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PhD Thesis

**Decoding Auditory Motion Direction And Location In hMT+/V5  
And Planum Temporale Of Sighted  
And Blind Individuals**

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## Abstract

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The research presented in this thesis addresses the neural mechanisms of auditory motion processing and the impact of early visual deprivation on motion-responsive brain regions, by using functional magnetic resonance imaging. Visual motion, and in particular direction selectivity, is one of the most investigated aspects of mammalian brain function. In comparison, little is known about how the brain processes moving sounds. More precisely, we have a poor understanding of **how the human brain codes for the direction of auditory motion and how this process differs from auditory sound-source localization**.

**In the first study**, we characterized the neural representations of auditory motion within the Planum Temporale (PT), and how motion direction and sound source location are represented within this auditory motion responsive region. We further explore if the distribution of orientation responsive neurons (topographic representations) within the PT shares similar organizational features to what is observed within the visual motion area MT/V5. The spatial representations would, therefore, be more systematic for axis of motion/space, rather than for within-axis direction/location. Despite the shared representations between auditory spatial conditions, we show that motion directions and sound source locations generate highly distinct patterns of activity.

**The second study** focused on the impact of early visual deprivation on auditory motion processing. Studying visual deprivation-induced plasticity sheds light on how sensory experience alters the functional organization of motion processing areas, and exploits intrinsic computational bias implemented in cortical regions. In addition to enhanced auditory motion responses within the hMT+/V5, we demonstrate that this region maintains direction selectivity tuning, but enhances its modality preference to auditory input in case of early blindness. Crucially, the enhanced computational role of hMT+/V5 is followed by a reduced role of PT for processing both motion direction and sound source location. These results suggest that early blindness triggers interplay between visual and auditory motion areas, and their computational roles could be re-distributed for effective processing of auditory spatial tasks.

Overall, our findings suggest (1) auditory motion-specific processing in the typically developed auditory cortex, and (2) interplay between cross- and intra-modal plasticity to compute auditory motion and space in early blind individuals.

**Keywords:** Auditory motion, PT, crossmodal plasticity, hMT+, fMRI.

## Overview

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The ability to finely compute auditory motion direction and localize sound sources is a critical, but under-investigated, cognitive process that most of the animal kingdom uses to efficiently interact with their dynamic environments. While the brain mechanisms underlying the processing of visual location and visual motion have received considerable attention, much less is known about how the brain implements spatial hearing.

The present thesis aims at investigating the neural mechanisms of auditory motion and localization in sighted and blind individuals. In chapter 2, we investigate the neural mechanisms underlying the processing of auditory directions and how this process differs from sound-source location. Chapter 3 focuses on how the lack of visual experience affects the functional organization of the brain regions typically involved in the processing of auditory and visual motion. Chapter 4 reviews the most important results and conclusions of each empirical work and links them with the general framework on the cortical representation of auditory motion and crossmodal plasticity. The following chapter will provide a review of the literature that inspired the empirical work conducted throughout the thesis. First, our review will focus on auditory spatial processing in the auditory pathway, and then will illustrate what we currently know about visual motion processing. The final part of the introduction will center on how brain reorganizes itself to adapt to the lack of vision.

## **Chapter 1**

### **General Introduction**

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## **1. GENERAL INTRODUCTION**

### **1.1. SOUND SOURCE LOCALIZATION**

The locations in space of somatosensory stimuli are mapped onto the sensory surfaces, i.e. retina and skin, before reaching a topographically organized primary sensory cortex. For instance, the location of a visual object activates specific cells in the retina that project to visual cortex and maintain their spatial relationships all the way to extrastriate cortex and even beyond (e.g. parietal, frontal) (Serenio & Huang 2006; Saygin & Serenio 2008; Harvey et al., 2013; Wandell & Winawer 2011; see review Wandell et al. 2007). This means that objects that are close to each other maintain their spatial relationship essentially intact as they proceed to higher visual levels (retinotopic organization). The somatosensory system also has a topographic (somatotopic) organization such that the location of a tactile event on the body activate selective region in the somatosensory cortex and regions close to each other occupy nearby regions of the cortex (the homunculus). In this regard, spatial hearing is a unique process in the auditory system. The auditory system, unlike visual or somatosensory, does not have a direct sensory surface containing receptors for the spatial position of sounds. The primary auditory cortex (Merzenich et al., 1974; Striem-Amit et al. 2011; Langers et al. 2014; De Martino et al. 2015) (and beyond Merzenich et al., 1974; De Martino et al. 2013), mirrors the organization of the cochlea by displaying a tonotopic (or cochleotopic) organization, showing a topological organization dependent on the frequencies of the sounds. While frequency is being mapped onto the cochlear sensory surface, the auditory space, however, relies on computations between binaural and spectral cues that arise at each external ear and between the ears (see for review Middlebrooks 2015; Middlebrooks 2002; Grothe et al. 2010). Binaural cues are based on the interaural time (ITD) and level differences (ILD), processed in different parts of the auditory pathway to derive the sound source location mainly in the horizontal plane (Blauert 1983; see for review Blauert 1997). While binaural cues rely on both ears for detecting and computing the level and the time difference of the sound reaching the eardrum, spectral cues are represented monaurally. The pinna (outer ear), head and torso modulate the spectral content of sounds depending on the direction of the source, such content is mainly essential for localizing sounds in the elevation and differentiating the sound sources from front and behind (Blauert 1997).



