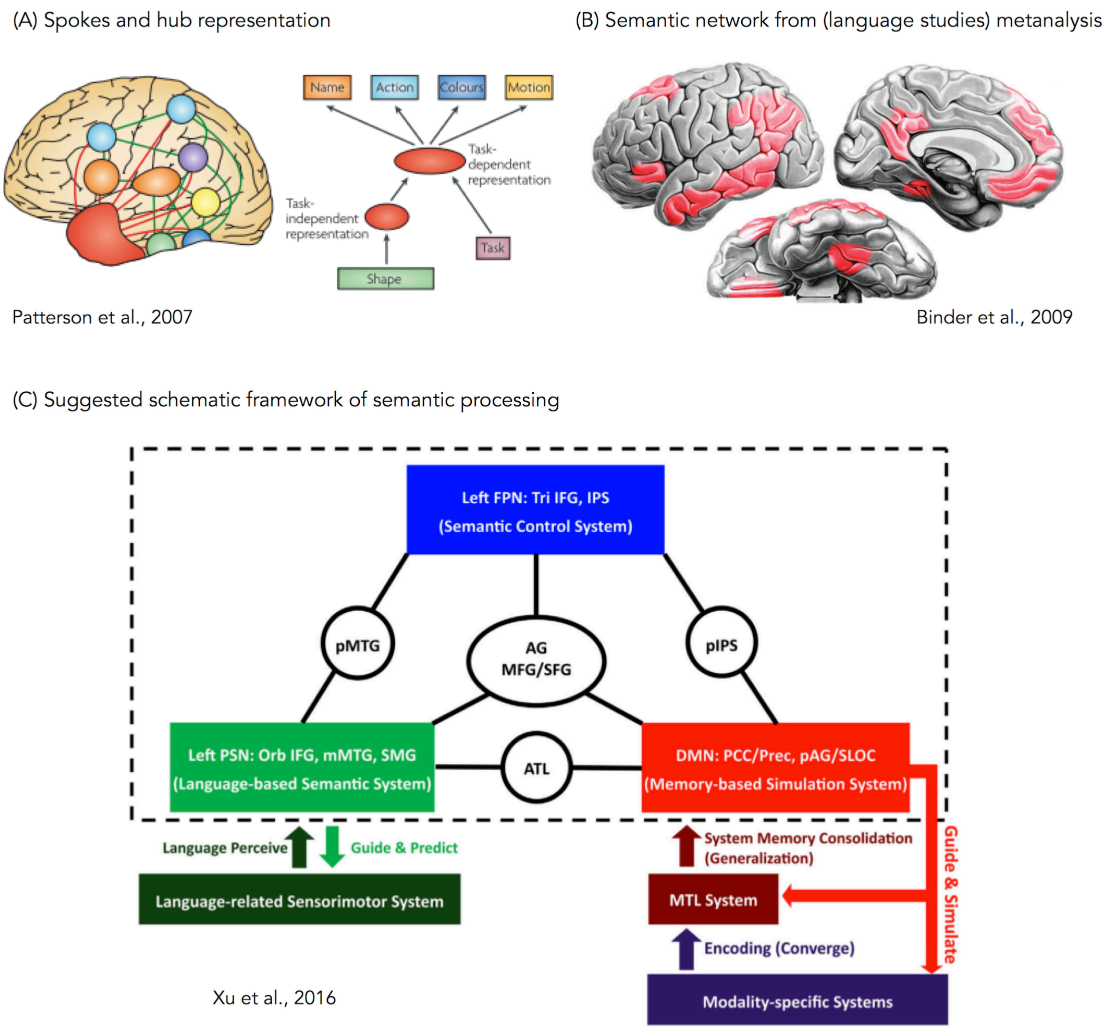
This theory emphasizes the involvement of the sensory systems in the acquisition, storage and retrieval of semantic knowledge (Barsalou, 2008; Martin, 2007). If concepts are constituted, at least in part, by mental simulations of our own perceptuo-motor experiences, then people with different sensory experiences, who interact with the environment in systematically different ways, should develop systematically different concepts (Casasanto, 2011). A strong version of the embodied theory of conceptual development therefore supports the idea that in the total absence of visual information since birth, the conceptual system should develop atypically. However, a vast amount of behavioral research speaks against this outcome (Bedny and Saxe, 2012). In fact, congenitally blind individuals show a structure of concepts and reasoning highly similar to the one of sighted people, also for the knowledge that were thought to strictly depend on vision (Landau et al., 1981; Marmor and Zaback, 1976). Probably the most striking example is the ability of blind people to use color words appropriately (Landau, 1983; Rosel et al., 2005). Based on the evidence of similar conceptual architecture in blind and sighted, despite their drastically different sensory experiences, the modern empiricists included in their theory the modality-flexible hypothesis (Bedny and Saxe, 2012). According to this enlarged view, concepts must be grounded in our sensorial perception, but they do not need to be visual (Barsalou et al., 2003; Gallese and Lakoff, 2005; Prinz and Barsalou, 2000; Pulvermuller et al., 1999; Wilson, 2002). Therefore, the same concept might be acquired through vision in sighted and through audition or touch in early blind individuals. Consequently these concepts will be stored in the format of visual images in the mind of sighted people and formatted as auditory or tactile representations in the mind of blind subjects

(Gallese and Lakoff, 2005; Meteyard et al., 2012). Following this view, two different sensorial representations might underlie a similar conceptual knowledge in blind and sighted people.

The convergence zone(s) theories

A distinct body of research investigating the conceptual system from a different perspective reporting a cortical network that is involved in processing meaningful stimuli from multiple modalities. Based on these data they suggested the presence in the brain of "convergence zones", a sort of high-level conjunction regions where concepts are processed in a more abstracted fashion (Barsalou et al., 2003; Damasio, 1989). A goal of this theory is to integrate the two lines of evidence as recently remarked by Binder: *"the evidence supports a hierarchical model of knowledge representation in which modal systems provide a mechanism for concept acquisition and serve to ground individual concepts in external reality, whereas broadly conjunctive, supramodal representations play an equally important role in concept association and situation knowledge"* (Binder, 2016). In the last two decades, a vast number of studies tried to identify and localize these convergence areas in the brain with different results probably due to the large number of tasks, material and analyses implemented (Binder et al., 2009; Hart et al., 2007; Patterson et al., 2007).

In 2007, Patterson and colleagues proposed the "hub and spokes" theory (see figure 1.4A) according to which different sensory, motor and linguistic regions represent the modal spokes while the bilateral anterior temporal lobe (ATL) acts as a convergence zone or hub that integrates the representations coming from all modalities (Patterson et al., 2007). This hypothesis is mainly based on evidences from patients affected by semantic dementia, a neurodegenerative disease characterized at the behavioral level by the progressive loss of receptive and expressive vocabulary and, more in general, the knowledge of everyday objects (Warrington, 1975), whereas at the neural level it is linked with ATL focal degeneration (Patterson et al., 2007).


(A) Spokes and hub representation

Patterson et al., 2007

(B) Semantic network from (language studies) metanalysis

Binder et al., 2009

(C) Suggested schematic framework of semantic processing

Xu et al., 2016

Figure 1.4: The convergence zones and the semantic network. (A) The distributed-plus-hub model. The modality- specific regions are connected between them (green lines) but are also connected to (red lines), and communicate through, a shared, amodal 'hub' (red area) in the anterior temporal lobes. At the hub stage associations between different attributes (e.g. shape and name, shape and action, or shape and colour) are all processed by a common set of neurons, regardless of the task. In the right side of the same panel there is the schematic illustration of the same model. *Adapted from Patterson et al., 2007.* (B) The large-scale semantic network of the human brain emerged from a metanalysis of 120 functional neuroimaging studies on the topic. *Adapted from Binder et al., 2009*. (C) Neuro-functional model for semantic processing derived from the investigation of its intrinsic functional connectivity pattern (illustrated in the dashed line box) and a broad range of neuropsychological and functional neuroimaging findings. Three stable modules corresponding to the default mode network (red rectangle), the left perisylvian network (green rectangle), and the left fronto-parietal network (blue rectangle) were individuated. The connector hubs bridging these systems are illustrated in circles. *Adapted from Xu et al., 2016.*

Even if there is a high agreement in the field for the involvement of ATL in semantic knowledge, several other regions have been proposed to play a critical role in the conceptual network. In 2009, Binder and collaborators performed a meta-analysis comprising 120 studies related to this topic, only taking into account works employing verbal material and including a comparison task that provided controls for orthographic, phonological, and general cognitive demands to the semantic task (Binder et al., 2009). They were able to isolate a left-lateralized network consisting of seven "nodes": (1) the inferior parietal cortex (angular gyrus and portions of the supramarginal gyrus); (2) the middle and inferior temporal gyri, extending into the anterior temporal lobe; (3) the ventromedial temporal cortex (fusiform and parahippocampal gyri); (4) the dorsomedial prefrontal cortex (superior frontal gyrus and posterior middle frontal gyrus); (5) the ventromedial prefrontal cortex; (6) the inferior frontal gyrus (mainly pars orbitalis); and (7) the posterior cingulate gyrus (PCC) and precuneus (see figure 1.4B).

Based on the resting-state functional connectivity profile of the above-mentioned regions, Xu and collaborators (Xu et al., 2016) found that these regions cluster in three dissociable systems (that they defined *modules*, see figure 1.4C), which broadly correspond to the default mode network (DMN), the left perisylvian network (PSN) and the left frontoparietal network (FPN). The DMN module, considered the memory-based simulation system, included the bilateral PCC with the adjacent precuneus, the bilateral-medial prefrontal cortices (MPFC), the angular gyrus (AG), the superior lateral occipital cortex (SLOC), the left superior frontal gyrus (SFG), and the middle portion of left fusiform/parahippocampal gyri. The PSN module, previously defined as the high-level language processing system (Fedorenko and Thompson-Schill, 2014; Julian et al., 2012) comprised the left middle temporal gyrus (MTG), the fronto-orbital and triangular parts (IFG), the middle frontal gyrus (MFG), the dorso-medial frontal gyrus (DMPFC), the left supramarginal gyrus (SMG), and the anterior part of left AG. Finally, the FPN module, involved in semantic control processing (Geranmayeh et al., 2012, 2014; Harel et al., 2014; Noonan et al., 2013), included the triangular part of the left IFG, the left intraparietal sulcus (IPS), and a left inferior posterior temporal region. Then, based on refined connectivity analyses, they also suggested which regions could play the roles of hubs between these three different systems or modules (see figure 1.4C). The left AG and the left SFG/MFG emerged as connector hubs of all three modules, the left ATL linked the modules DMN and PSN, the left pIPS connected modules DMN and FPN and the left pMTG resulted as the connector hub of modules PSN and FPN.

The work of Binder and collaborators and of Xu and colleagues represents an estimable attempt to review and integrate the enormous amount of data acquired on the topic of conceptual and semantic knowledge and to create a broad brain model that could explain the distributed functioning of this system at the neural level. However, one of the main limitations is that they include in their models only studies relying on verbal material (or regions derived from verbal material studies). In fact, even if we often deal with concepts using words and more in general language, we can access semantic knowledge also through sensory inputs coming from vision, sounds or touch. The level of similarity between the neural substrates underlying conceptual representations derived from linguistic or from sensory inputs is still under debate. The proposition of a unitary semantic system is rooted in neuropsychological studies on patients affected by semantic dementia. Indeed, Patterson and collaborators observed, in this population, a general loss of knowledge in different modalities and for all semantic categories. Based on these data they proposed that the bilateral ATL acts as an amodal, unitary "hub" for semantic knowledge (Patterson et al., 2007). Anatomo-clinical data show that ATL is affected by bilateral atrophy only in the moderate to advanced stages of the disease, and in this case the semantic impairment seems amodal, or at least multimodal. However, in the early stages of the disorder the atrophy of ATL is normally lateralized either on the right or on the left hemisphere and in these early cases, we often observe a modality-specific semantic impairment (Gainotti, 2011). In particular, a major atrophy of the left temporal lobe produces a loss of conceptual knowledge mainly at the lexico-semantic level while a greater atrophy on the right side mostly affects pictorial/sensory-related representations (Mion et al., 2010; Snowden et al., 2004, 2012). Based on these evidences, Gainotti suggested that "*the multimodal semantic impairment observed in advanced stages of semantic dementia is due to the joint disruption of pictorial and verbal representations, rather than to the loss of amodal knowledge, bilaterally supported by the ATL*" (Gainotti, 2011). Recently Gainotti (2014) extended this proposition from ATL to the whole-brain implementation of the conceptual network in general, promoting the idea that the left hemisphere is more involved in verbal knowledge, whereas the right hemisphere would participate more in non-verbal sensory-motor knowledge (Gainotti, 2014). This hypothesis is based on studies on both brain-damaged and healthy subjects. Several behavioral studies on patients with right or left-brain lesions showed that left brain damages selectively affect the verbal memory code, while right hemisphere injuries preferentially impair the pictorial code (Gainotti et al., 1994; Grossman et al., 2001; Whitehouse, 1981). In line with these results, several neuroimaging studies showed a similar effect also in healthy individuals. Indeed, several studies comparing the categorical processing of verbal material with non-verbal material (visual and/or acoustical) showed the emergence of a left lateralized network when the verbal stimuli were contrasted against the non-verbal stimuli (Humphries et al., 2001; Thierry and Price, 2006; Thierry et al., 2003). Coherently, in the same studies the opposite contrast of non-verbal stimuli versus words preferentially highlighted a right lateralized network (Gainotti, 2014).

Taken together, these evidences speak in favor of a semantic system based on several convergence zones organized in a distributed network. These semantic nodes seem to play different roles according to the modalities with which the information reaches the brain, with a possible major distinction between verbal and non-verbal stimuli represented in the left and right hemispheres, respectively (Gainotti, 2014).

The domain-specific theory

A further different perspective about the functioning of the semantic system is the one supported by the domain-specific theory. The basis of this theory can be found in a set of neuropsychological papers about patients showing semantic impairments for one, or more, categories of objects compare to other categories (for a review see Capitani et al., 2003). According to this theory, the object domain represents the main constraint to the organization of conceptual knowledge; more specifically the possible domains are those with an evolutionary relevant history, such as living animate (e.g. animals), living inanimate (e.g. plants), humans and tools (Mahon and Caramazza, 2009). Indeed, neuropsychological cases of selective impairment have been reported for multiple input modalities (mostly visual and linguistic) for those categories such as animals (Caramazza and Shelton, 1998), vegetables and fruit (Hart et al., 1985; Samson and Pillon, 2003), conspecifics (e.g. human; Miceli et al., 2000) and non-living items such as objects and tools (Laiacona and Capitani, 2001; Sacchett and Humphreys, 1992).

Mahon & Caramazza specified that *"one important aspect of the performance profile of patients with category-specific semantic impairment is that the impairment is to conceptual knowledge and not (only) to modality-specific input or output representations"* (Caramazza and Shelton, 1998; Mahon and Caramazza, 2009). This model suggests that the neural substrate of each domain of knowledge comprises a network of regions where the most relevant information for a given category converges, and this integration of information is mediated by an innately determined connectivity pattern (Mahon and Caramazza, 2009). An extreme expression of this theory resulted in the proposition of a metamodal organization of the brain based on metamodal operators, namely local neural networks, defined by a given computation that is applied regardless of the sensory input received (Pascual-Leone and Hamilton, 2001). Based on this hypothesis a new line of studies developed in order to show that some brain regions traditionally considered purely sensory-related might in fact be more abstracted than previously thought. In particular, the Ventral Occipito-Temporal Cortex (VOTC), a region traditionally considered to be organized by semantic categorization within the visual modality only, has been proposed to host more abstract (amodal) representation of domain-specific knowledge (Mahon and Caramazza, 2009).

In order to show that domain selectivity in VOTC is not necessarily dependent of vision, the study of the functional architecture of VOTC in born-blind individuals may provide unique answer to this question. Would category-selective regions emergence in the VOTC of early blind individuals?

1.2.4 How can blindness enlighten us about the nature of the Ventral Occipito-Temporal Cortex

A set of fMRI studies in healthy individuals demonstrated involvement of VOTC in non-visual, mostly tactile, object processing (Amedi et al., 2002, 2007, 2001; Pietrini et al., 2004; Snow et al., 2014; Zhang, 2004). These studies triggered the idea that VOTC, traditionally considered a purely visual area, could in fact host a more amodal representation of object knowledge than previously thought. More precisely, it was proposed that the lateral occipital cortex might represent object shape in an abstracted format (Amedi et al., 2002, 2007). However, the main critique received by this proposal was the possible implication of mental visual imagery, a process known to elicit occipital activation in sighted individuals in the absence of visual stimulation (Kosslyn et al., 1993; Slotnick et al., 2005). Therefore, it could be possible that the occipital activation reported in sighted individuals was simply the by-product of the visual imagery triggered by the non-visual stimulation. In line with this possibility, De Volder and collaborators (2001) reported reliable 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).

Consequently, many studies included early blind subjects in their sample to rule out the possibility that the activity in VOTC was a by-product of visual imagery and to further support the idea that domain selectivity in this region does not need vision to develop (for a review Ricciardi et al., 2014). Indeed, as already described in the section 1.1.2, several imaging studies, starting from this perspective showed strong similarities in the VOTC functional organization between sighted and blind groups during non-visual perception of different categories such as tools and manmade objects (Amedi et al., 2010; Peelen et al., 2013a, 2014; Pietrini et al., 2004), places (He et al., 2013; Wolbers et al., 2011b), body parts (Kitada et al., 2014; Striem-Amit and Amedi, 2014), words (Reich et al., 2011) and numbers (Abboud et al., 2015).

Most of the above-mentioned studies considered their results as strong evidence that the nature of VOTC is amodal and completely abstracted from sensory inputs. Here some examples:

"These results demonstrate that the representation of objects in the ventral visual pathway is not simply a representation of visual images but, rather, is a representation of more ***abstract features*** *of object form"* (Pietrini et al., 2004)

"[…] These findings establish the PPA/RSC network as critical in ***modality-independent*** *spatial computations and provide important evidence for a theory of* ***high-level abstract*** *spatial information processing in the human brain"* (Wolbers et al., 2011b).

"To the best of our judgment, this provides the strongest support so far for the ***metamodal theory****. Hence, the VWFA should also be referred to as the tactile word form area, or more generally as the (metamodal) word form area* (Reich et al., 2011).

"Thus, the EBA preference is present without visual experience and with little exposure to external body-shape information, supporting the view that the brain has a ***sensory-independent****, task-selective* ***supramodal*** *organization rather than a sensory-specific organization"* (Striem-Amit and Amedi, 2014).

"This is in accordance with previous results from our team suggesting that there is ***nothing visual*** *about the VWFA […]. This suggestion is in line with the theories of* ***the metamodal/supramodal organization*** *of the brain"* (Abboud et al., 2015).

"More generally, the highly similar categorical organization in individuals with and without visual experience, when performing identical task, suggests that

the large-scale organization of high-order visual cortex may ***not be primarily shaped by visual input*** *"* (He et al., 2013b).

"A great deal of the brain cortical functional architecture appears to be programmed to occur even in the absence of any visual experience and able to process non-visual sensory information, a property that can be defined as ***supramodality****. It is important to emphasize that such* ***supramodal cortical organization*** *is not merely the consequence of the plastic rearrangements – that of course also occur in the brain of individuals deprived of sight and are generally called cross-modal plasticity – but is a characteristic of the (human) brain itself, as it is indeed present also in sighted individuals"* (Ricciardi et al., 2014).

These statements, all taken from authoritative paper in the field, suggest that many regions previously considered part of the sensory visual system might be sensory-abstracted instead. Nevertheless, there are several aspects that make this hypothesis still debatable and I will argue that we lack definitive evidences to claim that VOTC, or part of it, is abstracted from the visual modality.

The first controversial point is the employment of blind participants to argue against the possibility of visual imagery. In fact, when including blind participants in a study it is important to take into account the key role of the functionally selective crossmodal plasticity. As described above, this is a mechanism based on an enhanced involvement of the occipital and occipito-temporal cortex of the early blind individuals, compare to sighted, for non-visual processing (Collignon et al., 2007; Sadato et al., 1998; Dormal et al., 2010; Bedny et al., 2011; Roder et al., 2002). For this reason, the employment of blind participants to support an abstract nature of VOTC is not straightforward since it remains possible, in principle, that similar activity in both groups relies on separate representational formats: visual in the sighted (visual imagery) and auditory/tactile in the blind. To show that the nature of VOTC is abstracted from sensory modalities, its functional profile should be indistinguishable in early blind for auditory stimuli and in sighted for auditory and visual stimuli. Some of the above-mentioned studies (Abboud et al., 2015; Reich et al., 2011; Striem-Amit and Amedi, 2014) did only include a group of early blind performing the task in the non-visual modality without including a sighted control group performing the same task in the same non-visual modality. By showing that EB activated the same VOTC clusters when compared to the sighted performing the same task in the visual modality (e.g. in Reich et al. 2011 activity of VWFA for written words in sighted and braille words in blind), they concluded that these data are in support of a meta-modal organization of VOTC. Nevertheless, the same data can be interpreted in support of a sensory-related nature of VOTC, visual in sighted and rewired toward non-visual modalities in case of early visual deprivation, as we discussed in the previous chapter.

The second controversial point is the evidence that low-level visual features of the stimuli, such as spatial frequency, eccentricity or shape, can explain the category selectivity ability of VOTC (Andrews et al., 2010; Baldassi et al., 2013; Rice et al., 2014). Moreover, a recent study on the monkeys' newborn visual system reported that the typical hierarchical and topographic organization is present at birth suggesting that it constitutes a proto-organization for the entire primate visual system (Arcaro and Livingstone, 2017). Recently, Bracci et al. (Bracci et al., 2017) proposed the feature-based categorical coding hypothesis according to which regions in the ventral stream do encode information about categories but in a format at least partially based on the visual features of the stimuli. Moreover, lesions to the VOTC are known to produce visual agnosia while preserving the processing of the same material by the other senses or based on linguistic material (Farah, 1991; Miceli et al., 2001; Rossion et al., 2003; Vandenbulcke et al., 2006; Warrington and McCarthy, 1994) supporting the idea that this region has a selective role in visual recognition (Grill-Spector and Weiner, 2014).

A further key point is that the observation of the engagement of the visual cortex in sighted during non-visual tasks is far from being unequivocal. In fact, many studies reported even deactivation in occipital regions of sighted brain during non-visual stimulation (Bedny et al., 2010; Collignon et al., 2013; Gougoux et al., 2005; Renier et al., 2010; Saenz et al., 2008; Voss et al., 2011). This deactivation might be triggered by inhibitory mechanisms that occur to reduce interference from distracting visual inputs (Laurienti et al., 2002).

In summary, the debate about the representational format of VOTC is still open. On one hand, there is a research line that strongly supports an amodal nature of this region and that proposed that vision is not even necessary for the development of VOTC. On the other hand, several findings speak against this sensory-abstracted nature, supporting a predominantly visual format of the representations in VOTC that might switch to non-visual preference in the case of early blindness. I specifically tried to address this debate in the study 1 (that I will present in Chapter 2).

1.3 The interconnection between plasticity in occipital and temporal cortices of early blind: the large-scale imbalance theory

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"A system is in equilibrium when the forces constituting it are arranged in such a way as to compensate each other, like the two weights pulling at the arms of a pair of scales."

- Rudolf Arnheim-

Entropy and Art: An Essay on Disorder and Order (1971)

1.3.1 The brain as an interconnected system

The British philosopher Alan Watts in one of his works said: *"[…] Everything in nature depends on everything else. So it's interconnected. And so the many patterns of interconnections, lock it all together into a unity, which is much too complicated for us to think about, except in very simple, crude ways"* (extract from "Conversation with myself", 1971). This concept of unity as result of interconnection between the parts is easily applicable to the brain. The unity of the human brain, made by approximately 86 billions of neurons (Herculano-Houzel, 2009), is indeed *"much too complicated for us to think about"* and this complexity resulted in a fragmented study of its functioning.

When we look at the literature about the blind brain we immediately realize that the great majority of the studies focused on the reorganization of the occipital cortex, neglecting in most of the cases the remaining regions of the brain. This kind of "selective" approach allowed neuroscientists to simplify the complex phenomenon of brain plasticity and to gather conspicuous amount of information about a specific component of this phenomenon (probably the most fascinating), which is how the visual cortex reorganizes in blind individuals. On the other hand, this approach prevented a more global investigation. Little is known on the way blindness affects the rest of the brain and whether the reorganization of the visual cortex occurs with (and it is connected to) changes in other brain regions. However, in the last decade some attempts in this direction have been done moving the study of brain plasticity toward a more global framework.

1.3.2 Intra-modal plasticity in the extra-occipital cortices of early blind individuals

As we discussed above, many studies investigated the reorganization of the occipital cortex following blindness. Much less is, however, known about the impact of early blindness on the functioning of the sensory cortices implementing the remaining senses.

The mainstream hypothesis in the approach of this topic is based on the experience-dependent plasticity theory (for a review see May, 2011). Many studies, indeed, demonstrated that enhanced skills or training in specific domain would impact in the structure and function of the brain. One of the most famous studies showing the experience-dependent plasticity, reported the expansion of the hippocampus (a subcortical structure known to be involved in space navigation tasks) in a group of London taxi drivers (Maguire et al., 2000). A study on the same line showed a grey matter increase in the V5/MT+ and in parietal regions in a group of subjects that underwent a training of juggling (Draganski et al., 2004). Moreover, several studies reported musical proficiency to be associated with volume enlargement of motor and auditory areas and their anatomical connections (Bengtsson et al., 2005; Gaser and Schlaug, 2003; Sluming et al., 2002). Starting from this perspective, we can assume that people with enhanced abilities in a specific domain would also show an expansion and a refinement in the brain region that controls that skill.

Blind individuals seem to compensate for their lack of vision by relying more on their auditory and tactile senses. Several studies showed enhanced abilities compared to sighted controls in many non-visual tasks (for a review see Kupers and Ptito, 2013) such as tactile letter recognition at the fingertips (Craig, 1999), tactile gratings orientation discrimination (Boven et al., 2000; Goldreich and Kanics, 2003), tactile acuity at the fingertips (Legge et al., 2008) voice processing (Föcker et al., 2012; Gougoux et al., 2009) speech discrimination (Dietrich et al., 2013; Starlinger and Niemeyer, 1981), sound localization (Jiang et al., 2016; Lewald and Getzmann, 2013; Röder et al., 1999) and odor discrimination and identification (Cuevas et al., 2009; Murphy et al., 2016). As I introduced above, some studies showed a causal relation between the occipital activity in early blind subjects and their enhanced non-visual skills (Amedi et al., 2007; Cohen et al., 1997; Collignon et al., 2007, 2009b; Gougoux et al., 2005; Kupers et al., 2007).

What about the non-visual sensory cortices primarily involved in these non-visual tasks? Several studies approaching the topic from the experience-dependent perspective, hypothesized an expansion and a refinement of these sensory cortices in EB (Gougoux et al., 2009). Studies on visually deprived animals from birth actually produced results in line with this hypothesis (for a review see Rauschecker, 1995). Enucleated cats and mice showed significant change in the somatosensory system: in both species, the facial vibrissae were longer and thicker. Moreover, in mice there was a concomitant increase in the size of the regions representing the vibrissae in the brain (Rauschecker and Tian, 1992). Similar results emerged also about the temporal cortex of visually deprived macaques (Meng et al., 2015; Petrus et al., 2014; Wang et al., 2017). For instance, a recent study reported increased volume and enhanced activation in the auditory cortex of visually deprived macaques compared to sighted controls during auditory stimulation (Wang et al., 2017). A first generation of studies on blind humans reported similar results promoting the idea that, also in humans, visual deprivation elicits an enhanced activity and a refinement of the non-visual sensory cortices. For example, a TMS study on blind braille readers reported an expansion of the sensory-motor cortical representation of the reading finger (Pascual-leone and Torres, 1993). Studies on the sense of smell showed that the superior olfactory performance in congenitally blind individuals is associated with an increased volume of the olfactory bulb (Rombaux et al., 2010) and that, during odor processing, they stronger activated higher order olfactory areas (Kupers et al., 2011). Works using event related potentials (ERP) reported electrophysiological changes in the auditory cortex of early blind, showing a lower peak latency of the waves Nb and P1 compared to a sighted control group (Manjunath et al., 1998; Naveen et al., 1997, 1998). An additional MEG study demonstrated that the tonotopic map in the core area of the temporal cortex expands in response to high and low frequency tones in blind compared to sighted individuals. A main problem with this study is that the blind group included both early and late blind participants (Elbert et al., 2002), two types of blindness that have been showed to trigger different kind of reorganization (Collignon et al., 2013).

Importantly, the way the intra-modal plasticity expresses in early blind is not really straightforward. In parallel with the studies reported just above, a different line of studies is suggesting the opposite tendency, namely a decreased recruitment of the sensory extra-occipital cortices compared to sighted controls during non-visual tasks. An fMRI study showed a lower signal volume in EB compared to SC within the temporal cortex when contrasting high versus low tones (Stevens and Weaver, 2009). In the same vein, Burton and colleagues (Burton et al., 2002b) showed lower somatosensory activation for braille reading in blind compared to sighted individuals. A further study focused on the morphological alterations in congenital blind reported an increased cortical thickness in visual regions of EB but a thinning in their auditory and somatosensory cortices compared to SC (Park et al., 2009). Similar kinds of results were found during the processing of different sounds categories. A decreased activity of parietal and frontal regions of blind compared to matched sighted controls emerged while they were listening to human action sounds (Lewis et al., 2011a).