### 1.1.1. Neural mechanisms for spatial processing

Sound waves reaching the external ears alter the air pressure and causes vibration in eardrum. Vibrations are carried into the cochlea, the hearing organ of the inner ear. Evoked vibrations transduced into action potentials in the cochlea and via auditory nerves, these neural signals are transmitted into the ventral and dorsal cochlear nuclei in auditory brainstem (Grothe et al. 2010). Cochlear nuclei and superior olive structures in the brainstem contain neurons showing differential activity for spatial cues. While neurons in medial superior olive complex (MSO) and lateral superior olive complex (LSO) compute ITD and ILD, respectively, dorsal cochlear nucleus (DCN) cells are sensitive for spectral cues (Goldberg & Brown 1969; Yin & Chan 1990; Boudreau & Tsuchitani 1968; Young et al. 1992; Imig et al. 2000). Early processing of spatial cues is followed by a topographic representation of location in the auditory pathway. Specifically, in barn owl nucleus laminaris, inferior colliculus (IC) and optic tectum show a topographic representation of acoustic space (Knudsen & Konishi 1978). Further studies in mammals also have demonstrated topographic organization in other subcortical nuclei (Palmer & King 1982; Middlebrooks & Knudsen 1984).

Even though numerous studies investigated the existence of *spatiotopic* organization in the auditory cortex across different species (e.g. avian, cats, primates), up to our knowledge, there is no evidence of point-to-point spatial representation in the auditory cortex (Middlebrooks & Pettigrew 1981; Rajan et al. 1990; Middlebrooks 2002; Middlebrooks & Bremen 2013; McAlpine et al. 2001; Derey et al. 2016; Ahveninen et al. 2006; Brunetti et al. 2005; Deouell et al. 2007). Yet, lesion studies have demonstrated the critical role of the auditory cortex for spatial hearing in humans (Sanchez-Longo & Forster 1958; Zatorre & Belin 2001; Duffour-Nikolov et al. 2012).

Auditory cortex neurons show large receptive fields to variety of spatial locations, indicating that instead of responding preferentially to a specific location in space, the neural response show broad spatial tuning (Recanzone 2000; Stecker et al. 2005; Miller & Recanzone 2009). Firing rates of neural populations that carry information about sound source are widespread over the auditory cortex (Miller & Recanzone 2009; M. Ahissar et al. 1992). Authors suggested that different cortical areas carrying sound location information could account for observed inhomogeneous sampling of space (e.g. lack of spatiotopy). The broad spatial receptive fields of neurons are unlikely to account for encoding auditory location, however population of neurons might be underlying mechanism of sound source localization (Mcalpine et al. 2001; Stecker et al. 2005; Miller & Recanzone 2009). Moreover,

majority of sound-location sensitive neurons in the auditory cortex show sharp discrimination of left vs. right sounds indicating preferential contralateral response (Middlebrooks & Green, 1991). These results led to *opponent-process* assumption in which sound locations are represented by the differences in the activity of neural subpopulations that are preferentially coding for the opponent space. The opponent population coding proposes that spatial hearing in the azimuth is encoded by a combination of broadly tuned neurons with overall preference for opposite acoustic hemifields (Day & Delgutte 2013; Mcalpine et al. 2001; Stecker et al. 2005).

The coarse preference to spatial locations in the auditory cortex could potentially indicate that the auditory cortex performs as a high-level associative area that integrates or segregates spatial cues in order to process complex stimuli. Similarly, high-level associative neurons in the visual cortex (i.e. extrastriate neurons) have bigger receptive fields and prefer more complex stimuli than neurons in the primary cortices. Therefore, they potentially integrate visual information in a more abstract level (spatially over a larger range) (Hubel and Wiesel 1965). By the same token, auditory neurons in the non-primary fields or regions that are higher up in the processing pathway, might be expected to integrate information over a larger range of auditory space (Rauschecker et al. 1995), instead of showing fine-tuned selectivity for wide-range of sound sources.

### **1.1.2. Functional organization of auditory cortex**

A dual-streams hypothesis proposes a framework to study spatial processing in the auditory cortex of mammals (Rauschecker & Tian 2000). In the visual cortex, the ventral stream is specialized for object recognition, and the dorsal stream for identifying where the object is (Haxby et al. 1991; Mishkin 1983; Goodale & Milner). Neuroimaging studies in humans support the existence of a dual-stream structure in both vision and audition. More recently, a third pathway was suggested for processing sensorimotor information for the auditory system (Kaas & Hackett 2000), however, the debate has been inconclusive about the presence of this third pathway (see for review Rauschecker 2017).