A possible explanation for this second line of findings could be that the lower demand for temporal cortex during processing of auditory stimuli in early blind is related to the enhanced activity in their occipital cortex for the processing of the same stimuli. In other words, the intra- and the cross-modal plasticity could be, in fact, part of the same global plasticity mechanism.

1.3.3 Cross-modal and intra-modal plasticity: two faces of the same coin?

Not many studies so far tried to integrate the two mechanisms of intra- and cross- modal plasticity into a more global and unitary view.

Only two studies in the literature directly investigated the interplay between the visual and the auditory cortices during the processing of acoustical stimuli in early blind compared to sighted controls (Dormal et al., 2016; Jiang et al., 2016). Both studies focused on auditory moving stimuli and on the brain regions normally recruited for motion within the visual cortex (hMT+) and the auditory cortex (*planum temporale*). Using multivoxel pattern analysis (MVPA), they showed that the ability to decode the different auditory motion stimuli was enhanced in hMT+ of early blind compared to sighted individuals. The opposite pattern was observed in the *planum temporale* that showed an enhanced decoding accuracy in the sighted when contrasted with the blind group (Dormal et al., 2016; Jiang et al., 2016). In addition, early blind subjects, when compared to sighted controls, showed enhanced functional connectivity between the right *planum temporale* and the right occipito-temporal regions (Dormal et al., 2016). These results suggest a large-scale imbalance in the brain network involved in auditory motion processing in early blind subjects. However, it is unclear if this balanced reorganization between auditory and visual regions in early blind individuals is specific to the processing of moving sounds or if is a general principle linked to the crossmodal plasticity observed in early blind people. Indeed, the literature is lacking an investigation of this imbalanced processing phenomenon for more natural stimuli such as real-world sounds from different categories (e.g. human, tools, etc.). Moreover, a direct correlation between the two kinds of plasticity has never been reported. These represent the main goals of the study 2 (that I will present in Chapter 3).

1.4 Investigate the brain with the fMRI: from the origins to innovative multivariate analyses

"What we observe is not nature itself, but nature exposed to our method of questioning."

– Heisenberg, 1958 –

1.4.1 Physical principles behind magnetic resonance

Magnetic resonance imaging (MRI) makes use of strong magnetic fields to create images of biological tissues. The main parts of MRI consist of a superconductive magnet to generate a static magnetic field, radiofrequency coils to register the magnetic resonance (MR) signal, gradient coils to obtain spatial information in the MR signal and shimming coils to guarantee as much as possible the uniformity of the magnetic field.

To understand how to create a brain image from these elements we need to rely on a set of physical principles.

All matter is composed of atoms, which contain three types of particles: protons, neutron and electrons. Approximately the 70% of the human body is composed by water that is made by hydrogen nuclei. These nuclei consist of single protons. One important characteristic of the protons of hydrogen is that they possess the nuclear magnetic resonance property and because of that they can be studied using magnetic resonance. Under normal conditions, thermal energy makes each proton to spin around itself generating an electrical current. This electrical current induces a magnetic field. However, under normal condition the spins of the hydrogen protons are oriented randomly and therefore cancel each other out (see figure 1.5A). We need to apply a strong magnetic field to increase their net magnetization. When placed within an external magnetic field, protons change their orientations in two possible directions: parallel or antiparallel to the magnetic field. The parallel alignment requires a lower amount of energy and it is slightly more stable, for this reason there will always be more protons in the parallel compared to the antiparallel state (see figure 1.5B).

MRI does not measure single nuclei but the net magnetization of all spins in a volume. The net magnetization can be considered as a vector with two components: a longitudinal component that is either parallel or antiparallel to the magnetic field and a transverse component that is perpendicular to the magnetic field.

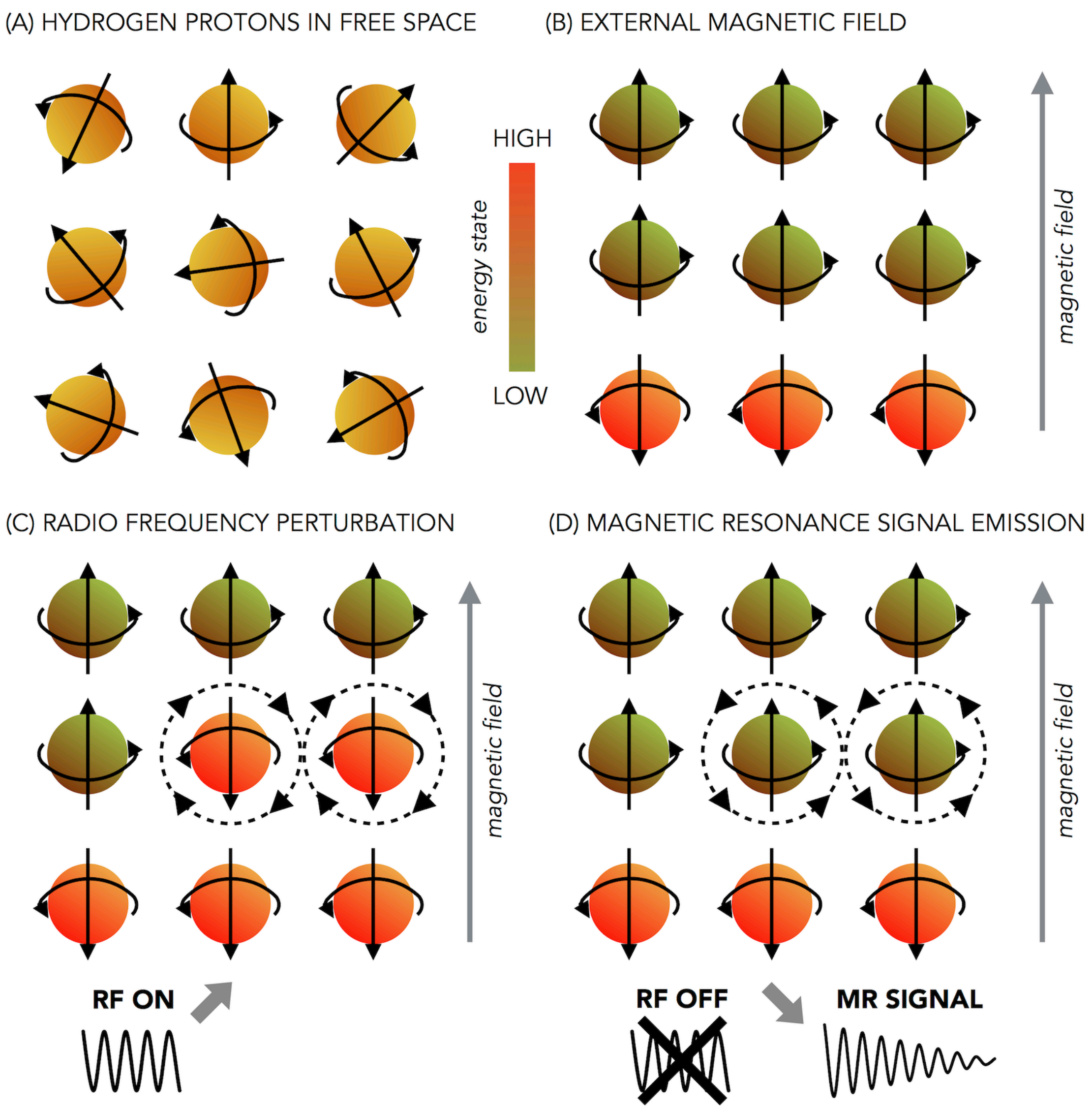

Figure 1.5: Representation of protons in the nucleus of a hydrogen atom (orange and green dots) sequentially exposed to an external magnetic field and to a radiofrequency pulse. The black straight arrows represent the orientation of the protons' spinning. The grey arrow represents the external magnetic field. (A) In the absence of external magnetic field the protons are randomly oriented (light orange dots). (B) When an external magnetic field is applied the protons align in the parallel low-energy state (green dots) or in anti-parallel high-energy state (dark orange dots). (C) When exposed to a radiofrequency (RF) pulse some of the protons in the low-energy state will absorb the energy from the RF pulse and switch to the high-energy state (few green dots become dark orange dots). (D) When the RF pulse is removed the protons that switched their alignment release the absorbed energy generating the Magnetic Resonance (MR) signal that we want to register and they go back to their initial low-energy state (few light orange dots become green again).

Importantly, we cannot measure the net under equilibrium conditions. We must perturb the equilibrium state of the spins and observe how they react to the perturbation. If energy is applied to the nuclei at a particular frequency, known as the resonant frequency, some low energy spins will absorb that energy and change to the high-energy state (see figure 1.5C). After the energy source is removed, some spins will return to the low-energy state by releasing that energy (see figure 1.5D).

This phase can be decomposed into two main relaxation processes. The excited protons in the high-energy anti-parallel state that go back to the low-energy parallel state cause the longitudinal relaxation and T_1 is the time constant associated with it. The second type of relaxation is the transverse one. An intrinsic cause for the transverse relaxation is represented by the loss of phase coherence of the protons due to the interaction between each other and T_2 is the time constant that describes this decay. However, an additional extrinsic cause for the transverse relaxation is the inhomogeneity of the external magnetic field, which increases the loss of phase coherence of the protons. T_2^* is the time constant that describes the decay of the transverse magnetization due to both the intrinsic and the extrinsic sources.

Measurement of these emitted energies, or MR signal, provides the data that go into our images.

1.4.2 From magnetic resonance to magnetic resonance imaging

One fundamental step to create brain images is to perform a spatial encoding of the MR signal. To do that we need to add, using gradient coils, a gradient field that distorts the main external magnetic field in a predictable fashion. This will cause the resonance frequency of protons to vary as function of their position. Since protons can only absorb energy sent at their resonance frequency, we can now change the frequency of the radio-frequency coil in order to register the MR signal in different locations of the brain. Using this technique, the MRI machine can register the MR signal from all slices of the brain, one at a time (see figure 1.6). Finally, the Fourier transformation will allow the image reconstruction from the raw MRI signal into spatially informative images.

Importantly, the MR signal differs according to the different biological tissues (e.g. white matter, grey matter). Several pulse sequences are available, each one emphasizing different properties of the brain tissues.

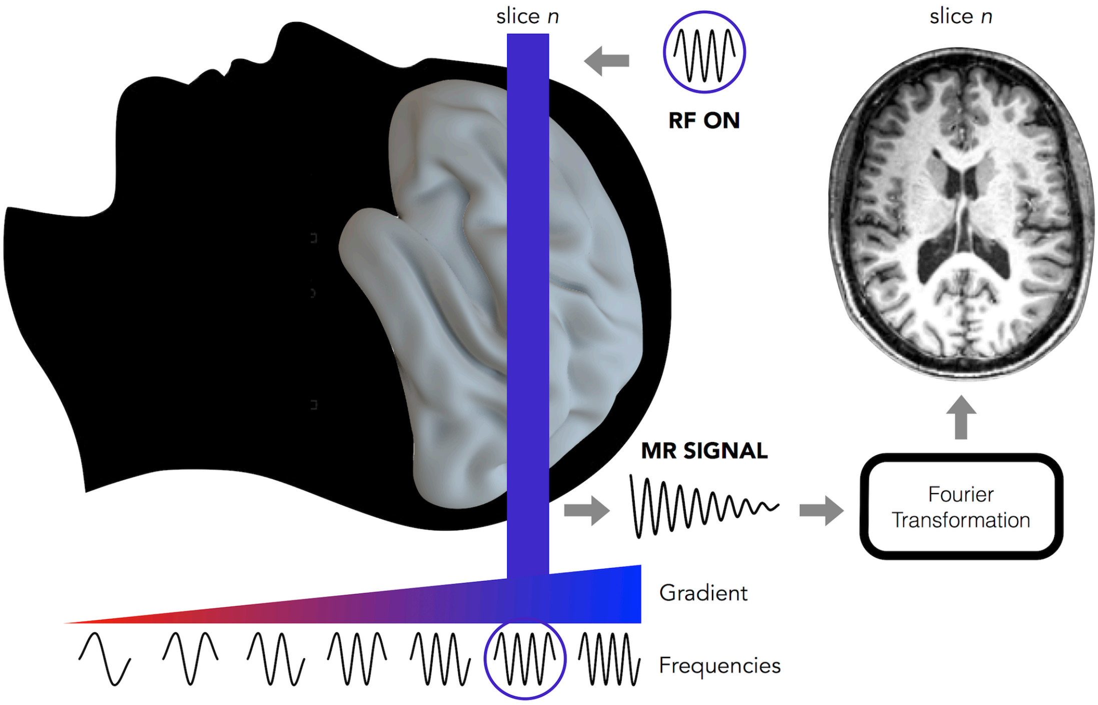

Figure 1.6: Representation of an MRI slice acquisition procedure. A gradient coil (represented by the red-to-blue triangle under the brain) makes the magnetic field strength gradually changing from one spatial location to the other. Consequently, also the resonant frequency (represented by the sinusoidal lines under the gradient) of the protons will be different at each location. To register a specific slice of the brain we need to send a RF pulse with the resonant frequency that characterizes that specific portion of the space. Only the protons with the same frequency as the RF pulses frequency will absorb and release the energy of the RF pulse allowing the registration of the MR signal only from the selected slice. Finally, using the Fourier transformation, we obtain the image of the selected brain slice (right panel).

We can emphasize different contrasts modifying some specific parameters of the pulse sequences, such as the time interval between successive excitation pulses (repetition time, TR) and the time interval between an excitation pulse and the data acquisition time (echo time, TE). For example, anatomical images that emphasize the contrast between the grey and white matters are normally created using pulse sequences with intermediate TR and short TE; they are also called T_1-wheigted images since they are based upon the T_1 value of the tissues. As we will see in the next paragraph, T_2^*-weighted images are used for BOLD-contrast fMRI; this kind of contrast is provided by pulse sequences with long TR and medium TE.

1.4.3 Scanning the activity of the brain: functional MRI

The possibility to scan the functioning human brain represents an important step in the progress of the human's brain investigation. The origin of the functional MRI lies on the brilliant idea that we can infer the brain activity looking at the changes in blood circulation. Angelo Mosso, a pioneer in functional brain imaging, proposed this technique in the book "Circulation of blood in the human brain"[1], published in 1879-80.

In his work he described how, using innovative (at that time) equipment and techniques (see figure 1.7A), he could register the blood flow in the brain and look at its changes while the person was performing cognitive tasks such as mathematical calculations (see figure 1.7B).

After this first attempt, several others came in succession for more than one century, till the machine that we currently use: the functional magnetic resonance imaging (fMRI). Almost nothing remains of Mosso's machine, but the main principle on which the fMRI is based stays the same: infer brain activity from the blood flow.

This indirect measurement of the brain activity is based on the idea that information processing activity of neurons increases their metabolism and they need enhanced level of energy. It is, indeed, the vascular system that supplies neurons with glucose and oxygen. Oxygen is attached to hemoglobin molecules and it is exchanged for carbon dioxide. Importantly oxygenated and deoxygenated hemoglobin have different magnetic properties: oxy-hemoglobin is diamagnetic while deoxy-hemoglobin is paramagnetic; the latter is therefore susceptible to magnetization when placed within a magnetic field.

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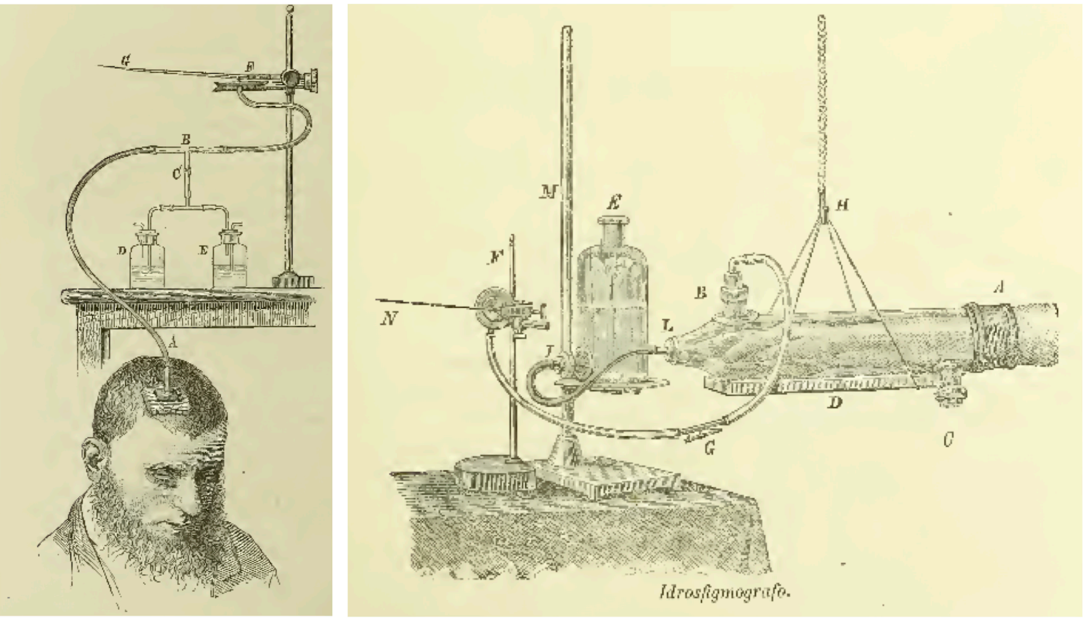
[1] Original title: "*Sulla circolazione del sangue nel cervello dell'uomo* "

(A) EQUIPMENT TO REGISTER BLOOD FLOW IN THE BRAIN & IN THE WRIST



(B) REGISTRATION OF BLOOD FLOW IN THE BRAIN AND IN THE WRIST DURING COGNITIVE TASK

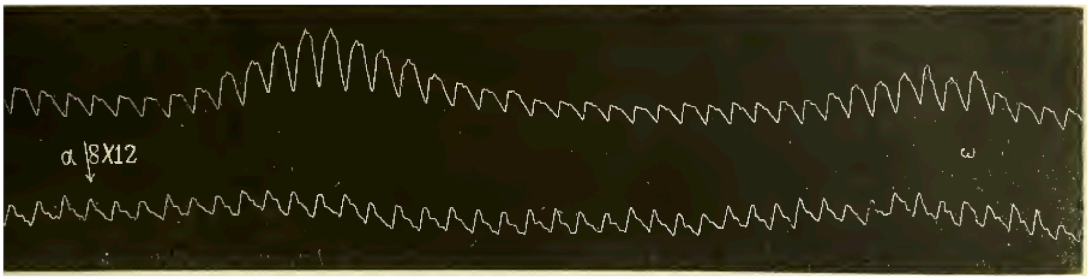


Figure 1.7: Representation of the first attempt to register the blood flow during cognitive tasks, employed by Angelo Mosso at the end of 19th century. (A) Machineries employed to register the blood flow at brain level (on the right panel) and at the wrist level (on the left panel) as a control region. (B) Brain blood flow (upper line) and wrist blood flow (lower line) during a mathematical task (i.e. multiplication). The symbol α and the arrow represent the onset of the task, the symbol ω represents the moment in which the subject gives the answer. The blood flow in the wrist does not show any change; while it increases in the brain suggesting a correlation between brain activity, blood flow and cognitive task performance.

Since the neuronal activity increases metabolic demands and oxygen consumption, this will lead to increase the amount of deoxygenated hemoglobin in respect of the oxygenated one. The ratio between the two affects the MRI signal and in particular the T2* decay and can be measured by a specific contrast called the blood oxygenation level dependent (BOLD) contrast (Ogawa et al., 1990). The change in the MR signal caused by neuronal activity is called hemodynamic response function (HRF). The HRF has normally a peak around 5-6 s after the presentation of an event and this peak is followed by an undershoot due to the decrease of MR signal amplitude.

The sequence most frequently used to measure BOLD-signal is a T2*-weighted echo-planar imaging (EPI) sequence (Mansfield et al., 1994). This technique allows the collection of an entire two-dimensional image by changing spatial gradients rapidly following a single electromagnetic pulse from a transmitter coil. It is the fastest acquisition method in MRI (100 ms / slice). We implemented this sequence in the data acquisition of the fMRI experiments that I present in the chapters 2 and 3.

1.4.4 Data preprocessing

The preprocessing step consists in a series of computational procedures that are applied to the fMRI data after image reconstruction and before the statistical analyses. The main aim of this step is to increase the signal to noise ratio. In other words, data preprocessing enhances BOLD signal and reduces the variability unrelated to the task in order to clean the data before the statistical testing. The main steps in the processing pipeline are: slice time correction, head motion correction, coregistration, normalization and spatial filtering (see figure 1.8).

Figure 1.8: Preprocessing pipeline of fMRI data.

Slice time correction.

Since each slice is acquired at a different time point within the TR, we use temporal interpolation to estimate the amplitude of the MR signal at the onset of the TR. In this way, all the voxels in the same volume “seems” to be registered at the same time.

Head motion correction.

Functional MRI analyses assume that each voxel represents a unique part of the brain; if the subject's head moves, this assumption is not respected.

Since the brain is the same in every image, we can use the rigid body transformation to coregister the images within each subject.

Coregistration

In order to have more precise spatial coordinates, coregistration is used to map functional and structural images of the same subject.

Normalization

The human brain has a huge anatomical variability in both size and shape. The aim of normalization is to compensate for these differences by coregistering the data into a common space. The most commonly used spaces are Talairach (Talairach and Tournoux, 1988) and MNI spaces.

Even if normalization is a powerful technique that allows groups comparison and enhance the statistical power of fMRI analyses, there is a main disadvantage that should be taken into account especially when we work with specific populations, such as in our case with blind individuals.

All normalization approaches are based on samples derived from standard population of fMRI subjects: educated young adults healthy and neurologically normal. The brain of other individuals, especially in the case of special populations, might differ in many properties from the brain of this standard population. For examples, blindness is associated with significant changes in the structure of the brain itself, particularly within the occipital cortex (Dormal et al., 2016; Jiang et al., 2016; Pan et al., 2007; Park et al., 2009). In order to avoid this problem, when working with special populations there are several possibilities that could be used in place of the standard normalization step.

One possibility is to use specific kinds of normalization that expressly take into account the problem of special population and increased variability across subjects. In study 1 instead to use a classical template (e.g. MNI) for the normalization we used a customized template created by the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra, (Ashburner, 2007) toolbox. DARTEL normalization takes the grey and white matter templates from each subject to create an averaged template that will be used for the normalization. The aim of this process is to increase the coregistration efficiency between individuals. The creation of a study-specific template using DARTEL should reduce deformations errors that are more likely to arise when co-registering single subject images to an unusually shaped template (Ashburner, 2007).

The second possibility consists in avoiding the normalization step. In study 2 we used the brain parcellation technique to avoid normalization preprocessing. In each subject, we used the anatomical scan to reconstruct the cortical surface of each hemisphere using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). The cortical anatomic segmentation can be performed according to different atlas such as the Desikan-Killiany (Desikan et al., 2006) and the Destrieux (Destrieux et al., 2010) atlas. Finally, it is possible to select the regions of interest (ROIs) individually defined in each subject.

Of course, these alternative techniques are not perfect and have their own disadvantages such as time consumption or, in the case of individually defined ROIs, the difficulty to run whole brain group analyses.

Spatial filtering.

This step, also known as smoothing, is the last in the classical fMRI data-preprocessing pipeline. The main goals of spatial filtering are to minimize the variability in brain shape and size across participants and to decrease the number of statistical comparisons (related to the number of voxels). It consists in the application of low-pass spatial filters to reduce the high-frequency spatial components. The most common technique is the introduction of a Gaussian filter that spreads the intensity at each voxel in the image over surrounding voxels. This step is not always recommended for multivariate kind of fMRI analyses.

1.4.5 General Linear Model

The general linear model (GLM) was introduced for the first time in the field of functional neuroimaging in 1995 (Friston et al., 1995) and after this first paper an increasing number of researchers embraced this technique to analyze their fMRI data. Nowadays the GLM is still highly used for fMRI analyses and most of the fMRI studies published in the neuroimaging field use this technique (Poline and Brett, 2012).

The GLM approach treats the data as a linear combination of model functions and uncorrelated noise. The goal of the GLM is to find the best weight for each model function to best explain the acquired data and to minimize the value of the noise. The standard GLM equation is given by

$$Y = X * \beta + \varepsilon$$

where Y refers to the observed data, that in the case of fMRI is the BOLD signal at various time points at a single voxel; X represents the several components that explain the observed data (e.g. the experimental conditions) and are included in the design matrix; β are the parameters that define the contribution of each component of the design matrix to the value of Y; finally ε refers to the error and represents the difference between the observed data Y and that predicted by the model $X\beta$. Basically the GLM wants to quantify, starting from a finished product (brain activity), the participation of each component (experimental conditions) in shaping the finished product.

1.4.6 Univariate analyses

The univariate analyses are used to investigate the relationship between cognitive variables at the level of individual brain voxels. This kind of analyses can address the question: "which region in the brain is more active for the condition 1 compared to the condition 2?" where the condition 1 and 2 could be, like in figure

1.9, viewing pictures of living stimuli (condition 1) and viewing pictures of non-living stimuli (condition 2).

In this case we can test at each voxel if the activity for the living pictures is significantly higher than the activity for the non-living stimuli simply subtracting the β values of the non-living stimuli from the β values of the living stimuli (see figure 1.9). This method has been extremely productive and contributed to rapidly expand the knowledge about the brain functions in the last 20 years. It is thanks to this method that the first generation of studies about crossmodal plasticity has been able to show increased activity in the occipital cortex of early blind compared to sighted subjects during non-visual tasks.

Thanks to this technique we also learnt most of the information about the representation of different categories in the brain. Arguably the most impacting example is the categorical subdivision in the visual ventral stream, mostly emerged using univariate fMRI analyses (see Grill-Spector and Weiner, 2014 for a review). Even if univariate analyses represent a powerful method to address certain kinds of question they have same disadvantages.

The main limitation is that they do not take in consideration the relationship between voxels, and because of that, they can succeed as a measure of representation only to the extent that individual voxels (in the case of whole brain approach) or regions as a whole (in the case we use the region of interest approach) distinguish between different types of representational content (Davis and Poldrack, 2013). This means that it is difficult, using this method, to find differences at a fine-grained level. In our example (see figure 1.9), we might expect that even if univariate analyses are able to individuate regions that are preferentially activated by the animate compared to the inanimate stimuli, probably they will fail in individuate voxels/regions showing finer within-category differences such as dogs versus horses.

1.4.7 Multivariate pattern analyses (MVPA)

In the last decade, the interest of cognitive neuroscience has increasingly moved towards new questions and new perspectives of approaching the investigation of the human brain functions. As it often happens, new questions need and bring new methods. The main characteristic of the new generation of analysis' techniques is that it does not look at single voxels but at groups (i.e. pattern) of voxels and for this reason they are called *multivariate* analyses. This kind of techniques gives more importance to the information, rather than the activation, contained in the different areas of the brain and it is more sensitive to the subtle differences compared to the univariate analysis. These methods extract the signal that is present in the pattern of activity across multiple voxels, even if each voxel considered individually might not show significant activation to any of the experimental conditions (Norman et al., 2006). In their seminal 2001 study, Haxby and collaborators presented pictures of different categories (e.g. faces, cats, man-made objects) to their participants and were able to show a distinct pattern of response for each category, inside the visual ventral pathway. Interestingly this was true also in those regions that, at univariate level, showed specific activation only for one category compared to the others (Haxby et al., 2001).

In the last decade, several multivariate techniques have developed. Among those, the two that are most often implemented are the multivariate pattern classification (MVP classification) analysis and the representational similarity analysis (RSA). Both analyses can be implemented using two different approaches: (1) predefined regions of interest (ROIs); (2) whole brain searchlight. The use of ROIs method is based on an *a-priori* assumption about the brain areas that can be related with the processing of the conditions in the experiment. The searchlight method, developed by Kriegeskorte et al., (2006), is based on the selection of a sphere centered at a voxel with a radius selected by the user; the measure of the radius determines the number of voxels included in the sphere. Then, moving the sphere, the analysis is repeated at all possible locations in the brain. On one hand the advantage of the searchlight approach is to avoid a predefined choice and to be more data-driven. On the other hand the ROIs approach, in the case of a strong a-priori assumption, can be the right choice to increase the statistical power of the analyses by decreasing the number of multiple comparisons.

I employed both these approaches in the studies described in the next chapters. In chapter 2 I ran MVP classification with the searchlight whole brain approach. In the chapter 3, instead, I directly used ROI approach; in this case I based the selection of the regions of interest on studies from previous literature.

MVP Classification analysis

MVP Classification analysis can address the question: "Is there (in the selected ROI or in the searchlight sphere) enough information to distinguish the stimuli from each condition?" This method is based on pattern classification techniques, in which the patterns that we want to classify are vectors of voxels activity values (Norman et al., 2006). Because classifiers rely on feature selectivity and a spatial inhomogeneity of feature-selective responses, only their conjunction can lead to biased responses in segregated voxels (Bartels et al., 2008).