In the auditory cortex, the “where” pathway was proposed to encompass the caudal portion of the superior temporal gyrus (including planum temporale) (Romanski et al. 1999; Rauschecker & Tian 2000), and the “what” pathway was proposed to encompass rostral areas of the cortex and preferentially process non-spatial, auditory object recognition information (Kaas et al. 1999; Romanski et al. 1999; Rauschecker & Tian 2000; Chevillet et al. 2011). Applying reversible cooling on cat auditory cortex demonstrated that deactivation of

posterior auditory fields (“where” pathway) resulted in sounds localization impairments, while deactivation of anterior fields (“what” pathway) resulted in pattern discrimination impairments (Lomber & Malhotra 2008). Furthermore, the cooling technique has shown that the posterior portions of cat auditory cortex have stronger impact on the spatial hearing abilities, rather than lesions in primary auditory region (Malhotra et al. 2008). Similarly, the cat auditory cortex shows greater spatial sensitivity in the dorsal zone (DZ) and in posterior auditory field (PAF) in sound localization (Stecker et al. 2005; Stecker & Middlebrooks 2003). In non-human primates, the caudomedial (CM) and caudolateral (CL) belt area neurons show greater spatial selectivity compared to neurons in A1 (primary auditory cortex) and anterior regions (Recanzone 2000; Tian et al. 2001; Woods et al., 2006; Miller & Recanzone 2009). Evidence from human neuroimaging studies strengthens the role of posterior fields in processing auditory location and motion (Warren et al. 2002; Brunetti et al. 2005; Krumbholz et al. 2005; Zimmer et al. 2006; Deouell et al. 2007), while the anterior auditory belt areas are primarily responsive to the spectro-temporal features of a sound,, crucial for the object identity (Griffiths et al. 1998; Barrett & Hall 2006; Hart et al. 2004).

### **1.2. Auditory motion processing in the auditory cortex**

A number of neurophysiological studies have investigated the processing of auditory motion cues in the brain stem and in the cortex (Altman et al., 1970; Ahissar et al. 1992; Spitzer and Semple 1993; Doan et al. 1999; Stumpf et al. 1992; Toronchuk et al. 1992; McAlpine et al. 2000). Neurons in IC show sensitivity to direction, location and extent of apparent motion cues in cats (McAlpine et al. 2000; Spitzer and Semple 1993). Furthermore, from IC to medial geniculate body and primary cortex, the proportion of direction selective neurons increases (Altman 1968; Altman et al., 1970; Altman 1987). However, there is no conclusive evidence whether these neurons exhibit selectivity specifically to motion direction or to spatial location (Poirier et al. 1997; McAlpine et al. 2000; Ingham et al. 2001).

A lesion study on two patients with auditory agnosia and two patients with auditory spatial deficits following left hemispheric lesions strengthens the notion of distinct processing pathways in the human auditory cortex (Clarke et al. 2000). More specifically, lesions including superior, middle and inferior temporal gyri and lateral auditory areas led to deficits in recognition of object sounds, however, auditory localization and motion perception were intact. Lesions in the supratemporal region (including Heschl’s gyrus, planum polare and temporale) led to severe impairments of motion perception and partial deficit in auditory localization, indicating a possible crucial role of dorsal stream for motion

perception. More recent studies have demonstrated auditory motion processing may take place in the further posterior parts of the temporal and parietal cortices (Lewald et al. 2009; Thaler et al. 2016).

Additionally, among auditory selective cortical regions in the posterior field, the planum temporale (PT) region seems to play a critical role in spatial hearing. The PT region is in the superior temporal gyrus, posterior to primary auditory cortex (Heschl's gyrus), and it is considered the homolog region of monkey CM and CL belt areas. Some authors have pointed toward a specific role in motion for this area (Poirier et al. 2017). However, other studies have suggested that PT engages in spatial hearing in general (Zatorre et al. 2002). Human functional magnetic resonance imaging (fMRI) studies indicate that the area PT is particularly responsive to spatial stimuli (Barrett & Hall 2006; Derrey et al. 2016), and it is preferentially activated by moving compared to static sounds (Baumgart & Gaschler-Markefski 1999; Bremmer et al. 2001; Rees et al. 1998; Hall & Moore 2003; Lewis et al. 2000; Pavani et al. 2002; Warren et al. 2002; Krumbholz et al. 2005). Multivariate pattern analyses support the notion that PT carries auditory motion information (e.g. content, direction of motion) (Alink et al. 2012; Jiang et al. 2014; Jiang et al. 2016; Dormal et al. 2016). However, whether PT plays a specific role for auditory motion or if it engages in the processing of spatial locations as well, remains a matter of debate. According to the snapshot hypothesis, motion can be inferred from snapshots of object positions, without a motion-specific mechanism (Grantham 1986; 1997). Early neurophysiological studies in animals reported direction-sensitive neurons in the auditory cortex (M. Ahissar et al. 1992; Toronchuk et al. 1992; Poirier et al. 1997; Doan et al. 1999), while a large portion of neurons that responded to moving stimuli showed sensitivity to spatial location with externalized sound stimuli (Poirier et al. 1997; Ingham et al. 2001). This led to the suggestion that the observed motion-related activity in PT may link to spatial and spectro-temporal components of the sounds, rather indicating preference to moving stimuli (Zatorre et al. 2002; Smith et al. 2010). Even so, a recent study in monkeys has demonstrated thoroughly that in CM and CL areas, the auditory motion activation is not merely due to sequential processing of sound source locations (Poirier et al. 2017). In humans, however, further research is needed to understand whether auditory motion perception is derived from motion specific neural processing or if motion and spatial localization rely on, at least partially, common neural mechanisms in the human PT. More specifically, if responses to auditory motion within PT could simply be due to computing various sound source locations, the representation of motion direction and location could rely on similar patterns. Alternatively, while some

aspects of the neural patterns might be shared across motion direction and location, representations of both auditory conditions could be unique.

The empirical work in study 1 was designed to characterize neural response within PT, to evaluate whether it reflects distributed information about auditory motion direction and spatial location, and if so, to quantify the extent of functional overlap between the representations of direction and location. Furthermore, we investigated the characteristic tuning of this region for separate directions and within-axis aggregated (i.e. opposite) motion directions. If the distribution of orientation responsive neurons (topographic representations) within the PT shares similar organizational features to what is observed in MT/V5, the spatial representations might therefore be more systematic for axis of motion/space, rather than for within-axis direction/location.

To deepen our understanding of motion and its representation in the cortex, the following section will briefly review the literature about the well-established visual motion area hMT+/V5. Following that, the third section is focused on studies investigating blindness and how sensory experience alters the intrinsic functional organization of auditory motion processing.

### **1.3. Visual Motion Processing Area MT+/V5**

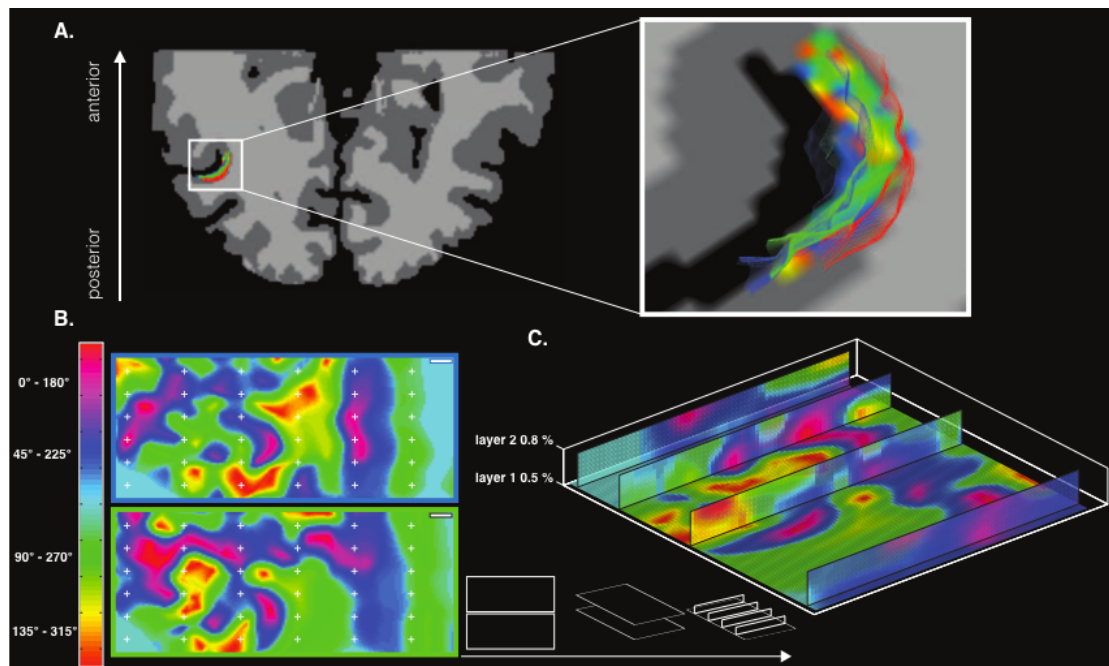
The primary visual cortex has a cortical columnar organization for orientation selectivity (Felleman and Van Essen, 1987; Hubel and Wiesel, 1968). Columnar organization suggests that neurons in the same column share the same receptive field and process the same information (Mountcastle 1956). In primary visual cortex, columnar organization is highly selective for orientation and motion direction (Hubel and Wiesel, 1974).