In the example presented in figure 1.9 we have stimuli from two different conditions (animate versus inanimate). To run the MVP classification analysis on this data we have (1) to label each pattern of activity according to the experimental condition that generated it, then (2) in the classifier training phase, we have to present a subset of these labeled patterns of activity to a multivariate patterns classification algorithm. In this way, the algorithm learns the function that links patterns of activity with experimental conditions. Finally, in the generalization testing step (3), new patterns of activity are presented to the trained classifier and we evaluate whether the classifier is now able to correctly associate the new pattern with the experimental condition that generated it (Norman et al., 2006). If the algorithm is able to perform the task with accuracy significantly higher than the chance level (that in our example with 2 conditions is equal to 50%) we can infer that in the tested region there is, indeed, enough information to distinguish between stimuli belonging to the two different categories (animate versus inanimate).

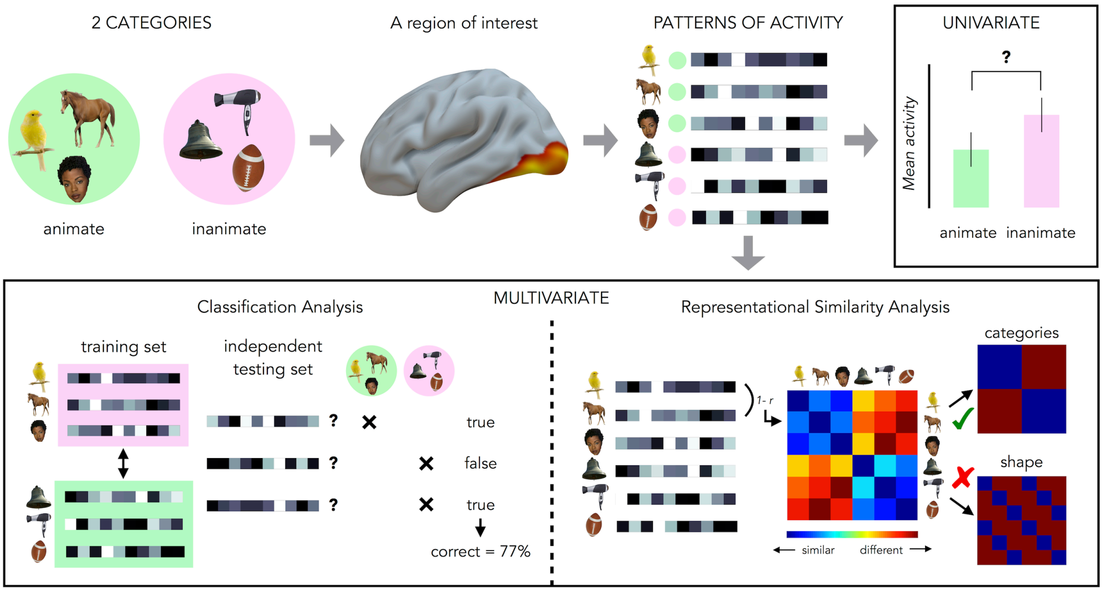


Figure 1.9: Representation of univariate and multivariate fMRI data analyses. In this example stimuli from two different categories (animate & inanimate) are presented (top-left) and the brain activity is extracted from a region of interest (ROI). In the univariate analysis (top-right) we compare the mean activity of the ROI for the animate stimuli with the main activity of the ROI for the inanimate stimuli to see whether the ROI is more activated by one category compared to the other. In the MVP classification analysis (bottom-left) the patterns of activity are divided into two data sets, a classifier is trained on the first set and tested on the second one. A successful decoding means that the ROI contains information about the different categories. Finally in the RSA analysis (bottom-right) we compute a neural dissimilarity matrix (DSM) based on the similarity between each pair of stimuli (red=different; blue=similar). Then, computing the correlation between the neural DSM and external models, we can test which feature of the stimuli is processed in the ROI (in this example is the categorical content and not the shape).

Representational similarity analysis (RSA)

RSA is a multivariate technique that aims to study the correspondence between the relations among the stimuli on one hand and the relations among their representation on the other hand (Kriegeskorte et al., 2008). Using this technique, we can address the questions: "How similar are the patterns generated by the different stimuli? And which features of the stimuli better explain this similarity?"

A key concept of RSA is the concept of dissimilarity: by comparing the activity patterns associated with each pair of stimuli it is possible to obtain a representational dissimilarity matrix (RDM). A RDM is a square with a width and height corresponding to the number of conditions and symmetric about a diagonal of zeros. Each cell of the RDM contains the dissimilarity value (e.g. one minus the correlation coefficient) between the brain activity patterns associated with the correspondent pair of stimuli. Even though many different measures can be employed to define the dissimilarity between patterns (e.g Euclidean/Mahalanobis distance or classification accuracy, see Walther et al., 2016), the most frequent method is the correlation measure. The RDM can be created not only based on the brain activity but also on the physical properties of the stimuli or related to behavioral performance (reaction time or explicit similarity judgments) of the participants. Then, it is possible to compare brain dissimilarity matrices and model dissimilarity matrices through a second-level matrices correlation, assessing which information is encoded in a specific area of the brain (see figure 1.9).

The main strength of RSA is that it compares representations at the level of the dissimilarity matrices and not at the level of the activity patterns. Thanks to this abstraction from the original space it is not needed to define the correspondence mapping between the representational units (i.e. voxels). This makes RSA a highly flexible tool, which allows relating brain regions, different subjects, species and modalities of brain activity measurement and also brain and behavior (Kriegeskorte et al., 2008).

1.4.8 Using multivariate analyses to investigate amodal regions in the brain

As I already anticipated, we can use the different analysis methods described above to address different questions. Interestingly, these techniques, especially the multivariate methods, are in constant evolution since each new field of research tries to adapt these flexible tools in order to address its own new research questions. A clear example is represented by a recent research branch with the aim to investigate the representational format of different brain regions. This question is difficult, if not impossible, to investigate with the classical fMRI univariate approach. However, the development of the new multivariate analyses opened the door to the possibility of better understanding the fine-grained information contained in a given region going beyond pure activation.

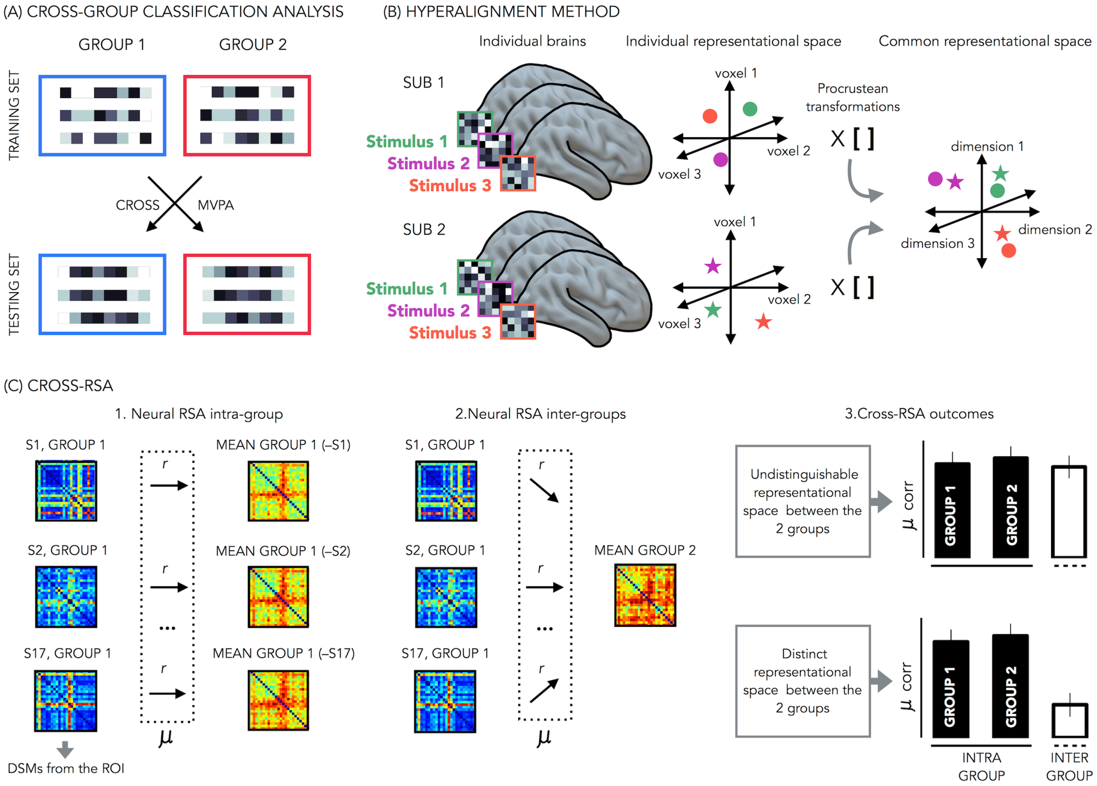


Figure 1.10: Comparing representational space between subjects. (A) Cross group classification analysis. In case of large ROIs it is possible to apply the cross-group classification analysis. The idea at the base of this analysis is to present the stimuli two different groups (e.g blind and sighted). Then, it is possible to train the classifier on the pattern of activities generated by one group for subsequent testing on the other group. If there is shared information in the two groups the classification will be above the chance level. (B) Hyperaligment metod. Hyperalignment aligns neural representational space of ROIs in individual subjects' into a common model space of the same ROI in high-dimensional space using Procrustes transformation (e.g. rotation). (C) Cross-RSA analysis. 1.To compute the neural RSA intra group the DSM of each participant is correlated with the mean DSM of his group excluding his own DSM; 2. to compute the neural RSA between group the DSM of each participant is correlated with the mean DSM of the second group; 3. in case the representational space is highly similar between the 2 groups the intra-group and the inter-group correlation will be comparable; on the contrary, if the representational space is different between the 2 groups the intra-group correlation will be higher than the inter-group correlation.

More specifically, in order to understand which brain regions are content-specific (e.g. conceptual information) and modality-invariant (i.e. amodal), several studies employed an innovative version of MVPA analysis, defined as cross-modal/conditions decoding technique (Bulthé et al., 2014; Fairhall and Caramazza, 2013; Jung et al., 2017; Man et al., 2012). The idea at the base of this analysis is to present the same stimuli in two different modalities/conditions. Then, it is possible to train the classifier on each modality for subsequent testing on the other modality. In this way, only the category-specific information that is shared by both modalities/conditions is informative to the classifier. This analysis has been considered, so far, as a method to isolate the regions that participate in the representation of different semantic categories independently of the modality through which the representations are accessed (Fairhall and Caramazza, 2013).

However, this technique is based on high-spatial-frequency patterns of response and it is really difficult to define a correspondence between these features across brains. As a consequence, this is a tool that should ideally be used within the subject space, with a new classifier model built for each brain. Cox and Savoy (2003) reported, indeed, a drop in the classifier performance if based on other subjects' data (Cox and Savoy, 2003). This performance decrement is link to the fact that the structure of the activity patterns differs across subjects (Haxby et al., 2011). This makes MVP classification a difficult method for between subjects and between groups' analyses. However there are some exceptions.

A possibility to successfully implement cross-groups decoding analysis (see figure 1.10A) is to use large ROIs (Hurk et al., 2017; Ricciardi et al., 2013). An example comes from a recent study where Hurk and collaborators applied MVPA across sighted and blind subjects to the whole VOTC. This technique allowed them to show that at this large-scale level there are, indeed, shared information between auditory representations of the stimuli in early blind and visual representations of the stimuli in sighted controls. The success of this technique relies on the fact that large-scale domain selective responses are found commonly in blind and sighted participants, as described above in paragraph 1.1.2. However, if we want to look at the representational format at a lower-scale level in functional-selective regions inside VOTC, such as FFA or PPA, it becomes difficult to assume shared pattern geometries of different stimuli from the same or different classes across separate subjects or groups. A very problematic interpretation issue would emerge especially from null results. It would be difficult, as a matter of fact, to define whether a chance-level accuracy decoding would be driven by a lack of shared representations across groups or by an inaccurate accordance between the features (i.e. voxels) across different brains.

Another attempt to use the classification analysis across subjects comes from the hyperalignment method (Haxby et al., 2011, see figure 1.10B). In this study, the authors proposed an innovative technique to align patterns of neural response across subjects into a common, high-dimensional space. To do that, they registered the brain responses of different subjects while they were watching a full-length movie and, based on these responses, they estimated the parameters to transform the individual voxel's space into a common space. Using the words of the authors: *"hyperalignment uses Procrustean transformations (Schonemann, 1966) iteratively over pairs of subjects to derive a group coordinate system in which subjects' vector trajectories are in optimal alignment. The Procrustean transformation is an orthogonal transformation (rotations and reflections) that minimizes the Euclidean distance between two sets of paired vectors"* (Haxby et al., 2011). In their paper they showed that, after hyperalignment, it is possible to perform classification analysis across different subjects with results much more accurate compared to the results obtained after the classical anatomical realignment. This technique is certainly an innovative and powerful tool, however it has yet never been tested across different groups. Therefore, it is difficult to predict if it would properly realign brains from two different populations, such as sighted and blind individuals. In addition, a non-negligible constraint of this technique is that it requires each participant to watch long film "only" for the realignment propose.

In order to bypass these constraints, **in study 1**, we innovatively adapt the use of RSA to investigate if the representational format of previously defined ROIs is or not abstracted from the input modality. We defined this analysis "cross-RSA" (see figure 1.10C). The RSA approach is based on the assumption that stimuli that are similar to each other will have similar representational geometries at the neural level. Importantly, the relative similarity of neural patterns elicited by each stimulus can be compared across subjects independently from their "absolute" and subject-specific representational framework. The cross-RSA technique is based on the comparison between correlation of brain dissimilarity matrices (DSMs) across subjects from the same group (figure 1.10C, left panel) and correlation of brain DSMs across subjects from different groups (figure 1.10C, central panel). We reasoned that if the coding properties of a brain region is truly abstracted from sensory input and experience, the inter-individual variability of the way this region encodes our stimuli space (expressed as brain dissimilarity matrices) should be equal between individuals of the same versus different groups (e.g. sighted in vision, sighted in audition, blind in audition). Alternatively, if sensory input or experience influence the way a brain region implements the representation of our stimuli space, then the inter-subject reliability of our brain dissimilarity matrices should be higher inside a group than across groups (see figure 1.10C right panel and refer to the chapter 2 paragraph *2.3.4.5* for a more detailed description of the analysis).

1.5 Summary and goal of this dissertation

In this chapter, I have reviewed compelling evidences that the occipital cortex in early blind is recruited during non-visual auditory and tactile tasks and that its reorganization seems to follow, at least partially, the typical functional architecture found in the occipital cortex of sighted individuals. In addition, I described some influential theories about the semantic system and its neural implementation in the sighted. Finally, I described how blindness might serve as a model to shed new lights on this topic.

Previous studies showed that the way SC and EB think about things is highly similar (Bedny and Saxe, 2012). However at the neural level a main difference has been identified in the enhanced recruitment of the occipital cortex for the processing of different categories through non-visual modalities in EB compared to SC (Collignon et al., 2012). Interestingly, several evidences support the idea that this reorganization does not take place in a stochastic manner but seems to follow the functional specialization of the colonized brain regions (Dormal and Collignon, 2011).

It is unlikely that a highly interconnected system like the human brain would reorganize one part of its circuits to extend its tuning toward a specific operation without altering the computational structure of the regions that typically code for this function. Simply put: what is happening in the auditory cortex of early blind individuals knowing that massive auditory computations are now carried out in the visually deprived occipital cortex? One of the main endeavours of the current thesis was therefore to explore the complex interplay between occipital and temporal regions in the brain of early blind people during auditory categorization processing.

In parallel, studies on the neural substrate of conceptual knowledge in sighted led to the proliferation of several theories about the format the brain uses to implement conceptual representations. These theories go from the two extremes. The purely empiricist proposition supposes that our knowledge is acquired through our senses and that most of our conceptual system is implemented in sensory regions (Martin, 2007). At the opposite extreme, it has been suggested that knowledge relies on an amodal organization of the brain which would be based on operators defined by a given computation that is applied regardless of the sensory input received (Pascual-Leone and Hamilton, 2001). Interestingly, regions classically considered part of sensory systems, such as VOTC, have been suggested to be part of this amodal network instead (Amedi et al., 2001; Mahon and Caramazza, 2009; Pietrini et al., 2004). In this context, the occipital recruitment in early blind for non-visual stimuli has been used to support the idea that VOTC does not need vision to develop and that, therefore, it can be consider part of the amodal network.

However many questions, at both technical and theoretical levels are still open about the implementation of the semantic system in the brain.

The general aim of the present dissertation was to investigate the semantic processing of categories presented in distinct modalities and to populations with different sensory experiences. Our goals were two folded: (1) understand whether there are brain regions that encode information about different categories regardless of input modality and sensory experience; (2) deepen the investigation of the mechanisms that drive cross-modal and intra-modal plasticity following early blindness and the way they express during the processing of different categories presented as real-world sounds.

2

HOW INPUT MODALITY AND VISUAL EXPERIENCE AFFECT THE NEURAL IMPLEMENTATION OF CATEGORICAL KNOWLEDGE IN THE HUMAN[2]

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[2] Paper submitted for publication.

Mattioni, S., Rezk, M., Cuculiza Mendoza, K.E., Battal, C., Bottini, R., Van Ackeren, M., Oosterhof, N.N., Collignon, O. (2017). ***How input modality and visual experience affect the neural implementation of categorical knowledge in the human brain***

2.1 Abstract

Perceptual categorization is an ubiquitous cognitive operation that animals and humans use to organize their sensory experience. However, the way sensory input and experience shape how categorical knowledge is processed and represented in the brain remains unclear. To address this fundamental question, we used fMRI to characterize the brain responses to 8 conceptual categories presented acoustically in sighted and early blind individuals, and visually in a separate sighted group. We observed that the right posterior middle temporal gyrus (rpMTG) is the region that most reliably decoded categories and selectively correlated with conceptual models of our stimuli space independently of input modality and visual experience. However, rpMTG maintained separate representational format between audition and vision, suggesting distinct representational geometries across the senses. As predicted, we also observed a robust enhancement in decoding auditory categories in the occipital cortex of blind individuals. Interestingly, this effect was lateralized to the right hemisphere. Moreover, in regions that typically show categorical preference for faces (FFA), tools (LO) and scenes (PPA), we found a correlation between the visual and the auditory representational geometry of the stimuli in both hemispheres for the blind, but only in the left hemisphere for the sighted. All together these results demonstrate how input modality and sensory experience massively impact on the neural implementation of categorical representations and highlight hemispheric asymmetries in their expression.

2.2 Introduction

All living organisms need to make sense of the profuse sensory world that surrounds them. They notably do so by grouping exemplars sharing similar perceptual features into the same class, a process called perceptual categorization (Edelman, 1998; Rosch et al., 1976).

For each modality, the process of perceptual categorization requires a series of hierarchical stages from the primary sensory cortices where stimuli are analysed on the basis of some physical properties, till secondary and higher sensory regions showing preferential tuning toward specific class of stimuli, independently of their low-level properties (Connolly et al., 2012; Kriegeskorte et al., 2008; Giordano et al., 2013; Leaver and Rauschecker, 2010). For instance, some regions in the middle and superior temporal gyrus/sulcus show preferential responses to voices (Belin et al., 2000) or the sound of mechanical objects (Dormal et al., 2017; Lewis et al., 2011b), while discrete regions in the lateral-occipital and ventral occipito-temporal cortices preferentially respond to faces (Kanwisher et al., 1997) or object's shape (Grill-Spector and Weiner, 2014).

Since concrete entities typically stimulate multiple senses, it was assumed that some convergence regions should represent conceptual knowledge in an abstract fashion, showing categorical selectivity independently of the sensory input (Barsalou et al., 2003; Binder, 2016; Damasio, 1989; Fairhall and Caramazza, 2013; Mahon and Caramazza, 2009). However, which brain regions represent concepts amodally remains controversial and their definition is variable across studies depending on the sensory input (e.g. images versus words versus sounds) and the type of data collected (e.g. lesion studies versus neuroimaging). For example, neuropsychological data highlighted a central role of the ATL as a convergence zone (Patterson et al., 2007); studies using linguistic material pointed out a wider left lateralized network including (but not limited to) the angular gyrus, the posterior middle and inferior temporal gyri, the posterior cingulate gyrus and the inferior frontal gyrus (Binder et al., 2009; Xu et al., 2016). Finally, studies relying on pictures and real-world sounds highlighted a similar network including also the right counterparts (Anderson et al., 2016; Humphries et al., 2001; Thierry and Price, 2006; Thierry et al., 2003). One additional question debated in the field concerns the format of the representation implemented by these convergence regions (Devereux et al., 2013; Fairhall and Caramazza, 2013; Jung et al., 2017; Man et al., 2012). Do the regions involved in the categorization of stimuli from multiple modalities encode abstract representations in a modality-invariant format or, alternatively, do they encode modality-dependent representations across different senses?

Perhaps more surprising, it was recently suggested that regions typically considered as purely visual may actually represent categorical information in a more abstracted fashion than previously thought (Mahon and Caramazza, 2009; Pietrini et al., 2004). One example is the lateral occipital complex (LOC), previously thought to selectively process object stimuli in the visual modality only (Malach et al., 1995) and more recently suggested to be modality-independent and to represent abstract features of object form (Amedi et al., 2002, 2001; Pietrini et al., 2004). Since similar categorical responses to non-visual stimulation were also observed in congenitally blind people, it has been suggested that the involvement of VOTC is not a by-product of visual imagery but rather the sign that the functional specialization of this region does not need vision to develop (Amedi et al., 2010; He et al., 2013; Hurk et al., 2017; Ricciardi et al., 2014). However, overlapping categorical response profile between blind and sighted might be underpinned by distinct representational formats (e.g. visual imagery in the sighted and crossmodal responses in the blind due to neuroplasticity). It is therefore crucial, in order to disentangle between these different possibilities, to access the format of the representation in the brain regions of different experimental groups (e.g. blind and sighted). In the current study we adapted a technique derived from RSA (Deen et al., 2017) in a way that allowed us to investigate how input modality and experience influence the representational format of a brain region.

The first aim of this study was to comprehensively investigate which regions implement categorical processing in an amodal, multimodal or modality-specific fashion in sighted individuals. Second, we wanted to understand how visual deprivation impacts on these categorical responses. One possibility is that blindness has no influence on the response properties of a region showing its independence from visual input. Alternatively, brain regions may alter their coding of non-visual modalities in early blind subjects; for instance, enhancing their categorical coding of sounds due to crossmodal plasticity. We paid a particular attention to regions inside VOTC typically showing categorical responses to specific visual domains of stimuli (e.g. FFA, PPA, LO), since the representational format (modality-invariant or sensory-related) of these regions is the centre of the current debates.

To reach our goals we carried out a comprehensive mapping of how sensory input and sensory experience impact on the way the brain categorizes information in 3 separate groups of participants (16 sighted in vision, 17 sighted in audition, and 17 early blind in audition). We relied on a combined set of multivariate analyses that allowed us to access the representational format of brain regions and to distinguish the neural code of categorical and physical representations of the stimuli. First, using MVPA (Haxby et al., 2001) we isolated the right posterior middle temporal gyrus (rpMTG) as the region able to decode categories in different modalities (vision and audition) and in people with different visual experiences (blind and sighted). We also identified an extended portion of the right occipital cortex (including portions of cuneus, lingual gyrus, posterior fusiform gyrus and the inferior occipital cortex) that showed robust enhanced auditory decoding in the early blind group, highlighting crossmodal reorganization. Then, using representational similarity analysis (RSA, Kriegeskorte et al., 2008) we further investigated the representational geometry implemented in these regions, across groups and modalities. In addition, we repeated similar analyses inside 6 ROIs along VOTC and we highlighted a main hemispheric difference in the way these regions implement auditory processing in blind and in sighted people.

2.3 Material and Methods

2.3.1 Participants

Thirty-four participants completed the acoustical version of the fMRI study: 17 early blinds (EBa; 10F) and 17 sighted controls (SCa; 6F). An additional group of 16 sighted participants (SCv; 8F) performed the visual version of the fMRI experiment. All the blind participants lost sight at birth or before 4 years of age and all of them reported not having visual memories and never used vision functionally (see table 2.1–SI). The three groups were age (range 20-67 years, mean ± SD: 33.29 ± 10.24 for EBa subjects, respectively 23-63, 34.12 ± 8.69 for SCa subjects, and 23-51, 30.88 ± 7.24 for SCv subjects) and gender ($\chi^2(2,N=50)=1.92$, $p=0.38$) matched. One blind subject performed only 2 out of the 5 runs in the fMRI due to claustrophobia; because of that we excluded her data from the decoding analyses since to compute the accuracy values we need to divide the dataset into training and testing sets and two runs would not be enough for the reliability of the results. All participants were blindfolded during the auditory task. Participants received a monetary compensation for their participation. The ethical committee of the University of Trento approved this study (protocol 2014-007) and participants gave their informed consent before participation.

2.3.2 Stimuli

A preliminary experiment was run in order to select the acoustical stimuli. Ten participants who did not participate in the main experiment were presented with 4 different versions of 80 acoustical stimuli from 8 different categories (human vocalization, human non-vocalization, birds, mammals, tools, graspable objects, environmental scenes, big mechanical objects) that could be reduced to 4 superordinate categories (human, animals, manipulable objects, big objects/places). We asked the participants to recognize the sound and then to rate, from 1 to 7, how much the sound was representative of its category. We selected only the stimuli that were recognized with at least 80% of accuracy, and among those, we choose for each category the 3 most representative sounds for a total of 24 acoustical stimuli in the final set (see table 2.2–SI). All sounds were collected from the database *Freesound* (https://freesound.org), except for the human vocalizations that were recorded in the lab. The sounds were edited and analysed using the software *Audacity* (http://www.audacityteam.org) and Praat (http://www.fon.hum.uva.nl/praat/). Each mono-sound (44,100 Hz sampling rate) was 2 seconds long (100msec fade in/out) and amplitude-normalized using root mean square (RMS) method.

We created a visual version of the stimuli set. The images for the visual experiment were coloured pictures collected from Internet and edited using *GIMP* (https://www.gimp.org). Images were placed on a grey (129 RGB) 400 x 400 pixels background.

2.3.3 Procedure

The experimental session was divided into two parts: first the subjects underwent the fMRI experiment then they performed a behavioural rating judgment task on the same stimuli used in the fMRI experiment.

fMRI experiment

Each participant took part in only one experiment, either in the acoustical or in the visual version. We decided to include two separate groups of sighted people, one for each modality, for two crucial reasons. First, we wanted to limit as much as possible the possibility of triggering mental imagery from one modality to the other. Second, since cross-group comparisons of representational dissimilarity analyses represent a core component of our analysis stream (see Method section 'CrossRSA' for further details), we wanted to ensure a cross-group variance comparable between blind versus sighted and sighted in audition versus sighted in vision.

The procedure for the two experiments was highly similar. Before entering the scanner, all the stimuli (either acoustical or visual) were presented to each participant to ensure perfect recognition. In the fMRI experiment each trial consisted of the same stimulus repeated twice. Rarely (8% of the occurrences), a trial was made up of two different consecutive stimuli (catch trials). Only in this case participants were asked to press a key with the right index finger if the second stimulus belonged to the living category and with their right middle finger if the second stimulus belonged to the non-living category. This procedure ensured that the participants attended and processed the stimuli. In the acoustical experiment, each pair of stimuli lasted 4s (2s per stimulus) and the inter-stimulus interval between one pair and the next was 2s long for a total of 6s for each trial (see figure 2.1A). In the visual experiment, each pair of stimuli lasted 2s (1s per stimulus) and the inter-stimulus interval between one pair and the next was 2s long for a total of 4s for each trial (see figure 2.1A). The use of a ''quick'' event-related fMRI paradigm balances the need for separable hemodynamic responses and the need for presenting many stimuli in the limited time-span of the fMRI experiment (Kriegeskorte et al., 2008). Within both the acoustical and the visual fMRI sessions participants underwent 5 runs. Each run contained 3 repetitions of each of the 24 stimuli, 8 catch trials and two 20s-long rest periods (one in the middle and another at the end of the run). The total duration of each run was 8min and 40s for the acoustical experiment and 6min for the visual experiment. For each run, the presentation of trials was pseudo-randomized: two stimuli from the same superordinate category (i.e. animals, humans, manipulable objects, non-manipulable objects) were never presented in subsequent trials. The stimuli delivery was controlled using the Psychophysics toolbox (http://psychtoolbox.org; Pelli, 1997) implemented in Matlab R2012a (The MathWorks).

Behavioral experiments

The behavioural experiment aimed to create individual behavioural dissimilarity matrices to understand how the participants perceived the similarity of our stimuli space (Kriegeskorte et al., 2008). Due to practical constraints only a subset of our subjects underwent the behavioural experiment (15 EBa, 11 SCa, 9 SCv). We created each possible pair from the 24 stimuli set leading to a total of 276 pairs of stimuli. In the acoustical experiment, participants heard each sound of a pair sequentially and were asked to judge from 1 to 7 how similar were the two stimuli producing those sounds. In the visual experiment, we presented each pair of stimuli on a screen to the participants and we asked them to judge from 1 to 7 how similar were the 2 stimuli.