In the visual cortex, many areas are selective for moving stimuli. One of the strongest motion-selective responses emerges from middle temporal visual area, MT/V5 (Dubner & Zeki 1971; Allmann & Kaas 1971; Maunsell & Van Essen 1983; Albright et al. 1984). In non-human primates, area MT contains an abundance of neurons selective for the direction of visual motion, and shows columnar organization of preferred direction of motion. Continuous representation of preferred direction of motion columns is occasionally disrupted by a set of columns preferring the opposite direction (see section 1.3.1). This suggests that the representation of motion axis in area MT/V5 is more systematic (Albright et al. 1984). Single-cell recordings and micro-stimulation experiments have demonstrated a direct role of MT/V5 in perceiving motion direction (Newsome et al., 1985; 1986; Cohen et al., 2004; Liu & Newsome 2005).

Using fMRI, the human homologue of MT/V5 (hMT+/V5) in the posterior part of the inferior temporal sulcus has been functionally identified by its strong preference for visual motion stimuli (Watson et al., 1993; Tootell et al. 1995; Dumoulin et al. 2000). The hMT+/V5 complex consists of the human homologue of MT, and the surrounding dorsal and lateral medial superior temporal areas (MSTd/MSTl). The coarse retinotopic organization in these areas shows that area MT responds to motion in the contralateral visual hemi-field, and MST responds to ipsilateral motion and processes more complex types of motion (e.g. visual flow) (Dukelow et al. 2001; Morrone et al. 2000; Smith et al. 2006). Similar to monkey V5, lesions in hMT+/V5 complex have been reported to result in akinetopsia, in which the patient is unable to perceive motion while visual perception for other types of visual stimuli is unaffected (Zeki 1991).

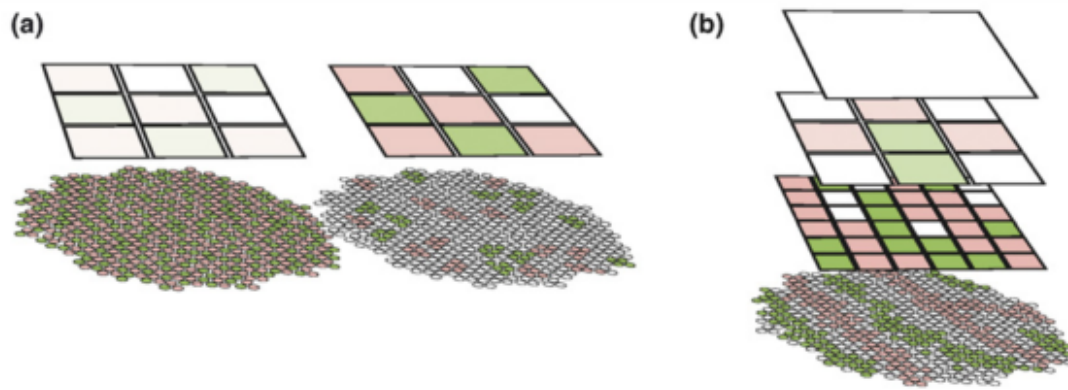
### **1.3.1. Columnar organization of MT/V5**

Motion direction preference in MT/V5 complex has also been investigated in humans by using standard and high-field fMRI techniques (Kamitani & Tong 2006; Tong et al. 2012; Zimmermann et al. 2011). The lack of columnar level spatial resolution in non-invasive human neuroimaging techniques prevents a direct identification of direction-selective responses in hMT+/V5 (Uğurbil et al. 2003). High-field human fMRI experiments show that a spatial resolution of 1.1 mm (iso-voxels) is close to the resolution needed to image columnar structures (Zimmermann et al. 2011; Rosa et al. 1988; Adams et al. 2007; Diogo et al. 2003). In primary visual cortex, reliable maps have been obtained for ocular and orientation columns (Cheng et al., 2001; Moon et al., 2007; Yacoub et al., 2007). High-field fMRI (7T) has revealed reliable axis-of-motion columns in hMT+/V5 (Zimmermann et al., 2011) arising from neighboring columns with preferred motion directions that are opposite (i.e. 180° difference, Figure 1), rather than individual direction-selective columns like those for orientation selectivity. Investigating single-direction of motion columns potentially requires employing higher spatial resolutions (Zimmermann et al., 2011; Emmerling et al., 2016).



**Figure 1. Illustration of columnar representation of axis of motion from high-field fMRI data.** The results of hMT+/V5 visual localizer experiment are projected onto cortical reconstructions of the left hemisphere. fMRI data sampling was focused at two cortical depths. B. Results of motion direction experiment in high-cortical sampling demonstrate columnar organization of axis of motion. C. An illustration of two cortical layers. Adapted from Zimmermann et al. (2011).