2.3.4 fMRI data acquisition and analyses

fMRI data acquisition and preprocessing

We acquired our data on a 4T Bruker Biospin MedSpec equipped with an eight-channel birdcage head coil. Functional images were acquired with a T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence (TR, 2000 ms; TE, 28 ms; flip angle, 73°; resolution, 3x3 mm; 30 transverses slices in interleaved ascending order; 3mm slice thickness; field of view (FoV) 192x192 mm2). The four initial scans were discarded to allow for steady-state magnetization.

A structural T1-weighted 3D magnetization prepared rapid gradient echo sequence was also acquired for each subject (MP-RAGE; voxel size 1x1x1 mm; GRAPPA acquisition with an acceleration factor of 2; TR 2700 ms; TE 4,18 ms; TI (inversion time) 1020 ms; FoV 256; 176 slices).

Before each EPI run, we performed an additional scan to measure the point-spread function (PSF) of the acquired sequence, including fat saturation, which served for distortion correction that is expected with high-field imaging (Zeng and Constable, 2002). Raw functional images were pre-processed and analysed with SPM8 (Welcome Trust Centre for Neuroimaging London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm/) implemented in MATLAB R2013b (MathWorks). Pre-processing included slice-timing correction using the middle slice as reference, the application of temporally high-pass filtered at 128 Hz, motion correction, spatial smoothing (using a 2mm FWHM) and normalization to a customized template created by the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (Ashburner, 2007) toolbox. DARTEL normalization takes the grey and white matter templates from each subject to create an averaged template that will be used for the normalization. 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 given that blindness is associated with significant changes in the structure of the brain itself, particularly within the occipital cortex (Dormal et al., 2016; Jiang et al., 2009; Pan et al., 2007; Park et al., 2009).

General Linear Model

The pre-processed images for each participant were analysed using a general linear model (GLM). For each of the 5 runs we included 32 regressors: 24 regressors of interest (each stimulus), 1 regressor of no-interest for the target stimulus, 6 head-motion regressors of no-interest and 1 constant. From the GLM analysis, we created two different input data for the following multivariate analyses. For the decoding analyses (MVPA; see below) we obtained a β-image for each stimulus (i.e. 24 sounds or images) in each run, for a total of 120 (24 x 5) beta maps. For representational similarity analyses (RSA; see below) we extracted one β-image for each stimulus (i.e. 24 sounds or images) across the 5 runs, for a total of 24 beta maps.

Multivoxel pattern analysis (MVPA)

MVPA was performed using the CoSMoMVPA (Oosterhof et al., 2016) toolbox, implemented in Matlab. We tested the discriminability of patterns for the eight categories using as classifier the Fisher linear discriminant (LDA; Hong and Santosa, 2016; Misaki et al., 2010). We performed a leave-one-run-out cross-validation procedure using beta-estimates from 4 runs in the training set, and the beta-estimates from the remaining independent run to test the classifier, with iterations across all possible training and testing sets (see figure 2.1B).

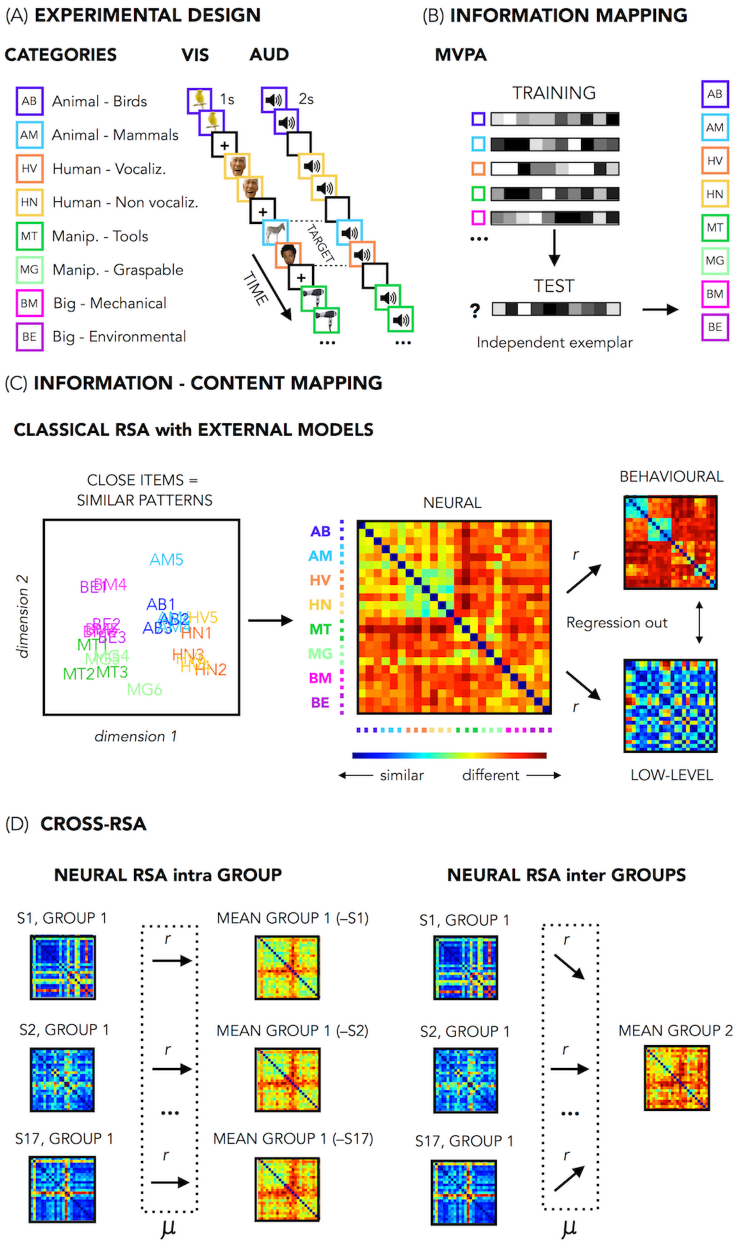


Figure 2.1: **Material, methods and analyses.** (A) Categories of stimuli and design of the visual (VIS) and auditory (AUD) fMRI experiments. (B) MVPA analysis: a classifier is trained on a set of patterns of activity generated by the different categories and, successively, it is tested on independent data. If the classifier is able to successfully classify the new data it means that the brain region contains information about the different categories. (C) Representational Similarity Analysis (RSA). On the left-panel multi-dimentional scaling is used to show the similarity between the neural representation of each stimulus and all the others (closer the items in the representation, closer their neural representation in the brain region); in the central part of the panel the correlation between the pattern of activity generated by each pair of stimuli is used to compute a neural dissimilarity matrix (DSM; red=different; blue=similar). Then, computing the correlation between the neural DSM and external models, it is possible to test which feature of the stimuli is processed in the brain region (e.g. behavioural/ low-level). (D) Cross-RSA analysis: to compute the neural RSA intra group (left panel) the DSM of each participant is correlated with the mean DSM of his group excluding his own DSM; to compute the neural RSA between group (right panel) the DSM of each participant is correlated with the mean DSM of the second group.

This procedure was implemented using a searchlight approach (Kriegeskorte et al., 2006) with a sphere containing 100 voxels. We applied a smoothing of 8 mm FWHM Gaussian kernel on each individual map before to enter the images into a second-level random effect analysis to test for group effects and differences.

To identify cortical regions showing a significant decoding in all groups we performed a conjunction analysis between the brain maps resulting from the three groups (i.e. EBa, SCa and SCv). We report voxel-level family wise error (FWE) corrected p values <0.05 for the entire brain volume. For the acoustical experiment, significant group differences between EBa and SCa were detected by a two-sample t-test using a p threshold of <0.05 corrected for multiple comparisons with Threshold Free Cluster Enhancement (TFCE; Smith and Nichols, 2009) method restricted to the occipital cortex (due to a priori hypothesis that crossmodal plasticity will express on those regions). To foreshadow our results, we observed one significant region from the conjunction analysis located in the right posterior middle temporal gyrus (rpMTG) and two regions from the contrast EBa>SCa, located in the occipital cortex, one more dorsal and one more ventral (see Figs XX and YY). We created three masks based on these regions: rpMTG mask with 475 voxels, rOCC-dorsal mask with 591 voxels and rOCC-ventral mask with 980 voxels (see figure 2.3C-D). The three masks were used as regions of interest (ROIs) in the subsequent representational similarity analysis (see next section).

Representational similarity analysis with external models

Representational similarity analysis (RSA; Kriegeskorte and Kievit, 2013) was performed using CoSMoMVPA (Oosterhof et al., 2016) toolbox, implemented in Matlab (r2013b; Matworks). We first created models containing the stimuli information we wanted to investigate (see figure 2.2). These models are in the shape of dissimilarity matrices (DSMs). A DSM is a square matrix where the number of columns and rows corresponds to the number of the conditions (24x24 in this experiment) and it is symmetrical about a diagonal of zeros. Each cell contains the dissimilarity index (1 – similarity) between two stimuli (Kriegeskorte and Kievit, 2013).

Behavioural DSMs. We used the pairwise similarity judgments from the behavioural experiment to build the behavioural DSMs. We computed one matrix for each subject that took part in the behavioural experiment and we averaged all the matrices of the participants from the same group to finally obtain three mean behavioural DSMs, one for each group (i.e. EBa, SCa, SCv; see figure 2.2). The use of averaged behavioural matrices, on partial or independent sample, has already been validated by previous studies (Connolly et al., 2012; Peelen et al., 2013b). Moreover, we also performed the analyses including only the subset of subjects that took part in the behavioural experiment using for each subject his own behavioural DSM and the results we obtained were similar to the results obtained on the whole group with the mean DMS of the group.

Physical DSM in the auditory experiment: pitch DSM. Pitch corresponds to the perceived frequency content of a stimulus. Previous studies showed that this physical property of the sounds is mostly represented in the primary auditory cortex (Formisano et al., 2003; Giordano et al., 2013; Leaver and Rauschecker, 2010). We computed a pitch value for each of the 24 acoustical stimuli, using the Praat software (Boersma & Weenink, 2009) and an autocorrelation method (Boersma, 2003). This method extracts the strongest periodic component of several time windows across the stimulus and averages them to have one mean pitch value for that stimulus. The size of the time windows over which these values are calculated in Praat are determined by the "pitch floor". Based on a previous study (Leaver and Rauschecker, 2010) we chose a default pitch floor of 60 Hz. Once we obtained one pitch value for each sound, we built the DSM computing the absolute value of the pitch difference for each possible pairwise (see figure 2.2). The pitch DSM was not significantly correlated with the behavioural DSM of neither SCa (r=-0.088, *p=0.14)* nor EBa (r= -0.034, *p=0.57*).

Physical DSM in the visual experiment: gist DSM. The GIST model synthetizes several low-level visual properties of the image (Oliva and Torralba, 2001, http://people.csail.mit.edu/torralba/code/spatialenvelope/). To create the GIST DSM, each image passed through a series of 32 Gabor filters (4 spatial frequencies and 8 orientations) producing 32 features maps. Then each feature map was divided into 16 regions and the values within each region were averaged. Finally, the concatenation of the 16 averaged values of all 32 maps gave a vector of 512 values that represent the GIST descriptor. We built the DSM computing 1 minus the Pearson's correlation between the vectors for each possible pairwise (n 276). The GIST DSM was significantly correlated with the SCv behavioural DSM (r=0.43, *p<0.001*).

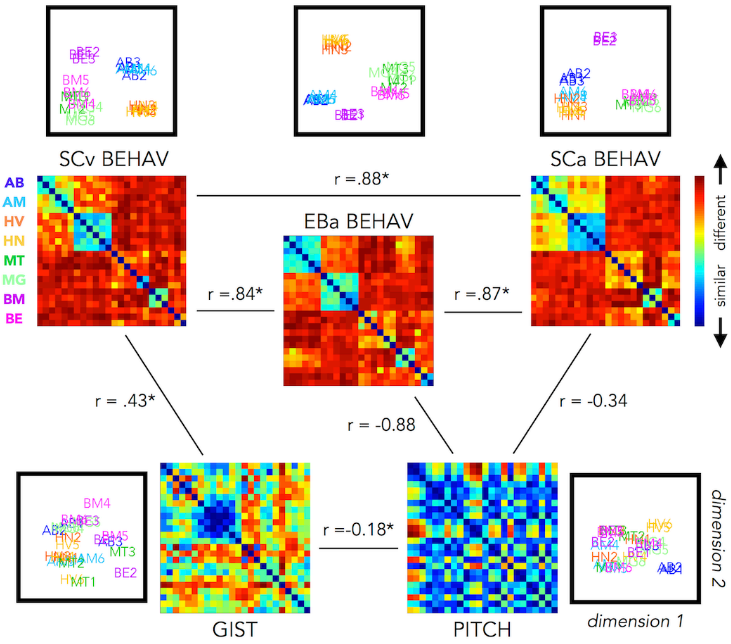


Figure 2.2: External models for RSA. On the top panel: behavioural ratings of the 24 stimuli (from 8 categories) performed by each participant and averaged within the 3 groups: sighted control in vision (SCv) and in audition (SCa) and early blind in audition (EBa). On the bottom panel: models built on low-level properties of the stimuli: gist for visual stimuli, pitch for auditory stimuli. The results are represented both using multi-dimensional scaling and dissimilarity matrix representations.

The second step, in RSA analysis, consisted in the extraction of the neural DSMs (Kriegeskorte et al., 2008) in the 3 ROIs (from MVPA results, i.e. rpMTG, rOCC-dorsal, rOCC-ventral), computing the dissimilarity between the spatial patterns of activity for each pair of stimuli. We extracted in every subject and in each of the 3 ROIs, the stimulus-specific BOLD estimates from the contrast images for all the 24 stimuli separately. We next computed all the pairwise correlations between them (1 – Pearson's correlation) in order to build the neural DSM for each ROI.

The last step consisted in comparing neural and external DSMs models using a second order correlation. Because we wanted to investigate each external model independently from the other, we relied on Pearson's linear partial correlation: in the auditory experiment, we removed the influence of the pitch similarity when we were computing the correlation with the behavioural matrix, and vice versa; in the visual experiment, we removed the influence of the GIST similarity when we were computing the correlation with the behavioural matrix, and vice versa. In this way, we could measure the partial correlation for each external model for each subject separately (see figure 2.1C). For the group-level analyses, significances within group were determined using permutation tests (100000 iterations), building a null distribution for these values by computing them after randomly shuffling the labels of the two external RDMs conditions. All the p Values are reported after false discovery rate (FDR) correction implemented using the matlab function *'mafdr'* (Benjamini and Yekutieli, 2001). Moreover, models (behavioural, physical) and groups (SCv, SCa, EBa) were entered in a 2x3 Repeated Measures ANOVA.

CrossRSA

To foreshadow the results obtained from the previous analyses, we observed that rpMTG region showed significant decoding accuracy for the 8 categories (MVPA analysis) in different modalities (i.e. vision & audition) and in groups with different sensory experiences (i.e. blind & sighted). Moreover, the same region revealed a significant correlation with conceptual, and not physical, DSM models (classical RSA). From these results, we still could not disentangle if the computational processing that takes place in this region is modality-independent (i.e. amodal) or if it keeps segregated the different modalities (i.e. multimodal).

Our idea was that comparing the functional profile of a specific brain region across subjects of the same group and between subjects of different groups could give us important insights onto the representational nature of brain regions. It was hypothesized that amodal regions would show indistinguishable functional profiles across modalities and experiences while multimodal regions would have highly similar representations between subjects that received the stimuli in the same modalities but different functional profile between subjects that received the stimuli in different modalities. Relying on this *a priori* (see figure 2.5–SI), we computed further analyses comparing directly the neural DSMs between subjects and groups.

To examine the commonalities of the neural representational space across subjects in the same group, we extracted the neural DSM from the rpMTG of every subject individually and then correlated it with the averaged neural DSM from all the other subjects from the same group (Op de Beeck et al., 2008; Bracci and Beeck, 2016, see figure 2.1D left panel). Crucially for the purpose of our experiment, we explored the commonalities of the neural representational space across the 3 groups (Deen et al., 2017). For each possible group pair (i.e. SCa/Sv; SCa/EBa; SCv/EBa), we computed the correlation between the neural DSM of each individual from one group with the averaged neural DSM of the other group (see figure 2.1D right panel). We ran this analysis twice for each group pairwise, exchanging the averaged and non-averaged group. Since in the three pairwise we did not find any significant difference between the two analyses we will report only the results of one combination: averaged SCv/non-averaged EBa, averaged SCa/non-averaged SCv, averaged SCa/non-averaged EBa. The significance of the intra and inter-groups correlations against zero were determined using permutation tests (100.000 iterations), building a null distribution for these values by computing them after randomly shuffling the labels of the RDMs conditions. The p values are reported after false discovery rate (FDR) correction (Benjamini and Hochberg, 2001). Moreover, to look at the differences between all the possible intra- and inter-group correlations we used a one-way ANOVA with the 6 group combinations as independent variable.

Analyses in VOTC regions of interest (ROIs)

We also ran further analyses in VOTC regions well known to show high selective preference for a specific category in the visual modality: the lateral occipital complex (LOC) typically showing response preference to objects; the fusiform face area (FFA) typically showing response preference to faces, and the parahippocampal place area (PPA) typically showing response preference to places or big non manipulable objects. We used six masks (i.e. left and right LOC, FFA, PPA) functionally defined from an independent study that identified the major face-, scene-, and object-selective regions in the ventral visual pathway (Kanwisher, 2010) in a relatively large group of subjects (n=30) (Julian et al., 2012; http://web.mit.edu/bcs/nklab/GSS.shtml). This procedure guarantees full independency between our data, in the 3 separate groups, and the definition of the ROIs.

In each group and for each region we extracted the 400 most discriminative voxels according to our 8 categories (De Martino et al., 2008; Mitchell and Wang, 2007) and we run MVPA on this subset of voxels using the same parameters described for the searchlight MVPA approach. Since in the case of ROIs the computational load is lower compared to the searchlight approach we implemented the support vector machine (SVM) as classifier. We repeated the same analyses using LDA as classifier for consistencies with the whole-brain searchlight approach and observed similar results (see figure 2.6–SI). For the group-level analyses, significances within group were determined using permutation tests (100000 iterations), building a null distribution for these values by computing them after randomly shuffling the labels of the stimuli. The p values are reported after false discovery rate (FDR) correction.

We wanted to investigate if the categorical representation of the stimuli present in these ROIs in the visual modality was maintained also when the stimuli where presented in the auditory modality in the SCa and in the EBa groups. To test this possibility, we extracted, in each region separately, the mean DSM from the SCv group and we correlated it with the DSM extracted from the same region in each subject in the auditory experiment. In other words, we used the visual DSM of one region to test how similar is the categorical representation of this region between vision and audition in sighted and in blind individuals. In this way, we obtained for every subject in the auditory experiment, and for each ROI, a correlation value with the visual model from the same ROI. For the group-level analyses, significances within group were determined using permutation tests (100000 iterations), building a null distribution for these values by computing them after randomly shuffling the labels of the stimuli and re-computing the neural DSMs in each iteration. The p values are reported after false discovery rate (FDR) correction. We then entered these values in an ANOVA with two within-subject factors: Region (LOC, FFA, PPA) and Side (left and right) and with Group (SCa and EBa) as between-subjects factor.

Since left LOC, left FFA and left PPA showed significant decoding accuracy in both modalities (visual and auditory) and significant correlation with the SCv DSM in both SCa and EBa we also performed, only in these ROIs, the cross-RSA analysis as described above (see figure 2.1D).

2.4 Results

2.4.1 Behavioural ratings results

We asked our participants to rate from 1 to 7 each possible pair of stimuli in the experiment they took part in (either visual or acoustic) and we built three dissimilarity matrices based on their judgments. A visual exploration of the ratings using the multidimensional scaling visualization (Edelman, 1998) revealed a clustering of the stimuli into 4 main classes: (1) Humans; (2) Animals; (3) Big Environmental; (4) Big mechanical and Manipulable (see figure 2.2). The three DSMs were highly correlated between them (SCa/EBa: r= .87, $p<0.001$; SC-A/SC-V: r= .88, $p<0.001$; EB-A/SC-V: r=.84, $p<0.001$) revealing similar way to group the stimuli across the three groups following mostly a categorical strategy to classify the stimuli (see figure 2.2). Based on this observation we used the behavioural matrices as a categorical/high-level model to contrast with the low-level models built on the physical properties of the stimuli (gist and pitch models).

2.4.2 Whole–brain searchlight analyses

MVPA.

Figures 2.3A and 2.3B show the results from the searchlight MVPA decoding in the three groups. An extended portion of the temporal cortex showed a significant above-chance decoding in the SCa group, while the occipital cortex, from the primary region until ventro-temporal regions, showed significant decoding in the SCv group. In the EBa group the regions showing a significant decoding included the temporal cortex, similar to the SCa, but also extended more posteriorly in occipital cortex. Figure 2.3C represents the results from the conjunction analysis between the three groups. The only region showing a significant decoding in all groups is located in the right posterior middle temporal gyrus (rpMTG, peak in the MNI coordinates: x= 60, y= -42, z= 6).

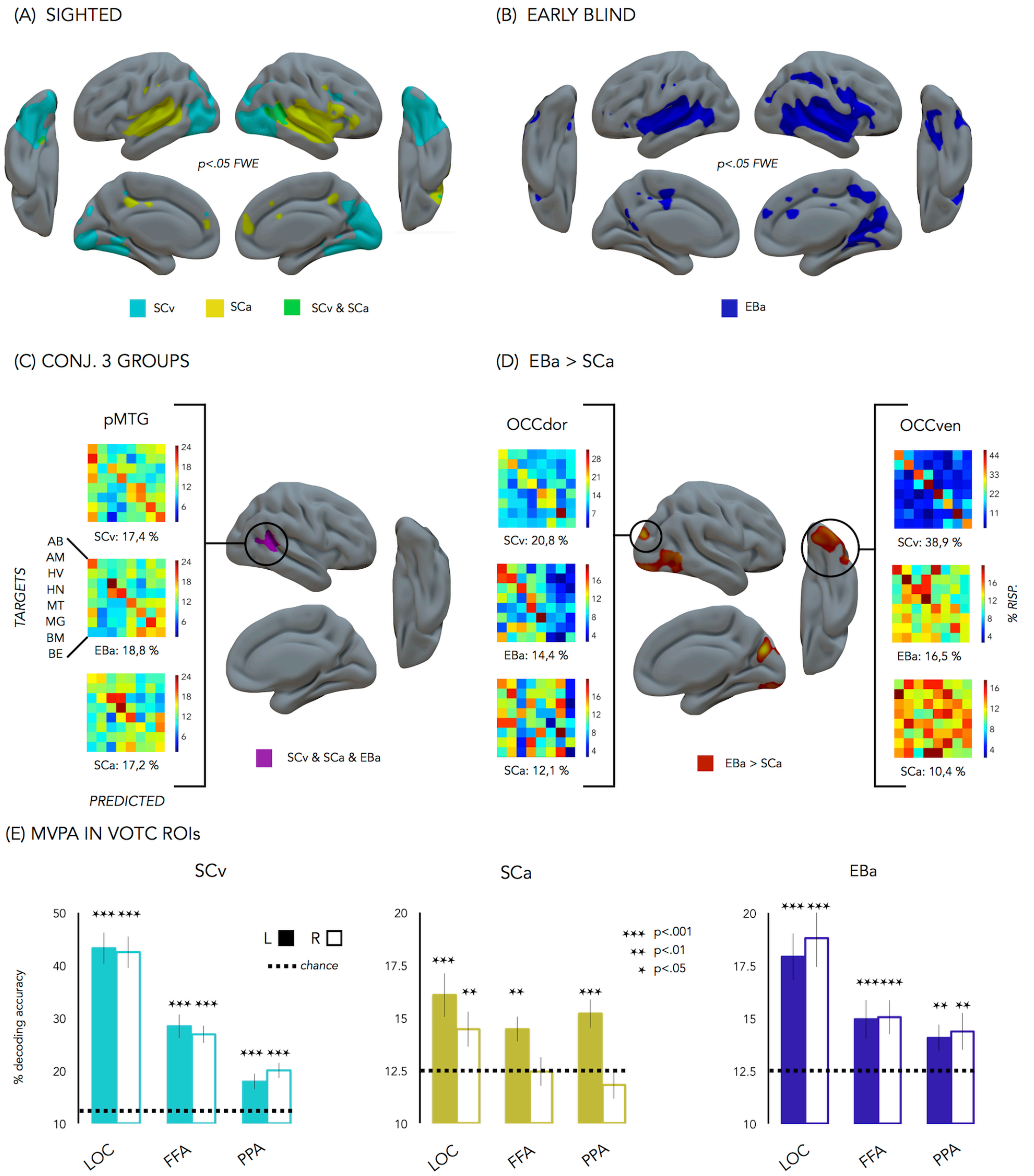


Figure 2.3: MVPA results. (A) MVPA searchlight results in the two groups of sighted: SC in vision (SCv, turquoise), SC in audition (SCa, yellow) and the overlap between the two groups (green). (B) MVPA searchlight results in early blind in audition (EBa). (C) Conjunction between the 3 groups and representation of the confusion matrix only for illustrative purpose (chance level is at 12.5%); *p <0.05 FEW corrected* (D) Contrast between EBa and SCs in the auditory experiment and representation of the confusion matrix only for illustrative purpose (chance level is at 12.5%); *p<0.05 TFCE-FWE corrected*; (E) MVPA results from 6 ROIs (left & right LOC, FFA and PPA) in SCv (turquoise), in SCa (yellow) and in EBa (blue). Full bars represent the left side (L) and empty bars represent the right side (R). The dashed lines represent the chance level of 12.5%. Error bars indicate SEM.

When directly contrasting the 2 groups (EBa>SCa, see figure 2.3D) we observed enhanced categorical decoding in the EBa group over an extended part of the occipital cortex, divided into two large clusters: one more dorsal centred on cuneus (rOCC-dorsal, 591 voxels, peak in the MNI coordinates: x = 8, y = -78, z = 24) and one more ventral including portions of the lingual gyrus, the posterior fusiform gyrus and the inferior occipital cortex (rOCC-ventral, 989 voxels, peak in the MNI coordinates: x = 14, y = -84, z = 20).

RSA with external models.

In order to better understand the representational content in rpMTG, we computed second order partial correlations between rpMTG DSM and the external models (i.e. behavioural & physical DSMs) for each participant. Figure 2.4A represents the results for the correlation between the rpMTG DSMs in the 3 groups and the DSMs external models (i.e. behavioural, pitch and GIST DSMs). As a reminder (see methods), all p values reported below are FDR corrected. The permutation test revealed that the neural similarity patterns in the ROIs was significantly correlated with the behavioural DSMs in the three groups: SCv (r=0.12; *p<0.001*), SCa r=0.09; *p<0.001*) and EBa (r=0.08; *p<0.001*). Instead, the correlation with the physical DSM was not significant in SCv (r=0.02, *p=0.11*) and in SCa (r=-0.003, *p=0.68*) group, but was significant in the EBa group (r=0.03, *p=0.02*). A 2X3 ANOVA with Feature (behavioural, physical) as within factor and Group (SCv, EBa, SCa) as between factors showed a significant main effect of feature ($F_{(1,47)}$= 15,41; *p<.001*) showing a significantly more behavioural than physical information in rpMTG. Neither the main effect of Group ($F_{(2,47)}$= 0.69; *p=0.51*) nor the interaction Feature*Group ($F_{(2,47)}$= 1,14; *p=0.33*) were significant.

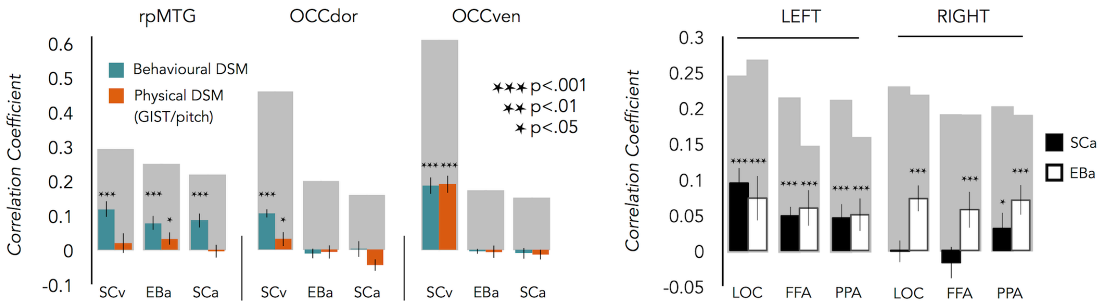
We applied exactly the same procedure to the rOCC-dorsal and the rOCC-ventral ROIs coming from the EBa>SCa contrast. Figure 2.4A represents the results from the three groups for the two ROIs. The permutation test in SCa and EBa groups revealed that the neural similarity patterns in both ROIs were not significantly correlated neither with the behavioural DSMs (rOCC-dorsal: SCa: r=0.002; EBa:

r=0.004; rOCC-ventral: SCa: r=-0.005, EBa: r=-0.002) nor with the pitch DSM DSMs (rOCC-dorsal: SCa: r=–0.023, EBa: r=–0.002; OCC-ventral: SCa: r=-0.007, EBa: r=0.002). The permutation test in the SCv group revealed, instead, a significant correlation between the behavioural DSM with both the neural rOCC-dorsal DSM (*r*=0.11; *p<0.001*) and the neural rOCC-ventral DSM (*r*=.19; *p<0.001)*. In the SCv group we also found a significant correlation between the GIST DSM and both the neural rOCC-dorsal DSM (r=0.03; *p=0.04*) and the neural rOCC-ventral DSM (*r*=0.19; *p<0.001*).