Another approach to investigate direction selective responses in hMT+/V5 with standard human imaging is by using multivariate pattern analysis (MVPA) that relies on machine learning algorithms. In a voxel, the blood-oxygen-level dependent (BOLD) signal consists of averaged responses of several cortical columns. MVPA exploits the BOLD signal across different voxels and treats this as an activity pattern. Classifiers are trained to use such multivariate samples of a group of voxels to learn patterns of activation and assign each pattern in the data to stimulus conditions (Norman et al. 2006; Haxby et al. 2001; Haynes 2015). MVPA has been used to decode motion direction information in early visual areas and in hMT+/V5 complex in humans (Kamitani & Tong 2006; Tong et al. 2012; Beckett et al. 2012), however in these studies, classifiers did not perform well in hMT+/V5, compared to early visual areas. The probable reason for such discrepancy in performance could be the existence of densely packed cortical columns with opposite direction preference, and not individual direction-selective columns (for a review see Bartels et al. 2008, Figure 2).



**Figure 2 Cortical functional organization and pattern classification analysis.** A. Schematic illustration of spatial distribution of motion direction selective columns in area X (left panel), in area Y (right panel). Area X has densely packed distribution of feature-selective columns, therefore, the classification of feature-based information is worse compared to that of area Y, as the gross spatial distribution of feature selectivity in Y allows better detection of feature information by the detectors. B. Illustration of how scanner resolution affects the outcome of the fMRI data analysis of the underlying brain area at the bottom level. Top level contains no information about the feature as it averages over the entire brain area. The second level with an increased resolution shows a pattern of voxels, allowing MVPA to reveal feature specific information. At the third level, actual functional organization can be reached using voxel-wise approach in high-resolution imaging. Adapted from Bartels et al. (2008).

The averaged signal from an area, for instance hMT+/V5, containing very closely spaced direction-selective columns, can nullify the direction selectivity of the area (Fig 2A, left panel). The spatial arrangement of directional preferences dictates the strength of the average signal and subsequently the performance of the classifier. Thus, a classifier could perform comparably on an early visual area with weaker directional preference as on direction-selective hMT+/V5 complex, if their spatial arrangement of the signals were different. (Figure 2A, right panel). With these methodological constraints in mind, these studies nevertheless indicate that MT+ is highly specialized for visual motion, and its function is preserved across different primate species.

#### 1.3.1.1 Plausible mechanisms underlying decoding

Pioneering studies in the field suggested that MVPA can bypass the spatial limitations and detect feature-specific information within the activity pattern of many voxels, based on the cortical columns at submillimeter scale (Kamitani & Tong 2005). The hypothesis relies on that cortical column responses lead to weak biases in each voxel. Resulted local biases contain information about orientation/direction preferences. Such biases can be measured by computing activity pattern of many voxels and reflect a stable selectivity for orientation (Kamitani & Tong 2005). However, this assumption seems to contradict with the low-spatial resolution of standard fMRI signal due to spatial spread of the underlying hemodynamic factors. If decoding stem from the biases (within each voxel)



emerged at the cortical columnar level (e.g. direction, and orientation selective columns) (Kamitani & Tong 2006; Bartels et al., 2008), then smoothing of the data would decrease the decoding accuracies (see Figure 2b). Recent evidence points to no influence of smoothing on the decoding accuracies, therefore, against the ‘biased sampling’ assumption (Op de Beeck 2010). Accordingly, studies conducted on early visual cortex proposed that decoding orientation preference reflects much larger scale (e.g. retinotopy) rather than columnar organization (Freeman et al. 2011; Freeman et al. 2013; Op de Beeck 2010). Answering the question of whether decoding of orientation/direction reflects fine-scale or large-scale biases (Kriegeskorte et al. 2010; Alink et al. 2013; Freeman et al. 2011; Freeman et al. 2013) have a particular importance to understand not only the functional organization of feature selectivity in the visual cortex, but also the types of information that can be detected in neural activity patterns (Swisher et al. 2010; Shmuel et al. 2010; Tong & Pratte 2012; Gardner 2010) and at the scale of individual voxels (Kay et al. 2008; Serences et al. 2009; Kriegeskorte et al. 2010).

Interestingly, high-field fMRI studies showed that the fMRI signal carries information related to both fine- and large-scale biases (Sengupta et al. 2017; Gardumi et al. 2016; Pratte et al. 2016). Combining voxels with similar visual field preferences that are determined in separate retinotopy measurements showed that classification accuracy was sustained even when voxels were averaged across substantial distance in the cortical surfaces (Beckett 2012). Large-scale, retinotopically restricted biases were suggested to play a role in classification. Although large-scale biases contribute to the performance of decoding, they are not the sole factors (Pratte et al., 2016). Modifications in the spatial filtering affect the performance of orientation decoding (Sengupta et al. 2017). Furthermore, a study conducted on the auditory cortex investigated the effect of spatial resolution and smoothing on the decoding accuracies on two different auditory tasks (Gardumi et al. 2016). The authors concluded that the influence of fine- and large-scale spatial biases depends on the specific task of interest. These studies support the notion that MVPA results could reflect the combination of both large-scale (e.g. retinotopy) and fine-scale (columnar) organizations. Similarly, in early visual areas and hMT+/V5 decoding of motion directions suggested to emerge from macroscopic organizational principles at the level of retinotopic maps, instead that from the functional organization of motion selectivity (Beckett et al. 2012; Wang et al. 2014). Although results in hMT+/V5 are inconclusive, overall evidence suggests that both retinotopy and columnar organizations seem to play critical role in decoding performance.