We also ran an ANOVA including as within factors the Region (rOCC-dorsal, rOCC-ventral) and the features (behavioural, pitch) and as between factor the Group (SCv, SCa, EBa). We found significant main effect of Region ($F_{(1,47)}$=29.39; *p<0.001*) disclosing enhanced correlation between the external models and the rOCC-ventral compare to the rOCC-dorsal and a main effect of Group ($F_{(2,47)}$=75.7; *p<0.001*). The Bonferroni post hoc analysis revealed that the correlation was significantly higher in the SCv group compared to both the EBa (*p<0.001*) and the SCa (*p<0.001*) groups.

CrossRSA.

The current results show commonalities in the neural representational space of rpMTG across participants belonging to the same group (intra-group correlation) and across participants belonging to different groups (inter-group correlation, see figure 2.4C). The permutation test revealed a significant intra-group correlation for all the three groups: SCv-SCv (*r*=0.29; *p<0.001*); EBa-EBa (*r*=0.25; *p<0.001*); SCa-SCa (*r*=0.22; *p<0.001*) showing commonalities in the way different person of a same group represent the stimuli space. The inter-group correlation was also significant for two combinations: SCa-EBa (*r*=0.24; *p<0.001*) and SCv-EBa (*r*=0.08; *p<0.001*). Only the inter-group correlation between SCa and SCv did not show a significant effect (*r*=0.01; *p=0.32*). We also run a One-Way Anova with Group Combination (i.e. SCv-SCv, EBa-EBa, SCa-SCa, SCv-EBa, SCa-SCv, SCa-EBa) as independent factor to check for significant differences across the group pairs. The Anova showed a significant effect of the Group Combination ($F_{(5,94)}$ =19.74; *p<0.001*). A Bonferroni post-hoc analysis revealed significantly higher correlation between all the three intra-group combinations compared to the correlation between the two audio-visual combinations: SCv-EBa and SCa-SCv. Also, the inter-group combination SCa-EBa showed a significantly higher correlation compare to the same two audio-visual combinations (SCv-EBa and SCa-SCv).



(A) RSA with EXTERNAL MODELS

(B) RSA with DSMs from the VISUAL EXPERIMENT

(C) CROSS-RSA

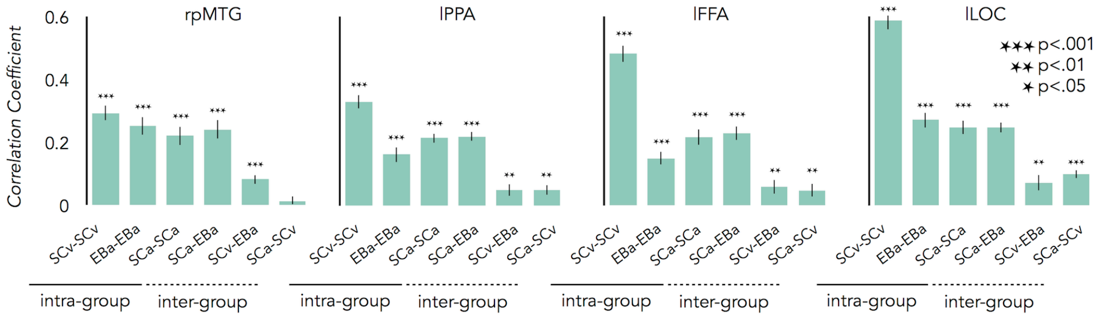


Figure 2.4: **RSA results.** (A) Cassical RSA results in the 3 clusters emerged from the searchlight analysis: pMTG, Occipital dorsal and Occipital ventral. Correlation between neural DSMs and behavioural DSMs are in green and correlation between neural DSMs and physical DSMs (pitch for auditory exp./gist for visual exp.) are in orange. For each ROI, the grey background bar represents the reliability of the correlational patterns in each ROI, which provides an approximate upper bound of the observable correlations between external models and neural data (Op de Beeck et al., 2008; Bracci and Beeck, 2016). Error bars indicate SEM. (B) Correlation between the neural DSM in the auditory experiment in the 2 groups (sihetd and blind) with the DSM from the same area in the visual experiment. (C) CrossRSA: for each ROI the first 3 columns represent the within group correlation and the last three columns represent the between group correlation.

2.4.3 VOTC regions of interest (ROIs)

MVPA

Figure 2.3E represents the results for the decoding accuracy in the SCa and EBa groups in the different ROIs. For each of the 6 ROIs (right and left LOC, FFA, PPA) and for both groups, we ran a permutation test. In the SCa group the decoding accuracy (DA) was significant in left LOC (DA=16%; $p<0.001$), in left FFA (DA=14%; $p=0.004$), in left PPA (DA=15%; $p<0.001$) and in right LOC (DA= 14%; $p=0.004$). In the EBa group the decoding accuracy was significant in left and right LOC (respectively DA=18%; $p<0.001$ and DA=19%; $p<0.001$), left and right FFA (respectively DA=15%; $p<0.001$ and DA=15%; $p<0.001$) and left and right PPA (respectively DA=14%; $p=0.01$ and DA=14%; $p=0.004$). Then we entered the decoding accuracy values from the VOTC ROIs in a repeated measure Anova with two within-subject factors: Region (LOC, FFA, PPA) and Side (left and right) and Group (SCa and EBa) as between-subjects factor. The results disclosed a significant main effect of Region ($F_{(2,62)}$= 12,32; $p<0.001$) showing that overall the decoding accuracy in LOC was higher compared to both FFA ($t_{(31)}$=3.4; $p<.001$) and PPA ($t_{(31)}$=4.55; $p<.001$). There was also a main effect of Group ($F_{(1,31)}$=6.76; $p=0.01$) showing an overall enhanced decoding accuracy in EBa compared to SCa. Moreover we found a significant main effect of side ($F_{(1,31)}$=7.17; $p=0.01$) disclosing a general significantly higher decoding accuracy in the left compare to the right side. Importantly, the interaction Side*Group was significant ($F_{(1,31)}$=15.2; $p<0.001$). Post-hoc analyses revealed that the decoding accuracy between the two groups did not significantly differ in the left hemisphere ($t_{(31)}$=0.53; $p=0.6$) but was significantly higher in the right hemisphere in EBa when compared to SCa group ($t_{(31)}$= 3.96; $p<0.001$). Moreover, the difference between the decoding accuracy in left and the right side was not significant within the EBa group ($t_{(15)}$= –0.9: $p=0.38$), but was significant within the SCa group ($t_{(16)}$= 4.5; $p<0.001$).

RSA

Figure 4B represents the results for the RSA correlation between the SCv DSM and each ROI brain DSM in the SCa and EBa groups. For each of the 6 ROIs (right and left LOC, FFA, PPA) and for both groups, we run a permutation test to look at the significance within group. In the SCa group the correlation was significantly different from zero in left LOC (r=0.09; *p<0.001*), in left FFA (r=0.05; *p<0.001*), left PPA (r=0.05; *p<0.001*) and to a lesser extend also in right PPA (r=0.03; *p=0.02*). In the EBa group the correlation significantly differed from zero in all regions: in left LOC (r=0.07; *p<0.001*), right LOC (r=0.07; *p<0.001*), left FFA (r=0.06; *p<0.001*), right FFA (r=0.06; *p<0.001*), left PPA (r=0.05; *p<0.001*) and right PPA (r=0.07; *p<0.001*). Then we entered the correlation values from the VOTC ROIs in a 3(Regions) X 2(Sides) X 2(Groups) ANOVA. The results showed a significant main effect of Side ($F_{(1,32)}$=8.36; *p=0.007*) explained by an enhanced correlation in the left compare to the right hemisphere and a significant interaction of Region*Side ($F_{(2,64)}$=4.17; *p=0.02*) and Side*Group ($F_{(1,32)}$=12.68; *p=0.001*) with a significantly enhanced correlation in the right hemisphere in the EBa compare to the SCa group.

crossRSA

Since only left LOC, left FFA and left PPA were able to decode our eight categories in the three groups and their stimuli representation in audition (in both EBa and SCa) showed a significant correlation with the representation in vision, we ran the crossRSA analyses to further investigate the possible amodal/multimodal nature of these regions. We tested in each of these regions the correlation values from each possible combination of group pairs (i.e. SCv-SCv, EBa-EBa, SCa-SCa, SCv-EBa, SCa-SCv, SCa-EBa) against zero using a permutation test (see figure 2.4C).

In left LOC the intra-group correlation was significantly different from zero for all the three groups: SCv-SCv (*r*=0.59; *p<0.001*); EBa-EBa (*r*=0.27; *p<0.001*); SCa-SCa (*r*=0.25; *p<0.001*) and the inter-groups correlation was significantly different from zero for all the three combinations: SCa-EBa (*r*=0.26; *p<0.001*), SCv-EBa (*r*=0.07; *p*= 0.009) and SCv-SCa (*r*=0.16; *p*<0.001). The one-Way Anova with Group

Combination (i.e. SCv-SCv, EBa-EBa, SCa-SCa, SCv-EBa, SCa-SCv, SCa-EBa) as independent factor showed a significant effect of the Group Combination ($F_{(5,94)}=68.73$; *p<0.001*). The Bonferroni post-hoc analysis revealed a higher correlation between the intra group correlation SCv-SCv and all the others (p<0.001 for all). There was also a higher correlation in the EBa-EBa and SCa-SCa intra-group combinations compared to the correlation between the two audio-visual combinations: SCv-EBa and SCa-SCv (*p<0.001* in all cases). Finally, the inter-group combination SCa-EBa showed a significantly higher correlation compare to the same two audio-visual combinations: SCv-EBa (*p<0.001*) and SCa-SCv (*p=0.03*).

In the left FFA the intra-group correlation was significantly different from zero for all the three groups: SCv-SCv (*r*=0.48; *p<0.001*); EBa-EBa (*r*=0.15; *p<0.001*); SCa-SCa (*r*=0.21; *p<0.001*) and the inter-groups correlation was significantly different from zero for all the three combinations: SCa-EBa (*r*=0.23; *p<0.001*), SCv-EBa (*r*=0.17; *p<0.001* and SCv-SCa (*r*=0.07; *p<0.001*). The one-Way Anova with Group Combination (i.e. SCv-SCv, EBa-EBa, SCa-SCa, SCv-EBa, SCa-SCv, SCa-EBa) as independent factor showed a significant effect of the Group Combination ($F_{(5,94)}=48.24$; p<0.001). The Bonferroni post-hoc analysis revealed a higher correlation between the intra group correlation SCv-SCv and all the others (*p<0.001* for all). There was also a higher correlation in the SCa-SCa intra-group combinations compared to the correlation between the two audio-visual combinations: SCv-EBa and SCa-SCv (*p<0.001* in both cases). While the intra-group correlation in the EBa-EBa was significantly higher than the correlation of the audio-visual combination SCa-SCv (*p=0.02*) Finally, the inter-group combination SCa-EBa showed a significantly higher correlation compare to the same two audio-visual combinations: SCv-EBa (*p<0.001*) and SCa-SCv (*p<0.001*).

In left PPA the intra-group correlation was significantly different from zero for all the three groups: SCv-SCv (*r*=0.33; *p<0.001*); EBa-EBa (*r*=0.16; *p<0.001*); SCa-SCa (*r*=0.21; *p<0.001*) and the inter-groups correlation was significantly different from zero for all the three combinations: SCa-EBa (*r*=0.2; *p<0.001*), SCv-EBa (*r*=0.05; *p=0.013*) and SCv-SCa (*r*=0.06; *p=0.002*). We also run a One-Way Anova with Group Combination (i.e. SCv-SCv, EBa-EBa, SCa-SCa, SCv-EBa, SCa-SCv, SCa-EBa) as independent factor and observed a significant effect of the Group Combination ($F_{(5,94)}=33.87$; *p<0.001*). Bonferroni post-hoc analysis revealed a higher correlation between the intra group correlation SCv-SCv and all the other combinations (*p<0.001* for all) and also a significantly lower correlation in the two audio-visual combinations (SCv-EBa, SCa-SCv) with all the other groups' combinations (*p<0.001* for all).

2.5 Discussion

In this study, we investigated how sensory input and visual experience shape the way the brain implements perceptual categorization. Our objectives were twofold: (1) finding which regions contain categorical information in both vision and audition and investigate if they do so using a format that is independent, or not, from input modality and visual experience; and (2) tackle how early-acquired blindness modulate the response properties of the occipital cortex to auditory categories and how occipital reorganization in the EB links to coding properties found in sighted individuals.

We found that the right pMTG (see figure 2.3A) is the region that most reliably decodes the eight presented categories independently of the input modality (in vision and audition in the sighted) and visual experience (in audition in the blind). These results are consistent with previous researches showing that pMTG is involved in the categorical processing of stimuli from multiple modalities (for univariate fMRI analyses: Beauchamp et al., 2004; Taylor et al., 2006; Thierry and Price, 2006; Thierry et al., 2003; for multivariate fMRI analyses: Devereux et al., 2013; Fairhall and Caramazza, 2013; Ricciardi et al., 2013). Our results extend these findings by detailing that rpMTG more specifically encode information related to the categorical properties significantly more than the physical features of our stimuli space, across the senses and similarly in blind and sighted people (see figure 2.4A left panel).

Do these results demonstrate that rpMTG is independent (Ricciardi et al., 2013) or immune (Mahon and Caramazza, 2009) to sensory experience or input? To define a brain region as amodal or abstracted from sensory input, we need to rule out the possibility that the region encodes information from separate modalities while keeping segregated format for each modality (see figure 2.5–SI). Using a multivariate approach that we called cross-RSA (see figure 2.1D), we first observed that the representation of our stimuli space was reliable across subjects from the same group. This finding is in support of a recruitment of pMTG for processing similar features of the stimuli within each modality and group (i.e. in sighted in visual, in sighted in audition and in blind in audition). Moreover, while the RDMs were significantly correlated between early blind and sighted in audition, the RDMs did not correlate across groups perceiving our stimuli from different modalities (see figure 2.4C left panel). These findings suggest that rpMTG maintains a modality-specific format of representation, supporting a multimodal rather than amodal nature of this region. This observation is in direct contrast with the predictions made by theories assuming that pMTG contains abstract representation of categorical knowledge (Fairhall and Caramazza, 2013; Ricciardi et al., 2013), while confirming that this region plays a role in coding categorical knowledge across the senses.

Similar conclusions were obtained in a paper exploring the representational format of pMTG using only visual material in sighted (Devereux et al., 2013). The authors presented object categories using pictures and written words and found that while the left pMTG contains categorical representation of the stimuli in both formats, it does not cluster them together, suggesting that the representational format of this region is material-dependent. Interestingly, our study highlighted that the right, but not the left, pMTG contains categorical information across groups and modalities. Actually, most of the previous studies showing that the left pMTG supports categorical representation included lexical stimuli (Devereux et al., 2013; Fairhall and Caramazza, 2013; Humphries et al., 2001; Thierry and Price, 2006; Thierry et al., 2003), whereas the conjunction of multiple, non-linguistic, modalities engages a bilateral (Beauchamp et al., 2004) or, more often, a right lateralized network (Jung et al., 2017; Man et al., 2012; Thierry and Price, 2006; for a review see Gainotti, 2014). Our results therefore support an involvement of the rpMTG in the representation of semantic concepts presented through sensory stimuli (in contrast of words) and revealed that the rpMTG represents categorical information in a modality-dependent fashion.

Interestingly, while rpMTG keeps separate the representations of concepts extracted from different sensory modalities, the auditory representation did not significantly differ between sighted and blind in audition. However, it is important to note that the representation of EB shows also a significant shared similarity with the representation of SC in vision (see figure 2.4C and figure 2.7–SI). These results are in line with the idea of segregate visual and auditory representations in rpMTG where, in the case of early blindness, we can observe a trace of crossmodal plasticity. In EB group, indeed, rpMTG might maintain its auditory representation stable while the visual representation could convert toward non-visual modality increasing the similarity of EBa and SCv representations.

We found that an extended portion of the right occipital cortex (including the cuneus, the lingual gyrus, the posterior fusiform gyrus and the inferior occipital cortex) showed higher categorical decoding of our auditory stimuli in early blind when compared to sighted individuals (see figure 2.3D). These results strongly support the idea that the enhanced auditory responses typically observed in the occipital cortex of EB are not an epiphenomenal byproduct of undifferentiated responses to any kind of non-visual stimuli, but, in stark contrast, that crossmodal plasticity triggers in these regions a reliable neural signature that can differentiate distinct auditory categories (Dormal et al., 2017). By zooming into independently and functionally defined portions of VOTC known to be highly selective for specific categories of visual stimuli (LOC, FFA and PPA bilaterally), we confirm the enhanced decoding in the blind compared to the sighted, especially in the right-sided ROIs (see figure 2.3E). One crucial interrogation arising from those previous observations is how the representational format of the auditory stimuli in these regions relates to the native representational format displayed for visual stimulation in sighted individuals. In order to address this question, we correlated the mean brain RDMs elicited by auditory stimuli in the SCa and EBa groups to the RDMs elicited by the visual stimuli in the SCv group. We observed significant correlations in all ROIs bilaterally in the EBa, while correlations were significant only in the left-sided ROIs in the SCa group (see figure 2.4B). These results suggest that the right VOTC is a sensory-related visual region that in the case of early visual deprivation rewires itself towards non-visual modality, but continues to link to the original functional architecture of those regions (Dormal and Collignon, 2011). In contrast, the left VOTC shows a different functional profile compared to its right counterpart. In SCa group all the left ROIs showed a significant decoding accuracy, meaning that also in the sighted these regions were able to distinguish the 8 categories presented acoustically. Moreover, in SCa, the decoding accuracy in the left ROIs were significantly higher than the one in the right side; and only in the left-sided ROIs the representational geometry elicited by acoustical stimuli correlated with the visual geometry in sighted.

Like we did for pMTG, we then asked whether these results mean that the nature of the left VOTC is modality-independent. Several studies, indeed, showed that the functional and connectivity profile of VOTC during the processing of different categories was highly similar between sighted in multiple modalities and also between blind and sighted (Amedi et al., 2002; Hurk et al., 2017; Pietrini et al., 2004; Wang et al., 2015).

Similar to those studies, we found a correlation between the visual and the auditory representations (i.e. neural dissimilarity matrices from the sighted group that underwent the visual experiment and the neural dissimilarity matrices from the sighted group that underwent the auditory experiments) in left LOC, left FFA and left PPA in the sighted. However, we also showed that the correlation of the stimuli representations within modality was significantly higher than correlations across the different modalities (see figure 2.4C), arguing against the sensory-abstracted nature of these regions.

Moreover, we showed that in all the ROIs in VOTC the visual representation in sighted and the auditory representation in blind do share information.

In summary, we observed that in sighted, decoding of auditory categories and the correlation between auditory and visual RDMs was stronger in the left than in the right hemisphere. Moreover, when compared to blind individuals who showed a more homogeneous response profile bilaterally, differences of decoding and correlations between auditory and visual RDMs were significantly higher only in the right hemisphere for the EBa vs SCa. These results suggest that the right hemisphere reorganizes itself in EB due to crossmodal plasticity and, importantly, its reorganization keeps relation with the native computational framework of this region but in a more sensory-based fashion compared to the left counterpart. In fact, visual deprivation seems to impact less in the processing of auditory categories in the left VOTC ROIs showing a similar functional profile in both EBa and SCa.

What might drive these different functional profiles of the right and the left VOTC? This hemispheric division of computational labor is reminiscent of what has been argued for the processing of semantic information in the anterior temporal lobe. Indeed some authors have proposed that the right ATL might be more involved in sensory-related processing, while the left ATL might be more involved in linguistic treatment (Gainotti, 2014; Humphries et al., 2001; Thierry and Price, 2006; Thierry et al., 2003). Based on our results, we suggest that a similar hemispheric subdivision could take place not only in high-associative regions like ATL but also in sensory-related regions, such as the ventral visual stream. In this case, the right VOTC would mostly be a sensory-related region (visual in sighted, reorganized toward non-visual modalities in the case of early blindness) while the left VOTC would not only represent visual information, but also represent more linguistic/semantic features of the stimuli in the sighted and the blind.

Such hemispheric differences in the representational format of VOTC may rely on distinct connectivity profiles between left and right VOTC (see Gainotti, 2017; Lambon Ralph, 2014 for similar reasoning with ATL). In this regard, a hallmark of the functional organization of VOTC regions is the presence of the visual word form area (VWFA) in the left hemisphere. This region shows a selective preference for written words compare to other symbolic material (Cohen et al., 2000; Dehaene et al., 2002). Direct structural connectivity between the VWFA and perisylvian language areas supports the notion that this region is at the interface between the ventral visual recognition system and the language system (Bouhali et al., 2014). Therefore, we speculate that the presence of an intrinsic connectivity bias between the left VOTC and the language system could trigger a more general involvement of the left VOTC for the linguistic/semantic processing of any type of stimuli. Support for this hypothesis can be found in a number of studies that have reported, in the sighted, the recruitment of left VOTC in linguistic processing. For instance, the lingual gyrus activates during auditory speech processing (Boldt et al., 2013; Hasson et al., 2006) and few studies reported a linguistically/semantic role of the visual world form area that goes beyond the one restricted to orthographical and pre-lexical processing of visual words (Glezer et al., 2009; Price and Devlin, 2011).

Moreover, structural (Bouhali et al., 2014) and functional (Richardson et al., 2011) connectivity has been reported between the superior temporal sulcus and several VOTC regions. In the absence of competitive visual input since birth, it is therefore hypothesized that linguistic material will preferentially extend their representation precisely in those left-hemispheric regions where an inherent bias may exist. Indeed, several studies have shown that linguistic information was in most of the cases preferentially processed in the left hemisphere (Arnaud et al., 2013; Bedny et al., 2011; Röder et al., 2002). Also the specific recruitment of a region consistently overlapping with the sighted left VWFA (Reich et al., 2011) has been reported in the early blind when reading Braille words (Reich et al., 2011; Sadato et al., 1996; Saxe et al., 2017) or embossed letters (Burton et al., 2006; but see Bedny et al., 2017).

In summary, our findings support the view that the left VOTC may implement some level of linguistic computation in sighted and blind people, potentially based on the intrinsic connectivity of this region with language-related structure in the temporal and inferior frontal cortex. However, this does not mean that VOTC act as a sensory-abstracted operator since we observed that the neural representational geometry of the stimuli was segregated across sensory inputs/groups. Importantly, the dramatically higher decoding accuracies and within group consistency observed with visual stimuli clearly demonstrate that the primary role of this region is anyway visual.

2.6 Conclusion

In conclusion, our study showed that the right pMTG contains reliable information about different categories of acoustical and visual stimuli independently of the input modality (in vision and audition in the sighted) and visual experience (in audition in the sighted and blind). However, this region maintains separate the representational format from the different modalities, revealing a multimodal rather than an amodal nature. In addition, we observed that VOTC showed distinct functional profiles according to the hemispheric side: the right VOTC emerged as a sensory-related visual region in sighted with the ability to rewires itself toward acoustical stimulation, via crossmodal plasticity, in case of early visual deprivation. Instead, the left VOTC showed an involvement in the acoustical categorization processing at the same degree in sighted and in blind individuals. We propose that this involvement might reflect an engagement of the left VOTC in more semantic/linguistic processing of the stimuli potentially supported by its enhanced connection with the language system. However also in the case of left VOTC, the representations from different modalities are maintained segregate, showing no trace of sensory-abstraction even in these regions.

2.7 Supplemental information

Subjects	Age(y)	Sex	Residual visual perception	Onset	Cause of blindness
EB1	30	M	Diffuse light	0	Damage to the optic nerve
EB2	33	F	No	0	Congenital cataracts
EB3	29	F	Diffuse light	4	Retinopathy
EB4	67	M	No	0	Congenital glaucoma
EB5	39	M	Diffuse light	0	Retinopathy
EB6	26	M	No	3	Infection of the eyes
EB7	34	F	No	0	Microphtalmia
EB8	28	M	No	3	Retinopathy
EB9	29	F	Diffuse light	0	Retinopathy
EB10	43	M	No	0	Retinopathy
EB11	35	F	Diffuse light	0	Hypoxia
EB12	36	M	No	0	Hypoxia
EB13	27	F	Diffuse light	4	Retinopathy
EB14	29	F	Diffuse light	0	Retinopathy
EB15	20	F	No	0	Retinopathy
EB16	34	F	No	0	Hypoxia
EB17	27	F	No	0	Damage to the optic nerve

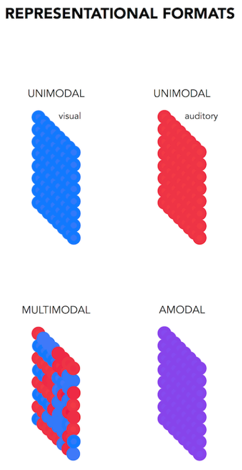
M,male; F, female

Table 2.1–SI : Characteristics of early blind participants.

CATEGORIES	STIMULI
BIRDS	Canary Owl Seagull
MAMMALS	Dog Donkey Horse
HUMAN VOCALIZATIONS*	Woman Man Man
HUMAN NON VOCALIZATIONS	Women laughing Man crying Women yawning
TOOLS	Hairdryer Saw Toothbrush
GRASPABLE OBJECTS	Guitar Keyboard Telephone
BIG MECHANICAL OBJECTS	Church-bell Traffic Train
ENVIRONMENTAL SCENES	Storm River Wind

*neutral faces in the visual experiment

Table 2.2 –SI: Categories and stimuli.



		MVPA			CLASSICAL RSA Categorical model			CROSS RSA						CROSS RSA
								Intra-groups			Inter-groups			
		SCv	SCa	EBa	SCv	SCa	EBa	SCv-SCv	SCa-SCa	EBa-EBa	SCv-SCa	SCv-EBa	EBa-SCa	Intra > Inter
PREDICTION	VISUAL	+	–	–/+	+	–	–/+	NA	NA	NA	NA	NA	NA	NA
	AUDITORY	–	+	+	–	+	+	NA	NA	NA	NA	NA	NA	NA
	MULTIMODAL	+	+	+	+	+	+	+	+	+	–/+	–/+/+	+	+
	AMODAL	+	+	+	+	+	+	+	+	+	+	+	+	–
RESULTS	right pMTG	+	+	+	+	+	+	+	+	+	–	+	+	+
	OccDorsal	+	–	+	+	–	–	NA	NA	NA	NA	NA	NA	NA
	OccVentral	+	–	+	+	–	–	NA	NA	NA	NA	NA	NA	NA
	left LOC	+	+	+	+	+	+	+	+	+	+	+	+	+
	right LOC	+	+	+	+	–	+	NA	NA	NA	NA	NA	NA	NA
	left FFA	+	+	+	+	+	+	+	+	+	+	+	+	+
	right FFA	+	–	+	+	–	+	NA	NA	NA	NA	NA	NA	NA
	left PPA	+	+	+	+	+	+	+	+	+	+	+	+	+
	right PPA	+	–	+	+	–	+	NA	NA	NA	NA	NA	NA	NA

* **SCv**: sighted controls – Visual exp.; **SCa**: sighted controls – Auditory exp.; **EBa**: early blind – Auditory exp.

* ***crossmodal plasticity in early blind***

Figure 2.5-SI: Predictions and results about the representational format of different ROIs. Since cross-RSA analyses are used to investigate the multimodal vs amodal nature of ROIs we considered successful decoding (MVPA) and significant correlation with categorical/high-level models (classical RSA) two prerequisites to perform crossRSA. NA=not applicable. + means significant results; – means not significant results.

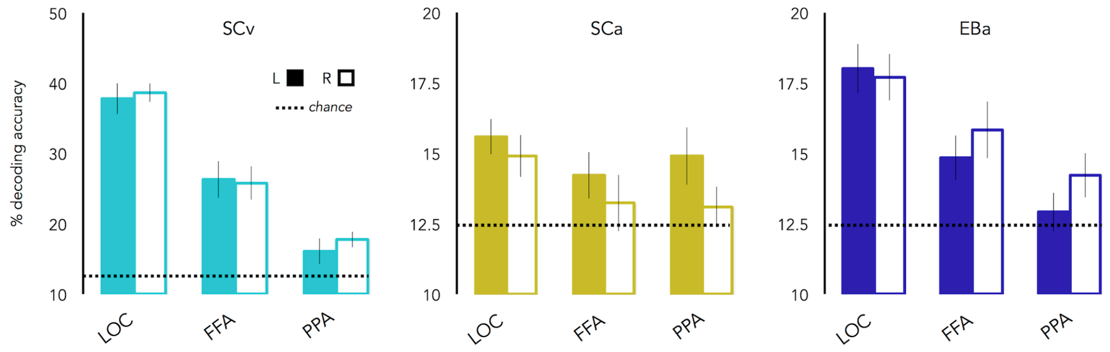


Figure 2.6-SI: MVPA results in ROIs using LDA classifier. MVPA results from 6 ROIs (left & right LOC, FFA and PPA) in SCv (turquoise), in SCa (yellow) and in EBa (blue). Full bars represent the left side (L) and empty bars represent the right side (R). The dashed lines represent the chance level of 12.5%. Error bars indicate SEM. The results are highly similar to the same analysis performed with SVM classifier.

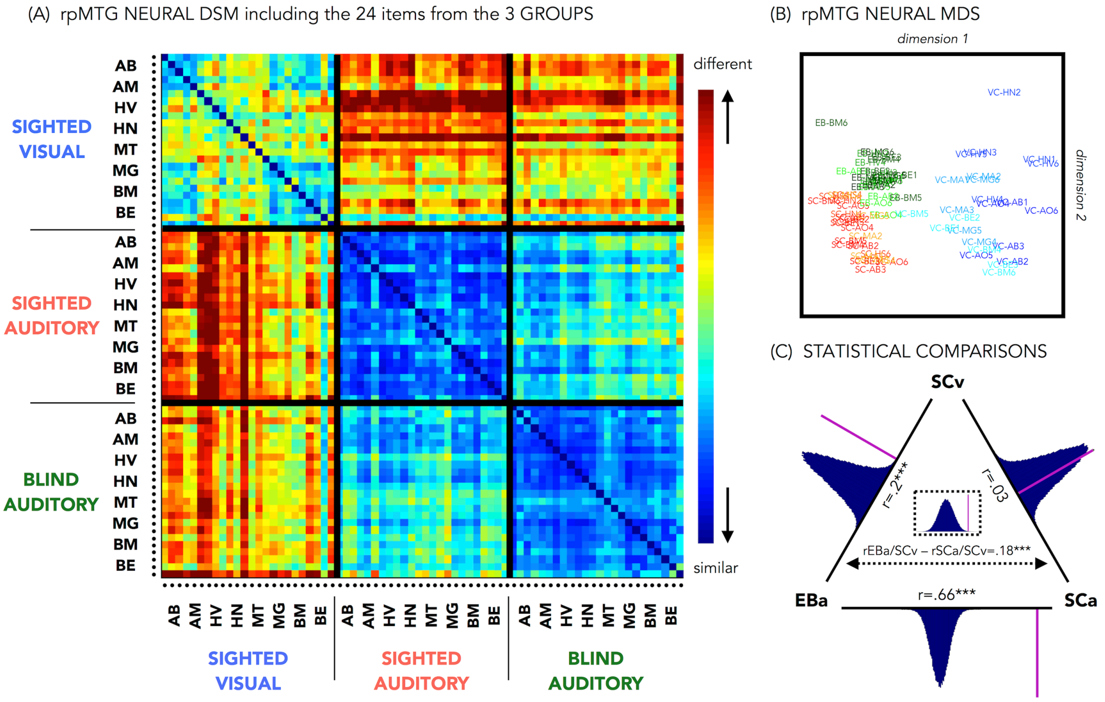


Figure 2.7-SI: Comparison of the mean pMTG neural DSMs from the 3 groups. (A) Neural dissimilarity matrix including participants from the 3 groups (SCv,SCa,EBa). The three main diagonal squares represent the correlation between subjects from the same group, the off diagonal squares represents correlation between subjects from different groups. (B) Representation of the same values using multi-dimensional scaling visualization. (C) Statistical comparisons using permutation test. To look at the significance of the correlation of the mean pMTG neural DSM between each pair of group we built a null distribution shuffling the labels of the stimuli, recomputing the DSMs and re-calculating the correlation between the DSMs for 100000 times. The pink bars represent the real correlation values. This analysis showed that the correlation between EBa and SCa (r=0.66; *p<.001*) and between EBa and SCv (r=0.2; *p<.001*) were significantly different from zero, whereas the correlation between the two groups of sighted in vision and audition was not significantly different from zero. We, finally, perform a further permutation analysis on the difference between the EBa/SCv and the SCv/SCa correlations showing that it is different: the correlation between EBa and SCv was significantly higher then the correlation between SCa and SCv (*p<.001*).

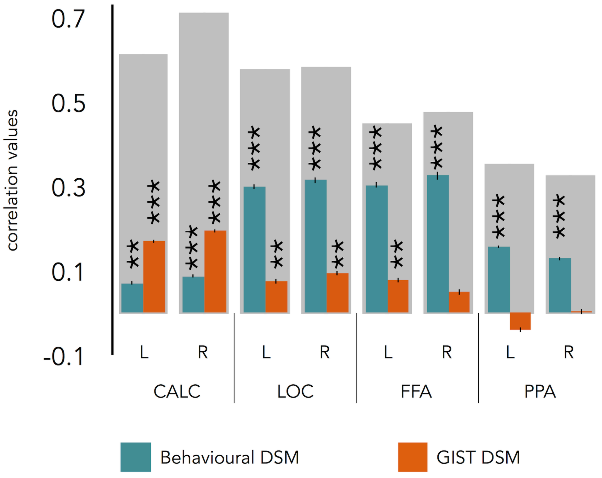


Figure 2.8-SI: RSA results with external models in Sighted Control-visual exp. (SCv) in the VOTC regions of interest. Classical RSA results in 6 ROIs: left & right LOC, FFA, PPA. Correlation between neural DSMs and behavioural DSMs are in green and correlation between neural DSMs and physical DSMs (gist model) are in orange. For each ROI, the grey background bar represents the reliability of the correlational patterns in each ROI, which provides an approximate upper bound of the observable correlations between external models and neural data (Bracci et al.,2016; Op de Beeck et al., 2008). Error bars indicate SEM.

3

THE BALANCED ACT OF CROSSMODAL AND INTRAMODAL PLASTICITY: ENHANCED REPRESENTATION OF AUDITORY CATEGORIES IN THE OCCIPITAL CORTEX OF EARLY BLIND PEOPLE LINKS TO REDUCED TEMPORAL CODING[3]

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[3] Paper in the final stage before submission

Mattioni, S., Rezk., Battal, C., Vadlamudi, J.,N.N., Collignon, O. (2017). ***The balanced act of crossmodal and intramodal plasticity: enhanced representation of auditory categories in the occipital cortex of early blind people links to reduced temporal coding***

3.1 Abstract

Early visual deprivation triggers enhanced representation of auditory information in the occipital cortex. How does this crossmodal plasticity mechanism impact on the temporal cortex that typically involves in similar auditory coding? To address this question, we used fMRI to characterize brain responses of early blind (EB) and sighted control (SC) individuals listening to sounds from four different categories (human, animal, objects and places). Multivariate pattern analysis was used to decode these four classes of stimuli into individually defined occipital and temporal anatomical parcels. We observed opposite effects of early visual deprivation on auditory decoding in occipital and temporal regions. While occipital regions contained more information about sound categories in the blind, the temporal cortex showed higher decoding in the sighted. Moreover, we observed a negative correlation between occipital and temporal decoding of sound categories in EB, suggesting that these intramodal and crossmodal reorganizations might be inter-connected. Interestingly, we found that this reorganization process mostly arises in the right hemisphere, which is also the most recruited during the task. We therefore suggest that the extension of non-visual functions in the occipital cortex of EB triggers a network-level reorganization that may reduce the computational load of the regions typically coding for the remaining senses.

3.2 Introduction

The enhanced involvement of the occipital cortex during tactile (Burton et al., 2002b; Pietrini et al., 2004; Sadato et al., 1996, 1998), auditory (Collignon et al., 2011; Poirier et al., 2006; De Volder et al., 2001), linguistic (Ackeren et al., 2017; Bedny et al., 2011; Röder et al., 2000) or memory (Amedi et al., 2003) tasks is probably the most ubiquitous consequence of early acquired blindness. This mechanism of crossmodal plasticity (CMP) is thought to be functionally relevant, and not a mere epiphenomenal consequence of sensory deprivation (Collignon et al., 2007). First, CMP may link to compensatory behaviours in the blind (Amedi et al., 2007; Gougoux et al., 2005). Second, disruption of occipital regions, either by brain lesion or by transient alteration of brain functions via transcranial magnetic stimulation, leads to disruption in non-visual behaviours (Cohen et al., 1999; Collignon et al., 2007, 2009b; Kupers et al., 2007). Finally, CMP is not a stochastic process but follows organizational principles known to be routed in the occipital cortex of sighted people (Dormal and Collignon, 2011).

Does the reorganization of the visual cortex occur together with changes in in brain regions coding for the remaining senses? As the brain is a highly interconnected organ, with specialized sensory systems continuously changing their interaction based on task demands (Jiang et al., 2004; Nair et al., 2014; Pelland et al., 2017), it is unlikely that early visual deprivation would affect exclusively the occipital cortex leaving the rest of the network unaffected. Little is known however about the impact of early blindness on the functioning of the remaining sensory systems.

Contradictory results emerged from previous literature about the way intra-modal plasticity in early blind people (EB) expresses. Studies on visually deprived animals suggested enhanced functional tuning of both somatosensory (Rauschecker and Tian, 1992; Rauschecker et al., 1997) and auditory (Meng et al., 2015; Petrus et al., 2014; Rauschecker and Harris, 1983; Wang et al., 2017) brain regions. A first generation of studies on blind humans similarly promoted the idea that visual deprivation elicits enhanced response and/or refined computation in the sensory cortices responsible for touch or audition (for a review on animals and humans see (Rauschecker, 2002). For example, a transcranial magnetic study on blind braille readers reported an expansion of the sensory-motor cortical representation of the reading finger (Pascual-leone and Torres, 1993). In the auditory domain, previous works showed lower auditory peak latency of event related potential recordings (Manjunath et al., 1998; Naveen et al., 1997, 1998; Röder et al., 2002), expanded tonotopic map in the core area of the temporal cortex (Elbert et al., 2002) and enhanced response to voices in the superior temporal sulcus (Fairhall et al., 2017; Gougoux et al., 2009) of blind people. In contrast to those results, several studies observed a decreased engagement of auditory or tactile sensory cortices during non-visual processing in early blind individuals (Bedny et al., 2015; Burton et al., 2002b; Dormal et al., 2016; Stevens and Weaver, 2009). An fMRI study showed lower somatosensory activation for tactile processing in blind compared to sighted individuals (Burton et al., 2002b). Similarly, lower signal volume was observed in the temporal cortex of early blind compared to sighted and late blind individuals for auditory processing (Stevens and Weaver, 2009). Moreover, a study focusing on morphological alterations in congenital blind reported an increased cortical thickness in visual regions of EB but a thinning in their somatosensory and auditory cortices compared to sighted controls (Park et al., 2009).

An intriguing possibility is that early visual deprivation triggers a redeployment mechanism that would reallocate part of the sensory processing typically tagging the preserved senses (i.e. the temporal cortex for the auditory stimulation) to the occipital cortex deprived of its most salient input. Two recent studies using auditory moving stimuli seem to bring partial support for this hypothesis (Dormal et al., 2016; Jiang et al., 2016). Using multivoxel pattern analysis (MVPA) they have shown that the ability to decode the different auditory motion stimuli was enhanced in hMT+ (a region typically involved in visual motion in sighted) of early blind while an enhanced decoding accuracy was observed in the sighted group in the planum temporale (Jiang et al., 2016; Dormal et al., 2016). In addition, early blind subjects, when compared to sighted controls, showed enhanced functional connectivity between the right planum temporale and the right occipito-temporal regions (Dormal et al., 2016).

However, whether such large-scale imbalance between occipital and temporal regions is specific to auditory motion processing or whether it reflects a more general mechanistic consequence of visual deprivation needs to be investigated. Moreover, whether the intramodal and crossmodal changes relate to each other remains unknown. In the present study, we presented natural sounds from different categories of stimuli (human, animal, object, places) in a group of sighted and early blind individuals. We relied on multivoxel pattern analyses (MVPA) to investigate the presence of auditory categorical information content in individually parcellated occipital and temporal brain regions. Moreover we employed representational similarity analysis (RSA) to observe the neural representations of our stimuli in the different parcels. Our idea was that the representation of the auditory stimuli would share enhanced similarity between occipital and temporal regions in EB compared to sighted controls. Our goal was to explore whether the functional reorganization following early blindness would manifest through both cross-modal and the intra-modal plasticity and, importantly, whether these two phenomenon would relate to each other.

3.3 Material and Methods

3.3.1 Participant

Thirty-four participants involved in our fMRI study: 17 early blinds (EB; 10F) and 17 sighted controls (SC; 6F). Blind participants were congenitally blind or lost their sight very early in life and all of them reported not having visual memories and never used vision functionally (table 1.1–SI). The two groups were age (range 20-67 years, mean ± SD: 33.29 ± 10.24 for EB subjects, range 23-63 years, mean ± SD: 34.12 ± 8.69 for SC subjects) and gender matched. One blind participant was able to only perform two out of the five runs of the experiment; for this reason, we excluded her from the analyses. All participants were blindfolded during the auditory task. Participants received a monetary compensation for their participation. The ethical committee of the University of Trento approved this study (protocol 2014-007) and participants gave their informed consent before participation.

3.3.2 Stimuli and Procedure

These two sections are similar to the ones of the study 1. Please refer to the paragraphs 2.3.2 and 2.3.3.

3.3.3 fMRI data acquisition and analyses

fMRI data acquisition and preprocessing

We acquired our data on a 4T Bruker Biospin MedSpec equipped with an eight-channel birdcage head coil. Functional images were acquired with a T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence (TR, 2000 ms; TE, 28 ms; flip angle, 73°; resolution, 3x3 mm; 30 transverses slices in interleaved ascending order; 3mm slice thickness; field of view (FoV) 192x192 mm2). The four initial scans were discarded to allow for steady-state magnetization. Before each EPI run, we performed an additional scan to measure the point-spread function (PSF) of the acquired sequence, including fat saturation, which served for distortion correction that is expected with high-field imaging.

A structural T1-weighted 3D magnetization prepared rapid gradient echo sequence was also acquired for each subject (MP-RAGE; voxel size 1x1x1 mm; GRAPPA acquisition with an acceleration factor of 2; TR 2700 ms; TE 4,18 ms; TI (inversion time) 1020 ms; FoV 256; 176 slices).

To correct for distortions in geometry and intensity in the EPI images, we applied distortion correction on the basis of the PSF data acquired before the EPI scans (Zeng and Constable, 2002). Raw functional images were pre-processed and analysed with SPM8 (Welcome Trust Centre for Neuroimaging London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm/) implemented in MATLAB (MathWorks). Pre-processing included slice-timing correction using the middle slice as reference, the application of temporally high-pass filtered at 128 Hz and motion correction.

Regions of interest

The anatomical scan was used to reconstruct the cortical surface of each hemisphere using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). The cortical anatomic segmentation was performed according to the Desikan-Killiany atlas (Desikan et al., 2006). We selected occipital and temporal ROIs having a size of at least 100 voxels (each voxel being 3mm isotropic) in each participant to obtain reliable decoding MVPA results (Norman et al., 2006).

Five ROIs were then selected in each hemisphere: Lateral Occipital, Lingual and Fusiform areas for the visual ROIs and the Middle Temporal and the Superior Temporal areas for the acoustical ROIs (see figure 3.1). Our strategy to work on a limited number of relatively large brain parcels has the advantage to minimise unstable decoding results collected from small regions (e.g. less than 100 voxels) and reduce multiple comparison problems intrinsic to neuroimaging studies (Etzel et al., 2013). All further analyses were carried out in subject space for enhanced anatomical precision and to avoid spatial normalization across subjects.

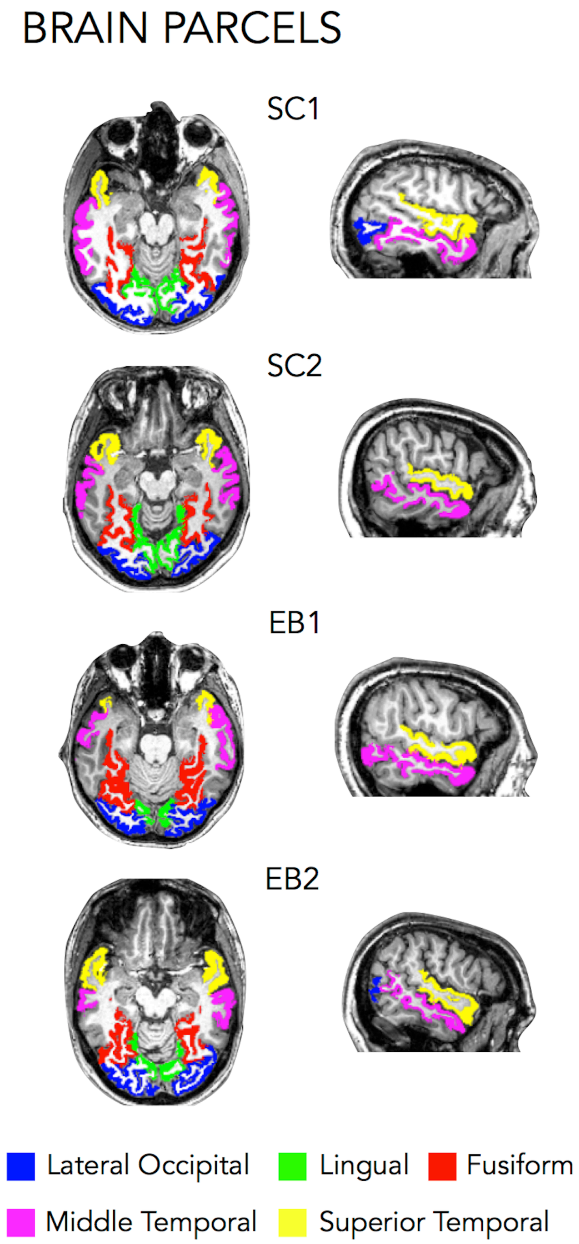

Figure 3.3.1: Example of brain parcels used as ROIs. Illustrative parcels in 2 sighted controls (SC) and in 2 early blind (EB) subject space. The parcels were obtained through the cortical anatomical segmentation implemented in FreeSurfer based on the Desikan-Killiany atlas.

General linear model

The pre-processed images for each participant were analysed using a general linear model (GLM). For each of the 5 runs we included 32 regressors: 24 regressors of interest (each stimulus), 1 regressor of no-interest for the target stimuli, 6 head-motion regressors of no-interest and 1 constant. From the GLM analysis we obtained a β-image for each stimulus (i.e. 24 sounds) in each run, for a total of 120 (24 x 5) beta maps.

Multivoxel pattern analysis (MVPA)

MVPA was performed using the CoSMoMVPA (Oosterhof et al., 2016) toolbox, implemented in Matlab (Mathworks). We tested the discriminability of patterns for the four categories using as classifier the Fisher linear discriminant (LDA; Hong and Santosa, 2016; Misaki et al., 2010). We performed a leave-one-run-out cross-validation procedure using beta-estimates from 4 runs in the training set, and the beta-estimates from the remaining independent run to test the classifier, with iterations across all possible training and test sets. This procedure was implemented in each ROI: we first extracted the 100 most discriminative voxels according to our 4 categories (De Martino et al., 2008; Mitchell and Wang, 2007) and we ran MVPA on this subset of voxels using the same parameters described above.

For each subject we averaged together the decoding accuracy values of the lateral occipital, the lingual and the fusiform cortices in order to have for each subject one value representing the mean occipital decoding and we averaged together the decoding accuracy values of the middle and superior temporal regions to obtain one value representing the temporal decoding (but see figure3.2 for results displayed separately for each ROI). We then entered these values in an ANOVA with two within-subject factors: Lobe (occipital and temporal) and Hemisphere (left and right) and with Group (SC and EB) as between-subjects factor.

Correlation analysis

Pearson's linear correlation coefficients were computed between the occipital decoding accuracy (averaging together occipito-lateral, fusiform and lingual ROIs) and the temporal decoding accuracy (averaging together middle and superior temporal ROIs). Significance was FDR corrected for these four correlations.

Representational similarity analysis (RSA) between ROIs

We used Representational Similarity Analyses in order to compare the representation of our stimuli set across different ROIs. This analysis allowed us to compare how similar were the representations of the auditory categories between *the occipital and the temporal parcels in the two groups. This analysis is based on the concept of dissimilarity matrix (DSM): a square matrix where the columns and rows correspond to the number of the conditions (24x24 in this experiment) and it is symmetrical about a diagonal of zeros. Each cell contains the dissimilarity index (= 1 – similarity) between two stimuli (Kriegeskorte and Kievit, 2013). First, we extracted the DSM (Kriegeskorte et al., 2008) in each ROI computing the dissimilarity between the spatial patterns of activity for each pair of stimuli. We extracted in every subject and in every ROI, the stimulus-specific BOLD estimates from the contrast images for all the 24 stimuli separately. We next computed all the pairwise correlations between them (using 1 – Pearson's correlation) in order to build the neural DSM for each ROI. Then, for each ROI we averaged the DSMs of the subject belonging to the same group. After this step, we obtained for each ROI the mean DSM for each group. Finally, for each group separately we computed the dissimilarity value between each pair of ROIs. We practically ran the same analysis of the first step but in this case, we used the ROIs in place of stimuli conditions (see figure 3.2A).*

We used multidimensional scaling (MDS) to visualize the dissimilarity structures between the ROIs (see figure 3.2C). MDS was performed using MATLAB function "mdscale".

To ran statistics about the differences between blind and sighted groups and to avoid the problem of multiple comparisons we averaged, in each subject, the DSMs in order to have only four main areas: left Occipital, right Occipital, left Temporal, right Temporal (see figure 3.2B). Then, for each possible pair of ROIs, significant differences between groups were determined using permutation tests (100000 iterations) building a null distribution based on t values computed after randomly shuffling the labels of the subjects from the two groups (see figure 3.2D). A significant result emerging for a pair of ROIs would mean that the neural representation of our stimuli in these two regions is more similar in one group compare to the other.

3.4 Results

3.4.1 MVPA results

MVPA results are represented in figure 3.2A.

The t test against the chance level (that for four categories is equal to 25%) revealed that the decoding accuracy was significantly different from the chance level in SC in the left temporal (33%, $p<0.001$) and right temporal (35%, $p<0.001$) ROIs. In the EB the decoding accuracy was significantly different from the chance level in all the four regions: left occipital (27%, $p=0.013$), right occipital (28%, $p<0.001$) left temporal (32%, $p<0.001$) and right temporal (33%, $p<0.001$). P values were FDR corrected for the 4 tests.

An ANOVA showed a significant main effect of Side ($F_{(1,31)}= 5.49$; $p=0.026$) with the right side decoding more than the left side and a significant main effect of Lobe ($F_{(1,31)}= 128.16$; $p<.001$) with the temporal cortex decoding more than the occipital region. Importantly there was also a significant effect of the interaction Lobe*Group ($F_{(1,31)}= 5.55$; $p=0.025$). This interaction reflected that overall the decoding accuracy in temporal regions was higher in SC than in EB, while the decoding accuracy was higher in EB than SC in occipital regions.

Correlation results

The correlation results are represented in figure 3.2C. In the sighted control group the decoding accuracy of the occipital ROIs showed a significant positive correlation with the decoding accuracy of the temporal cortex in the left side ($r=0.61$; $p=0.03$) but not in the right side ($r=0.18$; $p=0.48$). In the early blind group, there was no significant correlation between the decoding accuracy of the occipital regions and the decoding accuracy of the temporal cortex in the left side ($r=0.26$; $p=0.44$), whereas we observed a significant negative correlation in the right hemisphere ($r=-0.55$; $p=0.05$). P values were FDR corrected for the 4 correlation tests.

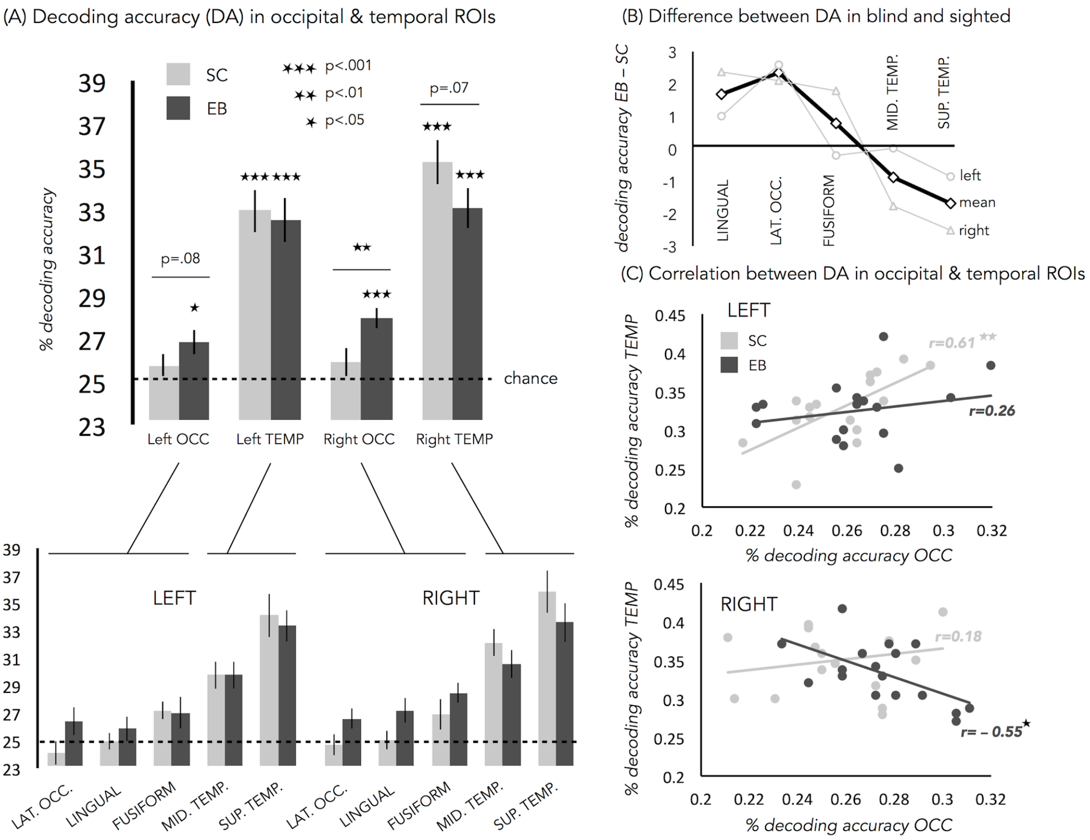

Figure 3.3.2: **MVPA and correlation results.** (A) In the upper panel is reported the decoding accuracy (DA) values in EB and SC in 4 main regions: left occipital, left temporal, right occipital, right temporal. The DA of each main region comes from the averaged DA of multiple ROIs included in the main regions reported in the bottom panel. (B) Difference in the DA of EB and SC in each ROI. Positive values represent higher DA in EB, negative values represent higher DA in SC. (C) Correlation between DA in the left (upper panel) and the right (bottom panel) occipital and temporal ROIs in the 2 groups.

RSA results

The RSA results are represented in figure 3.3.

MDS visualization (see figure 3.3C) illustrates that in EB the neural representations in the occipital ROIs are not more similar to the neural representations in the temporal ROIs compared to the SC, in fact looking at the figure 3.3C we can see that the distance between the occipital and the temporal ROIs is similar in the two groups. However form the MDS visualization emerges that the two groups mainly differ in the similarities between ipsi/contra-lateral representations of a specific ROI. We observed, indeed, that in sighted individuals the representation of the stimuli in one region tends to be similar to the representation in the corresponding contralateral region (e.g. the representation in the left superior temporal region is close to the representation in the right superior temporal region). On the contrary, the left and right representation in blind subjects appears more separate.

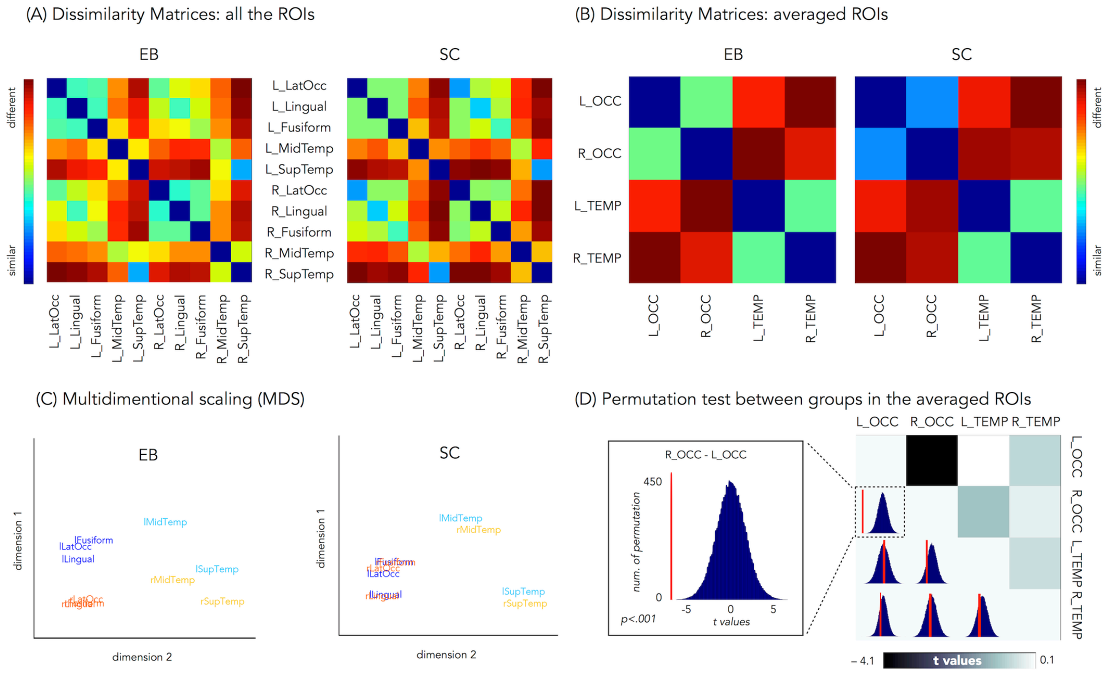

Figure 3.3.3: **Representational similarity analysis results.** (A) Dissimilarity matrices (DSM) for all parcels for the 2 groups separately (left: early blind, right: sighted controls). Each square in the matrix represents the correlation of the spatial geometry between two ROIs. Blue means that the spatial geometry (i.e. the representation of the stimuli) is really similar between two regions; red means that it is really different. (B) Dissimilarity matrices (DSM) after averaging the DSMs of all ROIs into 4 main regions. (C) Multidimensional scaling visualization for the 2 groups separately (left: early blind, right: sighted controls). More two brain regions share commonalities in the way they represent the stimuli more they appear close in the space. (D) Statistical analyses to compare the two groups. Each square of the upper triangular part of the matrix represents a t value resulting from a t-test between the EB and the SC. In the lower triangular of the matrix are reported the null distributions built to assess the statistical difference. Only the correlation between the left occipital and the right occipital ROIs is significantly different between the two groups as magnified in the left part of the panel.