Altogether, advanced fMRI analyses performed on the neural activity patterns should be carefully interpreted with the considerations of the underlying anatomical organizations, as well as large and fine-scale influences within the fMRI signal.

### **1.3.2. Development of hMT+/V5**

The ability to detect motion is one of the most important skills for survival. For this crucial skill, as mentioned above, the visual cortex contains a highly specialized region for visual motion perception that develops functionality in very early stages of life (Braddick et al. 2005; Gilmore et al. 2007). The perceptual preference to moving compared to static stimuli develops soon after birth, in as young as 1 month old infants (Volkman and Dobson 1986; Wattam-Bell 1996). Following motion preference, infants during their first 4 months develop visual evoked potentials for different motion directions, indicating direction selectivity (Braddick 1986, 2005; Hou 2009). Furthermore, evoked brain activity in infants between 4 to 6 months of age, shows differential response to coherent moving patterns (Gilmore et al. 2007; Shirai et al. 2009; Lee et al. 2013). These studies support the notion that visual motion area is highly organized from birth and develops very early in life, somehow pointing toward a genetically predetermined functional organization.

During early stages of development, even a short period of disturbance has, however, profound effects on motion perception. Individuals who were born with or developed dense bilateral cataracts show permanent impairments in their ability to perceive overall motion direction, even after their cataracts have been surgically removed soon after birth (Ellemberg et al. 2002; Hadad et al. 2012). Interestingly, global motion percept is intact when the visual deprivation occurs later, after 8 to 57 months of age (Ellemberg et al., 2002). Even if the development of motion perception and the functional tuning of brain regions toward motion processing is evident early after birth, the development and maintenance of this functional and perceptual organization is highly dependent on early visual experience (Collignon et al. 2015).

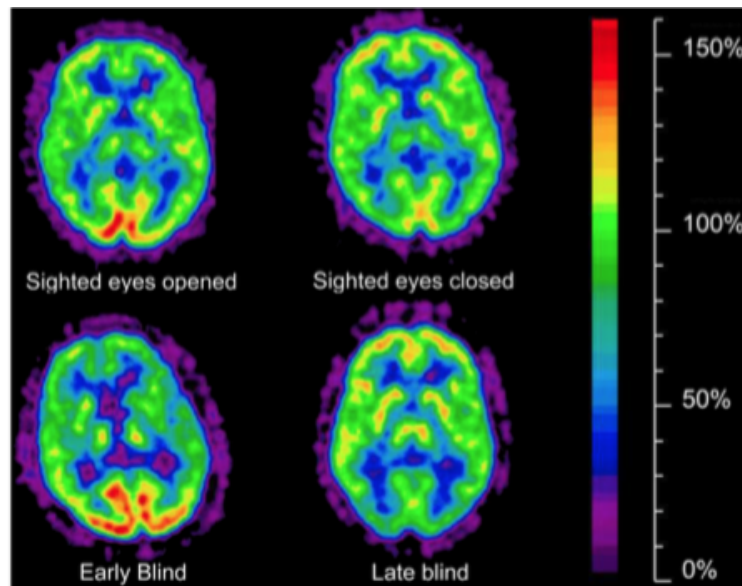
Thus far, the thesis has reviewed two key aspects. The first section provided a brief summary of how auditory motion and static location are represented in the auditory pathway and discussed putative motion-responsive regions in the auditory cortex. The second section was dedicated to the functional specialization of visual motion-selective area, hMT+/V5. The section that follows considers the impact of visual deprivation on the visual and auditory cortices.

### 1.4. PLASTICITY IN THE BLIND BRAIN

Research on blindness represents a unique opportunity to study neuroplasticity, which refers to our brain's ability to adapt to the environment and how our experiences throughout our lifetime reorganize neural pathways (Bavelier & Neville 2002). Lack of visual experience in early development, for instance, leads to massive reorganization of sensory cortices (see reviews Collignon et al. 2012; Dormal et al. 2012).

Congenital blindness, or blindness from birth, triggers cortical expansion in the tonotopic maps of the auditory cortex and increases the representation of the finger most used for Braille reading by the blind individuals within the somatosensory cortex (Pascual-leone & Torres 1993; Sterr et al. 1998; Elbert et al. 2002). These experience-dependent **intramodal** alterations in the primary sensory cortices of the congenitally blind can be explained by enhanced reading abilities and auditory processing skills (Elbert et al. 2002; Goldreich & Kanics 2003; Wong et al. 2011). In contrast, passive listening induces lower activity in the auditory cortex of congenitally blind than in late blind and sighted controls (Stevens et al. 2007; Watkins et al. 2013). Recent studies have reported that early visual deprivation results in reduced auditory motion information within area PT (Jiang et al. 2014; Jiang et al. 2016; Dormal et al. 2016).