We then averaged the ROIs in order to have only 4 main regions (i.e. left OCC, right OCC, left TEMP, right TEMP) and we ran permutations tests between groups for each possible pair of ROIs

Permutation tests show a significant difference only between the right and the left occipital ROIs (see figure 3.3D): the dissimilarity of the representations between the right and the left occipital ROIs is significantly higher in blind compare to sighted subjects (t (17) = –4.11, p<0.001 FDR corrected). No differences emerged between the occipital and temporal representations in the two groups, against our hypothesis that the representation in the occipital cortex of the EB would be more similar to the representation in their temporal cortex compared to the SC group.

3.5 Discussion

We investigated the link between cross-modal and intra-modal plasticity in early blind people during the processing of sounds from different categories. The most important result of this study was the between-groups differences in the decoding of acoustic categories (see figure 3.2A) that was reversed in occipital and in temporal regions (leading to a significant Group x Region interaction). Decoding accuracies in EB, when compared to SC, were enhanced in the occipital cortex but reduced in the temporal cortex. Interestingly, we observed that the blind participants that show the highest decoding accuracy in the occipital cortex are showing the lowest decoding accuracy in the temporal cortex; suggesting a link between intra-modal and cross-modal reorganizations after early visual deprivation (see figure 3.2B). From these results, we hypothesize that early visual deprivation triggers a relocation of auditory computation typically carried out in the temporal cortex toward the occipital cortex.

Previous neuroimaging studies have actually reported a decreased recruitment of auditory or tactile brain regions in EB when compared to SC when processing inputs from the remaining senses (Bedny et al., 2011, 2015; Burton et al., 2002b; Lewis et al., 2011a; Pietrini et al., 2004; Ricciardi et al., 2009; Striem-Amit et al., 2012a; Wallmeier et al., 2015; Watkins et al., 2012).

Indeed, a reduced intramodal recruitment of somatosensory regions has been reported during tactile discrimination processing (Burton et al., 2002b) and haptic object recognition (Pietrini et al., 2004) tasks; and reduced recruitment of temporal regions has been reported during an echo-acoustic localization task (Wallmeier et al., 2015), listening of motor action sounds when contrasted with environmental sounds (Ricciardi et al., 2009) and shape/location tasks using an auditory sensory substitution device (Striem-Amit et al., 2012a); reduced recruitment of prefrontal and infero-frontal regions during a words generation task (Watkins et al., 2012), listening of different sounds categories (Hurk et al., 2017; Lewis et al., 2011a) and language related tasks in both blind adults (Bedny et al., 2011) and blind children (Bedny et al., 2015). Moreover, several TMS studies reported an absence of disruptive effect of alteration in EB when applied over brain areas known to be functionally involved in SC such as inferior prefrontal regions during linguistic tasks (Amedi et al., 2004) sensory-motor cortex during tactile discrimination tasks (Cohen et al., 1997) and inferior parietal regions during sound localization tasks (Collignon et al., 2009a). These evidences support the idea that brain regions normally recruited for specific tasks in sighted might become less essential in EB in the case they concomitantly recruit occipital regions for the same task.

However, most of these studies did not focus on the link between intramodal and crossmodal reorganizations in early blind individuals. One exception comes from a recent study which demonstrated that the decoding of auditory motion direction is higher in hMT+/v5 but lower in the planum temporale of EB compared to SC (Dormal et al., 2016; Jiang et al., 2016). Our results strengthen and extend these data by showing that such imbalance between temporal and occipital involvement on sound processing is not specific to the processing of moving sounds but extend to the categorical coding of environmental sounds, therefore suggesting such mechanism might be a general principle underlying crossmodal reorganization. Actually, a similar imbalance mechanism has been reported by few studies on deaf individuals (Bottari et al., 2014; Cardin et al., 2016; Sandmann et al., 2012); suggesting that, in the case of early auditory deprivation additional visual computation performed within temporal areas decreases the perceptual load in occipital regions (Bottari et al., 2014). These results, therefore, suggest that the reallocation of the computational load from the regions coding for the spare senses to the reorganized cortex is not specific to visually deprived individuals but might be a general principle followed also by other kind of sensory deprivation.

Furthermore, this hypothesis is strengthened by our results showing for the first time that the higher the representation of auditory categories in occipital regions, the lower the representation in temporal areas; suggesting an intertwined link between intra-modal and cross-modal reorganizations after early visual deprivation.

Based on this hypothesis, we also reasoned that in the case the occipital cortex is not recruited for a specific non-visual task, the brain region primarily coding for that task would show similar degree of recruitment in EB and in SC, or even enhanced recruitment in EB due to the potential enhanced training of EB in the non-visual processing. One clear example is the processing of non-visual human stimuli. Several studies failed to display a crossmodal reorganization of the face network in early blind subjects during tactile face exploration (Goyal et al., 2006; Pietrini et al., 2004) and during vocal processing (Dormal et al., 2017). The absence of recruitment of the occipital cortex in processing auditory human stimuli in EB could explain the enhanced recruitment of STS during voice recognition in EB compared to SC (Gougoux et al., 2009).

Previous studies have shown an enhanced connectivity between occipital and temporal regions during sound processing in EB (Collignon et al., 2013; Dormal et al., 2016; Klinge et al., 2010). In our study we did not observe a more similar neural representation of the stimuli between temporal and occipital regions in EB compared to SC (see figure 3.3). A possible explanation could be that, even if both the occipital and the temporal areas of EB are involved in the processing of the auditory stimuli they might process different aspects of the stimuli, maintaining a distinct neural representation. Actually, this could be a more efficient way to reorganize a highly interconnected system rather than relying on a duplication of the same computational process.

An alternative explanation could be related to the fact that occipital and temporal regions participate in the processing of our stimuli at different moments post-stimulus presentation, potentially reflecting different computational processes. However, fMRI is not a proper technique to address such question based on higher temporal resolution. Future electrophysiological studies may therefore help in addressing such question.

Another open question relates to why we found this reverse correlation only in the right and not in the left hemisphere. There are at least two possible explanations for this lateralized effect. The first is that the flow of information between auditory and visual cortices may take place only between regions highly involved in the task. A general enhanced representation of the stimuli in the right compared to the left hemisphere emerged from our results. This effect is in line with the idea that the right hemisphere is more involved in processing sensory-related stimuli such as sounds or picture whereas the left hemisphere is more engaged in processing linguistic material (Gainotti, 2014; Thierry and Price, 2006). In support of this hypothesis there are several studies showing an increased involvement of the left occipital cortex of EB in language related tasks (Amedi et al., 2003; Bedny et al., 2011; Burton et al., 2002a; Röder et al., 2002). We might hypothesize that we would find in the left hemisphere a result similar to the one we found in the right hemisphere if we would include linguistic material among the stimuli. Another possibility, not mutually exclusive with the previous one, is that the processing in the left occipital cortex of the blind individuals could be negatively correlated with other brain regions than the temporal auditory cortex. Possible candidates could be the frontal and the prefrontal language areas, previously shown to have an increased connectivity with the occipital cortex in blind when compared to sighted individuals (Bedny et al., 2011; Bock and Fine, 2014; Liu et al., 2007; Watkins et al., 2012). In support of this possibility, a TMS study showed a decreased performance in a verb to noun generation task in SC but not in EB when transcranial magnetic stimulation was applied to the left inferior prefrontal cortex (Amedi et al., 2007).

When looking at the representations of the different sound categories (see figure 3.3C) we found a main difference between the two groups: in the SC group the left and the right homologous regions tended to be highly similar between them (e.g. the representation of the stimuli in the left middle temporal gyrus was similar to the representation in the right middle temporal gyrus). In the EB group, instead, the representations between the left and right homologous regions are more distinct compared to the sighted. This effect was stronger in the occipital regions where the representations of our stimuli space were highly distinct between the right and left regions in EB but were overlapping in the sighted controls (see figure 3.3C). These results are supported by previous functional connectivity data reporting decreased inter-hemispheric connectivity within the occipital cortex of blind people between both homologous and non-homologous regions (Bedny et al., 2011; Bock and Fine, 2014; Qin et al., 2013; Watkins et al., 2012; Burton et al., 2014; Pelland et al., 2017). These findings seem to point out two different kinds of processing happening in the left and in the right occipital lobes of blind individuals, in line with what we suggested above.

3.6 Conclusion

In the present study, using multivariate fMRI data analysis, we demonstrate that early visual deprivation produce a network-level reorganization, extending the non-visual functions of the occipital cortex and reducing the computational load of the auditory cortex. Our results suggest that the reorganization of the occipital (i.e. cross-modal plasticity) and temporal (i.e. intra-modal plasticity) cortices in early blind should be considered as part of the same reorganizational phenomenon that operates at the network level. We also found that in the specific case of sound categories the re-balanced reorganization takes place especially in the right hemisphere, which is also the most recruited during the task. We therefore suggest that the extension of non-visual functions in the occipital cortex of EB triggers a relocation of the auditory processing that may reduce the computational load of the regions typically coding for the remaining senses.

4

General Discussion

4.1 Recall of the general aims of the dissertation

The general aim of the present dissertation was to participate in the understanding of the semantic processing of categories presented in distinct modalities and to subject populations with different sensory experiences. The goal was twofold: (1) understand whether there are brain regions that encode information about different categories regardless of input modality and sensory experience; (2) deepen the investigation of the mechanisms that drive cross-modal and intra-modal plasticity following early blindness and the way they express during the processing of different categories presented as real-world sounds.

4.2 The semantic network and the neural format of the conceptual representations

4.2.1 The role of pMTG in the multimodal semantic processing

The study 1 highlighted a key role of the posterior middle temporal gyrus (pMTG) in processing different categories in multiple modalities and in groups with different sensory experiences. The role of pMTG in semantic cognition is supported by a large amount of neuroimaging studies, as confirmed by several authoritative reviews on this topic (Binder et al., 2009; Indefrey and Levelt, 2004; Vigneau et al., 2006).

Previous studies using univariate fMRI analyses reported the posterior middle temporal gyrus (pMTG) as a convergence zone between words presented visually and acoustically (Taylor et al., 2006; Thierry and Price, 2006), between verbal and non-verbal material (Thierry and Price, 2006; Thierry et al., 2003) and also between stimuli presented in different non-verbal modalities such as pictures and sounds (Beauchamp et al., 2004; Thierry and Price, 2006).

These studies highlighted the role of pMTG as a convergence semantic region. They cannot, however, speak about the format of the representation in this region due to the kind of analyses they employed. As we discussed in the general introduction (see paragraph 1.4.10), multivariate analyses represent a handy analytical tool to investigate the representational format of brain regions.

Using an innovative multivariate fMRI analysis, that we defined cross-RSA, we were able to investigate the representational format of rpMTG. We showed that the representations in the rpMTG are not sensory-abstracted; in other words this region takes part in the semantic processing of both visual and auditory modalities in sighted, however it appears to keep the representations from the two modalities at least partially segregated.

Based on our results, we concluded that rpMTG is a region involved in the multimodal processing of different categories but that the representational format of this region is not fully abstracted from its input modality since it is still possible to distinguish between the activity patterns produced by visual and auditory stimulation.

Our results partially contrast with the conclusions of a recent study supporting an amodal nature of pMTG (Fairhall and Caramazza, 2013). In this study, the authors presented pictures and auditory words from five different categories (fruit, tools, clothes, mammals and birds) and using cross-MVPA they isolated the posterior cingulate/precuneus and left pMTG/ITG as regions devoted to the amodal representation of the conceptual properties of objects (Fairhall and Caramazza, 2013). The use of cross-MVPA analysis, however, could mislead, in certain cases, the interpretation of the results about the representational format of a brain. It would be still possible, according to our point of view, that the significant results obtained using cross-MVPA in the study from Fairhall and Caramazza underline shared information about the stimuli in the two modalities (i.e. auditory words and pictures) but the patterns of activity generated by them could be still distinguishable, speaking against abstraction. This is indeed what our data suggest. We found that rpMTG is decoding different categories in the two modalities and that in both modalities it is processing information related to the conceptual aspects and not low-level properties of the stimuli. However the functional profiles generated from the two modalities are still distinguishable between each other. Our results are supported by a further study employing visual stimuli from six different categories in two formats: written words and pictures (Devereux et al., 2013). Using RSA, they found that the left pMTG encodes the representation of the stimuli in both formats but it does not cluster them together, suggesting that its nature is not modality-invariant.

Strikingly, we did not find among the multimodal regions, the perirhinal cortex (PRC), a region that has been shown to participate in the conceptual processing of stimuli from multiple modalities (Fairhall and Caramazza, 2013; Simanova et al., 2014; Taylor et al., 2006). One possible explanation for this absence is that PRC might have a different role compared to pMTG in the processing of multimodal stimuli that we did not capture with our task. There are evidences for a role of PRC in integrating different features into higher-level conceptual representations (Taylor et al., 2006) while pMTG seems to be less modulated by meaning variables (e.g. semantic congruency). Since in our study we did not ask to the participant complex cognitive tasks or the semantic manipulations of our stimuli, it is possible that we did not trigger the recruitment of PRC. Furthermore the multimodal nature of PRC has been recently questioned by authors showing a recruitment of the left PRC only for visual words and not for auditory ones (Liuzzi et al., 2015).

4.2.2 VOTC involvement in semantic categorization in sighted and in blind individuals

It has been suggested that VOTC could categorize information not only based on visual input but also on input coming from other senses (Amedi et al., 2002; Mahon and Caramazza, 2009; Pietrini et al., 2004; Wang et al., 2015).

In **study** 1, we investigated this aspect looking at how VOTC processed several categories presented in two different sensory modalities (i.e. visual and auditory in sighted) and in groups with different sensory experiences (i.e. sighted and blind individuals). From a more data driven approach, using MVPA in combination with a searchlight approach (Kriegeskorte et al., 2006), we observed that VOTC in SCv group and, to a lesser extent, in EBa group was able to successfully decode the eight categories. However, no decoding was observed in SCa group.

This finding does not support a sensory-abstracted neural format of VOTC. Previous studies, claiming an amodal nature of VOTC, might have underestimate the role of visual imagery in activate the ventral visual stream of sighted people for non-visual stimulation (Cichy et al., 2012; Kosslyn et al., 1995; Reddy et al., 2010; Stokes et al., 2009; De Volder et al., 2001) and the fact that the same region might be activated by crossmodal plasticity in EB. The inclusion of two different sighted groups for the auditory and for the visual version of the experiment, in contrast with previous studies (Devereux et al., 2013; Fairhall and Caramazza, 2013; He et al., 2013b; Peelen et al., 2013a), may have reduced the production of visual imagery and consequently also the brain activity in this region in the SCa group. Moreover, beyond the possibility of visual imagery, which is difficult to completely bypass, there are other research lines that support our results against a sensory-abstracted nature of VOTC. The first finding, crucial in respect of this topic, is that the activity of VOTC can be partially explained by low-level properties of visual stimuli such as spatial frequency, eccentricity or shape (Andrews et al., 2010; Baldassi et al., 2013; Rice et al., 2014). Our results in the visual domain also show a contribution of the physical properties of the visual stimuli in explaining the categorical selectivity of most of the regions in VOTC (see figure 2.8 – SI). In addition, lesions to the VOTC have been shown to produce a selectively visual agnosia (Farah, 1991; Rossion et al., 2003; Vandenbulcke et al., 2006; Warrington and McCarthy, 1994), supporting a key role of this region in visual recognition (Grill-Spector and Weiner, 2014).

When we zoomed into specific functional clusters of VOTC, we found, in line with the searchlight results, that in sighted the decoding accuracy was, as expected, dramatically higher in every ROI (left and right LOC, FFA, PPA) in the visual compared to the auditory modality (see figure 2.3E). Moreover, in EB the right ROIs showed crossmodal reorganization in the form of enhanced decoding accuracy of the auditory stimuli and increased correlation with the neural geometries generated by the visual stimuli in sighted (2.3E and 2.4B). In addition, this analysis highlighted some interesting aspect of the left VOTC that did not emerged from the searchlight analysis (probably due to the more severe statistics of the searchlight compared to the ROI approach).

The left VOTC showed a similar profile for the auditory stimuli between blind and sighted individuals, being able to significantly decode the auditory stimuli in both groups and showing in both blind and sighted a similar level of similarity with the visual representation in sighted. These results suggest a role of the left VOTC in the processing of auditory categories in both blind and sighted individuals. Does this mean that the left VOTC is supramodal? According to our data, this is not the case. In fact, we highlighted segregation between the functional profiles produced by the auditory and the visual stimuli, underlining that the format of representation is not abstracted from the sensory modalities.

4.2.3 Are there amodal regions in the brain?

From our perspective, to define a brain region amodal, it needs to (1) process conceptual/semantic information from multiple modalities and (2) show indistinguishable functional profiles for the same concept presented in different modalities.

A rich body of works, based especially on univariate fMRI analyses, reported several brain regions recruited during the semantic processing of information presented in multiple sensory-modalities (for review about multisensory and multimodal literature see (Beauchamp, 2005; Bertelson and De Gelder, 2012; Calvert and Thesen, 2004; Stein and Stanford, 2008). These studies show that there are several regions in the brain that are not purely unimodal but that take part in the processing of multiple modalities. Crucially, however, the overlap of activity for different input modalities does not represent a conclusive proof of an abstract format of representation. It is, indeed, possible that populations of neurons from different sensory modalities coexist in the same region making it a multimodal, but not an amodal, region. Recent studies based on multivariate fMRI analyses showed evidences in support of this possibility (Bulthé et al., 2014; Jung et al., 2017). For example, Bulthé and colleagues investigated the symbolic (e.g. digits) and non-symbolic (e.g. dots) representations of numerical cognition. They found several regions, such as the intraparietal sulcus, recruited during both types of representation. However, it was not possible, using the cross-conditions decoding technique, to train a classifier on the patterns of activity generated by one modality and successfully decode the patterns of activity produced by the other modality (Bulthé et al., 2014). This finding suggests that a region can be recruited for the processing of different modalities/materials but the neural representations from the two modalities might still not share much information between each other. In this case, only the first amodality assumption is respected (i.e. The region processes conceptual/semantic information from multiple modalities), but not the second (i.e. The region should also show indistinguishable functional profiles for the same concept presented in different modalities), therefore, these regions cannot be defined amodal.

In the last decade, the cross-modal/conditions decoding became a mainstream tool used to investigate amodal, or abstracted, properties of brain regions. The starting assumption is that if we can train a classifier in the patterns of activity generated by one modality and, based on this training, the classifier can successfully decode the patterns of activity generated by the second modality, this would be the proof of a sensory-abstracted representation (Fairhall and Caramazza, 2013; Jung et al., 2017; Peelen et al., 2010). However, even if cross-modal/conditions MVPA can provide useful hints about shared information within a brain region, it is very difficult to apply this technique across different subjects and group (see figure 1.10). In the study 1, we implemented a novel technique named cross-RSA that allowed us to compare the functional profile of brain regions across modalities and across groups. We, indeed, demonstrated that the nature of some regions, such as pMTG and VOTC, previously claimed to be amodal, using cross-MVPA, might not be amodal instead. These results underlie the importance to be cautious in the interpretation of the cross-decoding results in favour of a definite sensory-abstracted nature of a brain region.

4.3 Crossmodal plasticity and the way it expresses in the blind brain

4.3.1 The increased involvement of the EB occipital cortex in processing auditory categories.

The enhanced involvement of the occipital cortex in the processing of non-visual stimulation following blindness has already been shown in many previous studies (Bedny, 2017; Bedny et al., 2011; Collignon et al., 2007, 2009c, Dormal et al., 2016, 2017; Peelen et al., 2013a; Pietrini et al., 2004).

However, only a few fMRI studies in the literature investigated the processing of sounds from different categories in the occipital cortex of blind subjects (Amedi et al., 2007; Dormal et al., 2017; Hurk et al., 2017; Lewis et al., 2011a). Among these studies, only Hurk and collaborators implemented multivariate fMRI analyses to look at more fine-grained processing of the sounds in early blind individuals. They used as ROI the whole bilateral VOTC and one of their main findings was that VOTC was able to distinguish the activity patterns produced by the different auditory categories significantly better in early blind compared to sighted controls. Similarly, in our study 2, we showed that several regions in the occipital cortex of EB contain information about different auditory categories and are able to distinguish across them, both using searchlight and discrete ROIs inside VOTC. The searchlight approach highlighted an extended portion of the right occipital cortex that decoded the 8 categories significantly better than sighted. The two main clusters emerged from the searchlight approach were localized in the posterior right occipital cortex of the early blind including part of the posterior ventral stream (posterior portion of the lingual and the fusiform gyri) and part of the dorsal stream (mainly the cuneus). In addition, our ROIs approach underlined a general enhanced role of the ROIs inside VOTC (i.e. left and right LOC, FFA and PPA) of EB compared to SC in processing the auditory categories. However, this effect was mostly driven by the right ROIs that showed a bigger difference between the two groups compared to the left homologues. In study 2, we replicated these results in structural parcels (left and right: lingual gyrus, lateral occipital cortex, fusiform gyrus) obtained from the single subject brain segmentation. A main difference in the results of the second study was the lack of significant decoding accuracy in sighted for the auditory categories in left VOTC. Technical differences in the way we implemented the MVPA analysis could be a possible reason. First, the smaller size of the ROIs in the second (100 voxels) compared to the first study (400 voxels) represents a factor that might reduce decoding accuracy in MVPA (Gardumi et al., 2016; Norman et al., 2006). Moreover, in the first study the ROIs were defined functionally (in an independent group (from Julian et al., 2012) while in the second study we used structural ROIs extracted with cortical segmentation of each subject brain. Therefore, it is possible that in the first case we are targeting ROIs that are more specifically involved in the functional processing of different categories in sighted and this might also increase the decoding accuracy. Finally, a further element that might explain the different decoding accuracy is the inclusion of some portion of white matter or subcortical regions (Oosterhof et al., 2011), that is more likely in the first compare to the second study. In the first experiment we are, indeed, applying externally defined ROIs to our subject brains whereas in the second study the ROIs are built following the cortical structure of each subject.

To summarize, we found an enhanced involvement of discrete regions in the occipital cortex of blind individuals compared to sighted controls in processing auditory categories presented as real-world sounds. Moreover, when the analyses were done in bigger ROIs this effect was greater in the right than in the left side when compared to SC.

The next step, based on these findings, was to understand which kind of information is supporting this successful decoding in the occipital cortex of early blind.

4.3.2 The reorganized occipital cortex in EB: what is it coding for?

The evidence about the enhanced engagement of some regions in the occipital cortex of blind compared to sighted subjects for auditory stimuli does not give any information about the type of processing that is implemented in those regions. Does the reorganized occipital cortex of early blind individuals maintain a similar functional architecture as the one observed in sighted when processing visual stimuli? Are these regions characterized by a predetermined function that drives the way crossmodal plasticity expresses?

Our data show that the answer to these questions might not be the same for all the regions in the occipital cortex.

Our findings from the searchlight approach highlighted two extended clusters in the occipital cortex of blind individuals showing enhanced ability compared to sighted in decoding auditory categories. As expected, the same regions reported a decoding accuracy even higher in sighted for visual stimulation. In sighted we found that the two clusters encode significant information about both categorical and physical properties of the pictures. If in early blind these regions maintained the same functional properties just switching the sensory modality they should also encode information about at least one of these two features of the auditory stimuli. This is not what we found, however. In fact, neither categorical nor physical attributes of the auditory stimuli explained the activity in none of the two clusters. The lack of low-level coding in this posterior portion of the occipital cortex of EB suggests that these regions, coding for low-level visual properties in sighted, are not recycled for low-level processing of non-visual stimuli. A possible explanation for this result is that the pole of the occipital cortex in EB is the regions that distance itself the most from the native computation it typically implements (Bi et al., 2016; Buchel, 2003; Wang et al, 2015). Because V1 has a native computation that does not easily transfer to a similar computation in the remaining senses, it may therefore rewire itself for higher-level functions. Indeed, several fMRI studies found an increased activity in the posterior occipital regions in early blind compared to sighted controls during high-level cognitive tasks such as auditory verb generation (Burton et al., 2002a), verbal memory (Amedi et al., 2003), episodic retrieval (Raz et al., 2005) semantic judgment (Burton et al., 2003; Noppeney, 2003) and speech processing (Bedny et al., 2011; Röder et al., 2002). Büchel, in the attempt to find an explanation for these results suggested the "reverse hierarchy" theory suggesting that in early visually deprived individuals a different form of hierarchy can arise in their occipital cortex and in this new architecture V1 seems to become a higher-tier area (Büchel, 2003). It would be interesting to investigate whether external models based on linguistic properties of the stimuli (e.g. language statistic, see Baroni et al., 2009) would, at least partially, explain the enhanced information that we found in the two posterior occipital clusters of EB. Our design does not allow us to implement this analysis because the language-statistic DSM based on our stimuli space will highly correlate with categorical models. Future studies should investigate this point using a set of stimuli in which the categorical and the linguistic dimensions should be as much as possible orthogonal to each other.

In the above-mentioned study using sounds from multiple categories, Hurk and collaborators showed that it was not possible in V1 to successfully predict the patterns of activity produced by auditory stimuli in EB from the patterns of activity generated by visual stimuli in SC (Hurk et al., 2017). This could be a further proof that in the posterior occipital regions there are not many shared information between the representations in the two groups. On the contrary in the same study, the cross-group decoding was possible in the global VOTC ROI (Hurk et al., 2017).

Thanks to our design, we were able to look at the representational geometries of our stimuli inside several discrete regions included in VOTC: LOC, FFA and PPA, in the left and right side separately. We directly compared the representation of the auditory stimuli in early blind with the representation of visual stimuli in sighted controls and we found that they shared similarities in all the six regions. This was not the case in SC where only the ROIs in the left side shared similarities between auditory and visual representations.

These evidences suggest that the crossmodal plasticity manifests in these regions rewiring them toward non-visual sensory modalities but maintaining, at least partially, the category-selective structure similar to the one existing in sighted individuals for visual processing (Dormal and Collignon, 2011; Striem-Amit et al., 2012b).

How can we reconciliate these two, apparently contrasting, pieces of evidence? It seems that the more posterior and the more anterior portions of the occipital cortex in early blind individuals follow different "rules" in the way the crossmodal plasticity expresses.

A possibility, compatible to our results, is that the crossmodal plasticity would try to maintain the functional architecture of a brain region as similar as possible to the original one. However, the degree of similarity will depend on the intrinsic structure that characterizes each region. It looks reasonable that for the regions inside VOTC it would be easier to maintain their functions even after rewiring toward non-visual modalities (Dormal and Collignon, 2011). Most of these regions are, indeed, involved in processing categories of object that could be represented also in non-visual sensory-motor modalities (e.g. the concept of "cup" can be easily accessed through motor-tactile sensation as well as the concept of "tomato" can be based on taste and touch; see Bi et al., 2016 for a more detailed discussion of the topic) compared to more posterior regions involved in the core analysis of the low-level visual properties (Desimone et al., 1985; Ungerleider and Haxby, 1994) of the stimuli (e.g. concepts such as luminance or spatial frequency are pure visual concepts difficult to access with any other sensory modality). In this case the new role of the region in EB will be necessarily more different from the original one compared to what happens in VOTC, even if it will not be completely unrelated to the original function. Recently, a study from our group showed that the primary visual cortex of EB synchronizes to the temporal dynamics of comprehensible speech (Ackeren et al., 2017). This could be considered the auditory substitute of the lip-reading processing in the visual modality, a mechanism that has been shown to be implemented in the occipital cortex in sighted (Luo et al., 2010; Park et al., 2016). These findings support an involvement of the posterior occipital cortex of EB in the sensory signal of speech. Moreover, they suggest that also in the posterior occipital cortex of EB the functional reorganization does not take place in a stochastic way, but it is still constrained by the natively functional architecture of specific brain regions and networks (Ackeren et al., 2017).

A potential alternative is represented by the proposition of a pluripotent occipital cortex that would process speech in an abstract fashion, purely reflecting higher-level operations similar to those observed in prefrontal regions (Bedny, 2017). Further studies are needed to disentangle between these two possibilities.

4.3.3 An Integrating view of intra-modal and cross-modal plasticity in blindness: the large-scale unbalance theory

A concomitant increase in occipital recruitment and reduced temporal recruitment in EB individuals

In study 2, we investigated the brain reorganization following early blindness from a wider perspective. The main aim of this study was to determine whether changes in the occipital cortex of EB (i.e. cross-modal plasticity) occur in isolation or rather together with changes in the other brain regions encoding for the remaining senses (i.e. intra-modal plasticity). We found, indeed, a co-occurrence of cross- and intra- modal plasticity in early blind during the processing of sounds from different categories. More specifically the decoding of different acoustic categories in EB and SC was reversed in occipital and in temporal regions, with a significant Group x Region interaction. We found an increased level of information in occipital regions (i.e. lingual gyrus, lateral occipital complex and fusiform gyrus) of EB compared to SC concomitant with a reduction of the decoding accuracy in the temporal regions (i.e. middle and superior temporal gyri).

Actually, this result is not so unexpected as we might believe. Previous studies indeed suggested the co-occurrence of enhanced recruitment of the occipital cortex together with a decreased recruitment of brain regions coding for the remaining senses in EB when compared to SC (Bedny et al., 2011, 2015; Burton et al., 2002b; Hurk et al., 2017; Lewis et al., 2011a; Pietrini et al., 2004; Ricciardi et al., 2009; Striem-Amit et al., 2012b; Wallmeier et al., 2015; Watkins et al., 2012). All these studies together are pointing to a recurrent pattern of results that extends to multiple stimuli and tasks.

However, most of these works often neglected the results about the intramodal reorganization and concentrated selectively on the reorganization of the occipital cortex. One exception is the recent study from Hurk and collaborators (2017). They found that the selectivity for auditory stimulation in the visual cortex was stronger in blind individuals than in controls while was stronger in the auditory cortex in sighted compare to blind individuals and they discussed it in the light of a possible interplay between the deprived and non-deprived cortices.

In support of this hypothesis several TMS studies reported an absence of disruptive effect of TMS in EB, but not in SC, when applied over the inferior prefrontal regions during linguistic tasks (Amedi et al., 2004) sensory-motor cortex during tactile discrimination tasks (Cohen et al., 1997) and inferior parietal regions during sound localization tasks (Collignon et al., 2009a). These evidences support the idea that brain regions normally recruited for specific tasks in sighted might become less essential in EB in the case they concomitantly recruit occipital regions. A similar idea was recently proposed based on the observation that the decoding of auditory motion direction is higher in hMT+/v5 but lower in the planum temporale of EB compared to SC (Dormal et al., 2016; Jiang et al., 2016). Our results strengthen and extend this hypothesis by showing that such imbalance between temporal and occipital involvement on sound processing is not specific to the processing of moving information but extend to the categorical coding of environmental sounds. Interestingly, it is possible that this reallocation of the computational loading from the regions coding for the spare senses to the reorganized cortex is not specific of visually deprived individuals but might be a general principle followed also by other kinds of sensory deprivation. For example, a similar imbalance mechanism has been reported by few studies on deaf individuals (Bottari et al., 2014; Cardin et al., 2016; Sandmann et al., 2012).

An interesting result emerging from our study is that the blind participants that show the highest decoding accuracy in the occipital cortex were showing the lowest decoding accuracy in the temporal cortex. From these results, one may hypothesize that early visual deprivation triggers a relocation of auditory computation toward the occipital cortex.

Based on these observations, one could expect that when the occipital cortex is not recruited for a specific non-visual task, the brain region primarily coding for that task would show similar degree of recruitment in EB and in SC, or even enhanced recruitment of EB due to the potential enhanced training of EB in the non-visual task. One illustrating example might be found in FFA, a region that seems more resistant to cross-modal reorganization in EB (Wang et al., 2015; Xu et al., 2016). Many studies, indeed, failed to show a crossmodal reorganization of FFA for non-visual human, or face-related, stimuli (Dormal et al., 2017; Goyal et al., 2006; Pietrini et al., 2004). This lack of occipital recruitment might potentially explain the enhanced recruitment reported in STS during voice recognition in EB compared to SC (Gougoux et al., 2009). In other words, reduced activity in the temporal cortex would only be observable for the domains that remap onto occipital networks in EB. Actually, the absence of occipital recruitment for a specific non-visual task could even express as an enhanced recruitment of temporal regions due to the increase reliance on non-visual inputs in EB. This is indeed what was observed in an ERP study investigating low-level sounds processing and did not observe enhanced recruitment of the occipital cortex in EB but found an increased activity of the temporal areas (Naveen et al., 1997).

Absence of increased similarity between the occipital and temporal neural representations of auditory stimuli in EB compared to SC.

A key question relates to how the auditory information can reach the occipital cortex of blind individuals during auditory stimulation. Studies in kittens demonstrated that cortical connections between the auditory and the occipital cortices are eliminated during the synaptic pruning phase in the sighted sample (Innocenti et al., 1988) while the same projections remain in kittens deprived of vision at birth (Berman, 1991; Yaka et al., 1999). In the same line, Karlen and collaborators (Karlen et al., 2006) showed that early blind opossums develop novel connections to V1 from auditory, motor and somatosensory thalamic regions and also from auditory, somatosensory and multimodal cortices. In humans, several studies reported an increased functional connectivity between occipital and temporal cortices during auditory processing (Collignon et al., 2011; Dormal et al., 2016, 2017; Klinge et al., 2010; Sani et al., 2010; Watkins et al., 2012). In contrast, other studies reported a decreased functional connectivity between early visual and temporal cortices at rest (Bedny et al., 2010, 2011; Burton et al., 2014; Liu et al., 2007). Interestingly, a recent study tried to clarify this controversial data by directly comparing the functional coupling between temporal and occipital networks at rest with the functional correlation between the same regions during an auditory task (Pelland et al., 2017). They reported higher occipito-temporal correlations in activity during the task than at rest in EB and the reverse pattern in SC, showing that there is indeed an enhanced connectivity between occipital and temporal cortices of early blind that emerges specifically during auditory processing.

Importantly, such pathways have also been observed in adult sighted primates (Falchier et al., 2002; Rockland and Ojima, 2003) and humans (Beer et al., 2011). Early visual deprivation may potentially elicit the maintenance and/or reinforcement of intermodal connections between temporal and occipital cortical areas, allowing in this way the auditory information to reach the occipital cortices. Conclusion In the light of these findings it is not straightforward to explain why we failed in uncovering a more similar neural representation of the stimuli between temporal and occipital regions in EB compared to SC (see figure 3.3). Indeed, when we looked at the similarity of the functional profiles (i.e. neural dissimilarity matrices) between the occipital and the temporal ROIs we did not find an increased similarity in the EB compared to SC. A possible explanation for this missing result could be that, even if both the occipital and the temporal areas of EB are involved in the processing of the auditory stimuli they might process different aspects of the stimuli maintaining a distinct neural representation. Actually, this could be a more efficient way of reorganization rather than creating a duplication of the same process.

An intriguing alternative explanation could be related to the timing of the processing. In the above-mentioned study, Pelland and colleagues reported an enhanced connectivity between occipital and temporal areas during active tasks (Pelland et al., 2017) in contrast with a reduced connectivity during rest (Bedny et al., 2011; Bock and Fine, 2014; Burton et al., 2014). The authors suggested that the reason of this result might lie in the multiple implication of the reorganized occipital cortex of early blind in several sensory and cognitive tasks (Amedi et al., 2003, 2004; Bedny et al., 2011; Burton et al., 2006; Collignon et al., 2013; Dormal et al., 2017; Noppeney, 2007; Pietrini et al., 2004). Because of this multiple implication the occipital lobe in EB may not show any specific connectivity pattern, however when involved in a specific auditory tasks, this working state will constrain the occipito-temporal connections (Pelland et al., 2017). A similar interpretation could also explain our results. It is, indeed, possible that the occipital regions in EB are participating in multiple processes of the auditory stimuli and that the neural activity of this region is changing rapidly during the processing of the stimuli. Due to the scarce temporal resolution of fMRI (Scott A. Huettel; Allen W. Song; Gregory McCarthy et al., 2004) we average together neural representations from multiple time windows potentially cancelling out the differences of the neural representations along the time flow. Studies based on MEG/EGG recording, which have a much higher temporal resolution, are needed to disclose whether an enhanced correlation between the occipital and temporal neural representations of auditory categories in early blind emerges at one specific time point of the processing (Ackeren et al., 2017).

4.4 Different roles of left and right hemispheres in processing different categories

One recursive result that both studies pointed out was a different role of the left and the right hemispheres in categorizing our stimuli space. More specifically, we pointed out several lateralized results: the overlap of the decoding for sounds and pictures in SC and sounds in EB emerged in the right pMTG; the enhanced recruitment of the occipital cortex in EB compared to SC for the processing of auditory categories takes place in the right occipital cortex; the imbalanced mechanism of crossmodal reorganization also emerged only between the right occipital and the right temporal cortices. Moreover, the left VOTC showed a more similar profile between the EB and SC in processing auditory categories.

All together, these results suggest that right hemisphere seems to be more involved in sensory-related processing of stimuli and the left hemisphere more based on propositional/linguistic processing of the information.

These results are reminiscent of the hypothesis that has been mostly proposed for high-level/associative regions (Gainotti, 2014). Gainotti accumulated evidences from both healthy subjects and brain damage patients reporting a copious amount of previous studies in line with this hypothesis. Table 4.1 is readapted from this review and contains a list of behavioural and neuroimaging studies on healthy subjects and brain-damaged patients confirming the different format of verbal/sensorial conceptual representations between the right and left hemisphere. From these studies emerge a greater weight of verbally coded information in the left hemisphere in comparison to that of the non-linguistic stimuli in the right hemisphere (Gainotti, 2014). In fact, processing of verbal material is strongly left lateralized whereas processing of non-verbal, sensory-related, material is often bilateral with a trend toward right lateralization. For instance, Taylor and colleagues (2005) observed the activity of the right pMTG/STS during the processing of both visual and auditory words (Taylor et al., 2006). Thierry and collaborators in the conjunction between environmental sounds and words found the left anterior and posterior MTG (Thierry et al., 2003). The same author, in a comprehensive study including auditory and written words, sounds and pictures of environmental places reported the right pMTG when contrasting non-verbal (sounds & pictures) versus verbal (auditory and written words) material (Thierry and Price, 2006). Beauchamp and colleagues using pictures and sounds of tools and animals reported bilateral pSTS/pMTG from the conjunction between the two modalities (Beauchamp et al., 2004). In addition, two recent studies employing multivariate fMRI analyses pointed out that left pMTG was recruited in the processing of both visual words and pictures (Devereux et al., 2013) and also that it contained shared information between the pattern of activity generated by auditory words and pictures (Fairhall and Caramazza, 2013).

AUTHORS	METHODS	RESULTS
Behavioural studies in normal subjects and brain-damaged patients		
Whitehouse, 1981	Explored in R and LBD patients aspects of pictorial and verbal encoding in two forced-choice recognition memory experiments.	Left hemisphere injury selectively impaired verbal memory coding, whereas right hemisphere damage preferentially impaired pictorial coding
Grossman and Wilson, 1987	Asked right and left BD patients and normal controls to evaluate perceptual and conceptual stimuli for their degree of category membership.	The left-hemisphere patients showed anomalies in categorizing the conceptual but not the perceptual items, while the reverse was true fort he right of hemisphere patients.
Nieto et al., 1999	Carried out two lateral tachistoscopic experiments in normal subjects, to test semantic capabilities of the left and right cerebral hemispheres, through categorization tasks with verbal and pictorial presentation.	Right visual field advantages were obtained for verbal presentations in both category-membership and category-matching tasks. However, no significant visual field differences were found for any pictorial presentation.
Gainotti et al., 1994	Constructed two very similar tasks of verbal and pictorial memory and administered them to control subjects and patients with R and L hemispheric lesions.	Word recognition was selectively impaired by left and picture recognition by right brain injury, but the difference between R and LBD patients was significant only on the test of verbal memory, whereas the trend in opposite direction observed on the test of pictorial memory was non-significant.
Shibahara and Lucero-Wagoner, 2001	Used a semantic priming paradigm to examine whether perceptual or conceptual properties of word meanings would be associated with the left or right hemisphere.	The results indicated that perceptual information is available only in the right hemisphere while conceptual information is available in both hemispheres.
Neuroimaging investigations in normal subjects and brain-damaged patients		
Thierry et al., 2003	Used functional neuroimaging in normal subjects to compare semantic processing of spoken words to equivalent processing of environmental sounds, after controlling for low-level perceptual differences.	Words enhanced activation in left temporal (LT) regions while environmental sounds enhanced activation in the right temporal (RT) areas. The LT involvement in comprehending words was extensive than the RT involvement in processing non-verbal sounds.
Thierry and Price, 2006	Developed these studies, comparing conceptual processing of verbal and non-verbal stimuli in both visual and auditory modalities.	They found that left temporal regions were more involved in comprehending words (heard or read), whereas the right temporal cortex was more involved in making sense of environmental sounds and images.

Acres et al., 2009	Administered four verbal and non-verbal tasks (including words and pictures categorization) to patients with R and L temporal lesions and correlated their behavioural scores with the lesion and correlated their behavioural scores with voxel-based measures of neuronal integrity	Performance on the verbal tasks correlated with the lesion of left inferior and anterior temporal regions, while performance on the non-verbal tasks correlated with the lesion of analogous right temporal areas. The L with temporal lobe was more involved in word categorization than the right in pictures categorization.
Butler et al., 2009	Used voxel-based morphometry to correlate performance on verbal and nonverbal versions of a semantic association task in patients with neurodegenerative diseases.	They found material-specific correlations, greater for verbal stimuli in left temporal regions than for non-verbal stimuli in the right fusiform gyrus.
Hocking and Price, 2009	Presented subjects simultaneously with one visual and one auditory stimulus and instructed them to decide whether these stimuli referred to the same object or not. Verbal stimuli consisted of spoken and written object names, whereas non-verbal stimuli consisted of pictures of objects and naturally occurring object sounds.	Verbal matching increased activation in the left temporal lobe, whereas non-verbal matching increased activation in the right fusiform region.

Table 4.1: Studies on right/left differences in the semantic network. Results of neuropsychological investigations that have compared memory or conceptual disorders observed with visual, auditory and verbal material in right and left brain-damaged patients and of experiments conducted with similar material to test the semantic capabilities of the left and right hemisphere in healthy subjects. R: right, L: left, BD: brain damaged. Adapted from Gainotti et al., 2014.

Our study extends these findings by showing that the right pMTG successfully decoded visual and acoustical categories in sighted and acoustical categories also in visually deprived individuals, confirming a prominent role of this region in processing stimuli from multiple sensory-modalities. In addition, we also demonstrated that the neural representations generated in rpMTG by different modalities are still distinguishable one from the other underling a multimodal nature of this region, therefore not sensory-abstracted.

Interestingly, in study 1, we also found that the right VOTC is purely visual in sighted and, only in the case vision is lacking, they rewire themselves toward non-visual modality. The left-sided VOTC seems, instead, less visually imprinted, showing the ability to decode auditory stimuli also in the sighted. These results suggest that the right VOTC reorganizes itself in EB due to crossmodal plasticity and its reorganization keeps relation with the native computational framework of this region but in a more sensory-based fashion compared to the left counterpart. We, indeed, showed that in the left VOTC the neural representations of the auditory stimuli, in both sighted and blind groups, were correlated with the visual representation in sighted, whereas in the right side the correlation with the visual representation was specific of the EB. Actually, visual deprivation seems to impact less on the processing of auditory categories in the left VOTC showing a similar functional profile in both EB and SC in audition (see figure 4.1).

Based on our results, we suggest that an hemispheric specialization, similar to the one proposed for associative higher-level areas (Gainotti, 2014), could take place also in more sensory-related regions such as the ventral visual stream. The right VOTC would mostly be a sensory-related region (visual in sighted, reorganized toward non-visual modalities in the case of early blindness) while the left VOTC would not only represent visual information in sighted, but would also represent the stimuli in a more linguistic/propositional way, both in SC and EB.

According to this hypothesis we should be able to observe two kinds of evidence. First, the crossmodal plasticity in early blind should express in the occipital cortex following the left lateralization for linguistic material and show bilateral or right lateralization for sensory-related non-verbal material. Second, we should see a recruitment of the left VOTC also in sighted for non-visual stimuli. There is indeed a vast amount of studies in the literature supporting this hypothesis.

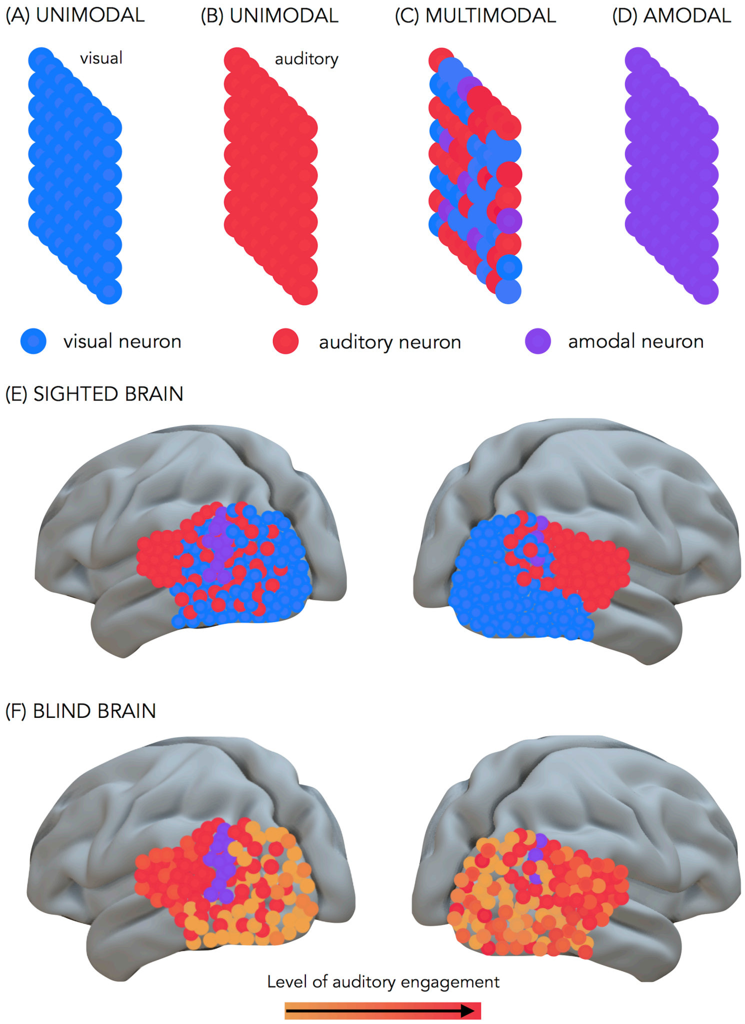

Figure 4.1: Schematic illustration of the occipital and temporal cortices representational format based on our data and on studies from the previous literature. Panels (A,B,C & D) represent the possible representational formats. (E) In sighted individuals the right hemisphere appears purely sensory-related, visual in the occipital cortex and auditory in the temporal cortex. The two populations of unimodal neurons coexist together in pMTG making this region multimodal but still sensory-related. In the left hemisphere the occipital cortex is recruited also during auditory processing and this involvement might reflect an engagement of the left VOTC in more semantic/linguistic processing of the stimuli potentially supported by its enhanced connection with the language system. Consequently, the left pMTG might also be more sensory-abstracted compared to the right homologous. (F) In case of early visual deprivation we will observe an enhanced effect of crossmodal plasticity on the right occipital cortex. This, originally, pure visual cortex will be, indeed, rewired toward the auditory modality. In the left hemisphere the reorganization will be less drastic since already in sighted this cortex is not purely visual. Moreover the extension of non-visual functions in the occipital cortex of EB triggers a network-level reorganization that may reduce the computational load of the temporal regions (represented in the figure by the colour gradient from orange to red)

In EB individuals the linguistic network includes a clearly left-lateralized occipital network. Left "visual" areas in EB activate for braille reading (Büchel et al., 1998b; Burton et al., 2002b; Reich et al., 2011; Hamilton and Pascual-Leone, 1998;

Sadato et al., 1996; Saxe et al., 2017), for listening auditory speech (Amedi et al., 2003; Arnaud et al., 2013; Bedny et al., 2011; Burton et al., 2006; Peelen et al., 2013a) and during word generation task (Amedi et al., 2003; Burton et al., 2002a).

Moreover, few studies reported increased response in EB left occipital areas during linguistic tasks compared to difficult non-linguistic perceptual and working memory tasks (Bedny et al., 2011c; Bedny, Pascual-Leone, Dravida & Saxe, 2011d).

These results strengthen the idea that left occipital cortex recruitment during language tasks in EB is linked to language processing specifically (Bedny, 2017; Bedny and Saxe, 2012).

On the other hand, the specific recruitment of the right occipital cortex in EB is often observed during auditory localization (Collignon et al., 2007, 2009c; Gougoux et al., 2005; Poirier et al., 2006; Weeks et al., 2000) or auditory motion processing (Dormal et al., 2016).

Importantly, some studies have even reported that the left occipital areas take part in the linguistic processing of stimuli even in sighted people. For example, activity of the lingual gyrus was observed during the processing of auditory sentence comprehension (Hasson et al., 2006) or during listening to auditory speech (Boldt et al., 2013). Finally, several studies reported a linguistically/semantic role of the visual world form area that goes beyond the one restricted to orthographical and pre-lexical processing of visual words previously suggested (Glezer et al., 2009; Price and Devlin, 2011). Our findings support a recruitment of the left VOTC, in both blind and sighted subjects, for a semantic or even a linguistic processing automatically triggered by the categorical sounds.

What might drive this hemispheric difference in the representational format of VOTC? One explanation could be related to their different connectivity profiles. In this regard, a key role in the functional organization of VOTC might be played by the visual word form area (VWFA) in the left hemisphere. This region shows a selective preference for written words compared to other symbolic visual stimuli (Cohen et al., 2000; Dehaene et al., 2002). Direct connectivity between the VWFA and perisylvian language areas supports the notion that this region is at the interface between the ventral visual recognition system and the language system (Bouhali et al., 2014, Richardson et al., 2011). Therefore, we speculate that VWFA could serve as entrance door for linguistic information inside the left VOTC and facilitate its involvement, beyond the visual nature of this region, in linguistic processing of the stimuli. A recent study also reported that visual deprivation strengthens the functional connections between the occipital regions and more anterior regions typically recruited in language processing (Deen et al., 2015).

A further question is whether also the other cortices involved in our stimuli processing will reflect this lateralization that emerged in the recruitment of the occipital cortex.

We, indeed, reported that the between-groups difference in the decoding of acoustic categories was reversed in occipital and in temporal regions (leading to a significant Group x Region interaction). More specifically, decoding accuracies in EB, when compared to SC, were enhanced in the occipital cortex but reduced in the temporal cortex. Interestingly, when we looked whether in EB there was a correlation between the recruitment of the temporal and the occipital cortices during the categorical processing of the auditory stimuli, we found a significant negative correlation only in the right hemisphere. In other words, we observed that the blind participants that showed the highest decoding accuracy in the right occipital cortex were showing the lowest decoding accuracy in the right temporal cortex and vice versa. The same correlation did not emerge from the left hemisphere. Combining together the results from both studies we observe an enhanced degree of crossmodal reorganization in the right occipital cortex of EB during categorical processing of auditory stimuli, in addition this increased recruitment of the right “visual” regions correspond to a decrease in the recruitment of their right auditory regions (see figure 4.1).

Once again, this effect is in line with the idea that the right hemisphere is more involved in processing sensory-related stimuli such as sounds or picture whereas compared to the left hemisphere (Gainotti, 2014; Thierry and Price, 2006). We might hypothesize that we would find in the left hemisphere a result similar to the one we found in the right hemisphere if we would include linguistic material among the (Amedi et al., 2003, 2007; Bedny et al., 2011; Büchel et al., 1998b;

Burton et al., 2002a; Hamilton and Pascual-Leone, 1998; Merabet et al., 2008; Röder et al., 2002; Sadato et al., 1996).

Another possibility is that the processing of auditory categories in the left occipital cortex of the blind individuals could be negatively correlated with other brain regions than the temporal auditory cortex. Possible candidates could be the frontal and the prefrontal language areas, previously showed to have an increased connectivity with the occipital cortex in blind when compared to sighted individuals (Bedny et al., 2011; Bock and Fine, 2014; Liu et al., 2007; Watkins et al., 2012). In support of this possibility, a TMS study showed a decreased performance in a verb to noun generation task in SC but not in EB when transcranial magnetic stimulation was applied to the left inferior prefrontal cortex (Amedi et al., 2007)). Therefore, an interesting follow-up of the present study would be to include linguistic material in order to test whether the left VOTC would enhance its response profile (since directly using linguistic material) and would allow the comparison of the representational format of the brain activity that linguistic stimuli would generate compared to sounds and picture stimuli.

In conclusion (as we represented in figure 4.1) we hypothesize that, according to previous literature, the right hemisphere is more sensory-related whereas the left side is more language-related. This subdivision in sighted takes place with a different gradient from the more high-level associative regions, such as ATL or pMTG, till the more sensory-related areas such as the ventral visual stream. In the case of early visual deprivation, the way crossmodal plasticity expresses will reflect this subdivision, showing enhanced crossmodal reorganization in the right occipital cortex for more sensory-related non-visual stimuli, whereas the left occipital cortex might be more devoted to linguistic processing of non-visual stimuli, enhancing the recruitment of a linguistic network that it is already there in sighted individuals.

4.5 Conclusion and future directions

In this dissertation I tried to investigate two crucial questions in the field of cognitive neuroscience: (1) How is semantic knowledge implemented in the brains based on separate sensory inputs? (2) What is the impact of visual experience on the neural structure of our semantic system? The present work participates in our understanding of how sensory input and sensory experience impact on the way the brain implements conceptual knowledge.

In study 1, we identified the right pMTG as the region that most reliably implements the representation of different categories in audition and vision and across sighted and blind groups. However, this region maintains separate the representational format from the different modalities, revealing a multimodal rather than an amodal nature. In addition, we observed that VOTC showed distinct functional profiles according to the hemispheric side. The stimuli representation in the right VOTC showed a pronounced visual format in sighted and, only in the case of early visual deprivation, they were involved in the representation of auditory stimuli. On the contrary, the left VOTC showed an involvement in the categorization of sounds at the same degree in sighted and in blind individuals. We speculated that this involvement might reflect an engagement of the left VOTC in more linguistic processing of the stimuli potentially supported by its enhanced connection with the language system. Future studies including linguistic material would help assessing whether the left VOTC more specifically represents linguistic stimuli when compared to real-world sounds and picture stimuli. Our prediction is that we would observe a stronger recruitment of the left occipital cortex/VOTC in both sighted and blind using auditory words compared to real-world sounds and potentially even stronger in early blind due to the crossmodal plasticity effect. In addition, similarly to what we found in left VOTC for sounds and pictures processing, we expect to find different neural representations for different modalities of presentation (e.g. auditory and written words) reflecting that this region maintains partially segregated representational format depending on the modality input.

Another interesting avenue for the future would be to rely on RSA analysis using the linguistic properties of the stimuli as external models based on (Baroni et al., 2009). This would determine if the functional profile of pMTG and VOTC would, at least partially, be explained by linguistic information. Our design does not allow us to implement this analysis because we mostly relied on object's concepts and therefore the language-statistic DSM based on our stimuli space is highly correlated with our categorical models. Future studies could investigate this point using a set of stimuli in which the categorical and the linguistic dimensions should be as much as possible orthogonal to each other. Finally, when we speak about the fact that our studies investigate the "conceptual system", we are well aware that this deceivably simple statement does not reflect the tremendous complexity of the number and type of concepts the human mind can deal with. To take just an example, our studies do no investigate the differences between abstract and concrete concepts; and investigating how early visual deprivation may specifically impact on those separate types of concept may reveal extremely interesting in better understanding how sensory experience shape high-level cognition (Does visual experience impact on the way we represent "freedom" as it does to the representation of a "banana"?).

In study 2, we observed opposite effects of early visual deprivation on auditory decoding in occipital and temporal regions. While occipital regions contained more information about sound categories in the blind, the temporal cortex showed higher decoding in the sighted. This unbalance effect was stronger in the right hemisphere where we also observed a negative correlation between occipital and temporal decoding of sound categories in EB. These last results suggest that the intramodal and crossmodal reorganizations might be inter-connected. We therefore propose that the extension of non-visual functions in the occipital cortex of EB may trigger a network-level reorganization that reduce the computational load of the regions typically coding for the remaining senses due to the extension of such computation in occipital regions. Here again, future studies should investigate whether the introduction of linguistic material among the stimuli would trigger such imbalanced reorganization more robustly in the left hemisphere between occipital and temporal (or between occipital and infero-frontal language-related) regions.

Finally, a further interesting follow-up for both studies would be to investigate the existence of a sensitive period in order for the imbalanced network-level reorganization to occur in case of visual deprivation. A way to investigate this possibility would be to include an additional group of individuals that lost their vision late in life. If vision has to be lost during an early sensitive period in order to reallocate the computational loading from the temporal/frontal/parietal cortices to the occipital one, then we should not be able to see this imbalanced reorganization in the group of late blind (Collignon et al., 2013; Jiang et al., 2016).

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