In addition to intramodal plasticity, visually deprived occipital regions start to respond to other sensory inputs (Rauschecker 1995). This form of brain reorganization is called **crossmodal** plasticity as opposed to intramodal plasticity. Massive crossmodal plasticity has been reported in the occipital cortex of early blinds. A pioneering neuroimaging study found higher metabolic activity in early blind visual cortex in response to auditory spatial localization tasks compared to their blindfolded sighted peers (Wanet-Defalque et al. 1988). This study was followed by another positron emission tomography (PET) study showing higher glucose consumption in early blinds compared to both sighted and late blind people in the visual cortex (Veraart et al. 1990) (Figure 3).



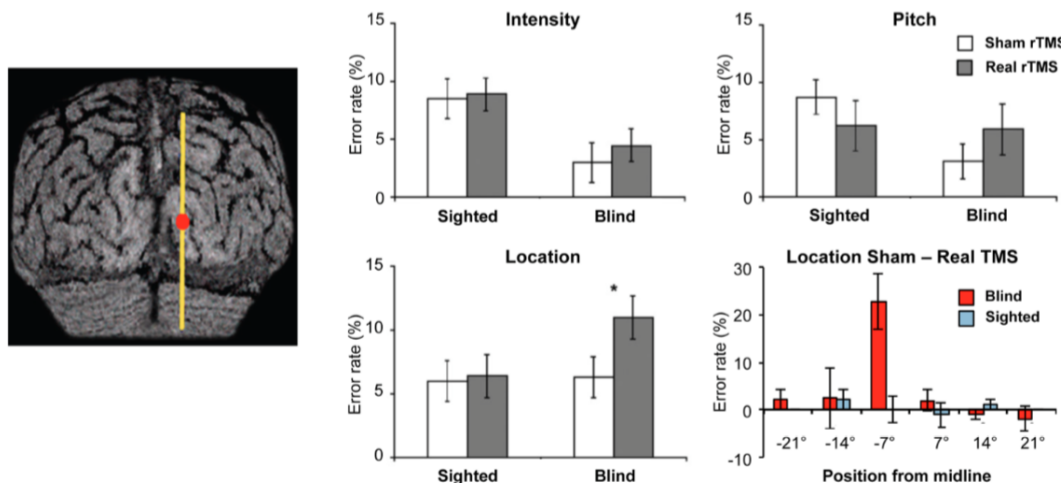
**Figure 3. Glucose metabolisms in sighted and blind subjects.** In the top panel, the consumption of glucose was presented in sighted subjects (left: eyes open, and right: eyes closed), in the bottom panel glucose consumption of early blinds (right) appears higher than in sighted subjects eyes closed and than in late blind subjects (left). Adapted from Veraart et al. (1990).

Braille reading activates the occipital cortex in blind subjects but not in the sighted controls (Sadato et al. 1996; Büchel et al. 1998). In addition to tactile stimuli, auditory (Kujala et al. 2005; Roeder et al. 1999; Weeks et al. 2000) and language related (Röder et al. 2000; Burton et al. 2002) tasks activate the visually deprived occipital cortex. Visually deprived occipital cortex is not only responsive to a variety of verbal tasks but its response profile becomes actually similar to that of classical language areas (Bedny et al. 2011).

#### 1.4.1. Functional relevance of crossmodal plasticity

Correlation between neural activity and the improved abilities of blinds demonstrated that these cross-modal alterations might potentially be compensatory (Amedi et al. 2003; Gougoux et al. 2005; see Benetti et al. 2017 for a similar example in congenitally deaf people). However, correlation does not mean causation. Transcranial magnetic stimulation (TMS) can be used to gain further causal evidence that cross-modal plasticity is not just an epiphenomenon but functionally links to the processing of the remaining senses. Indeed, TMS is a useful tool to demonstrate a causal link between a specific brain region and a particular cognitive operation. Interfering with occipital regions alters braille reading in blind individuals and induces tactile sensations in the fingers of blind Braille readers (Cohen et al. 1997; Kupers et al. 2007). In contrast, occipital stimulation causes no disruption in identifying Roman letters in sighted controls. Furthermore, repetitive TMS decreases

accuracy of verb generation in congenitally blind but not in blindfolded controls (Amedi et al. 2004). TMS on right dorsal occipital regions disrupts performance on sound localization only in blind individuals, but does not alter the discrimination of pitch and intensity in sound processing tasks (Collignon et al. 2006). This study suggests that regions typically involved in visuo-spatial processing (right dorsal occipital stream) in sighted individuals are recruited in audio-spatial processing in the blinds (Figure 4).



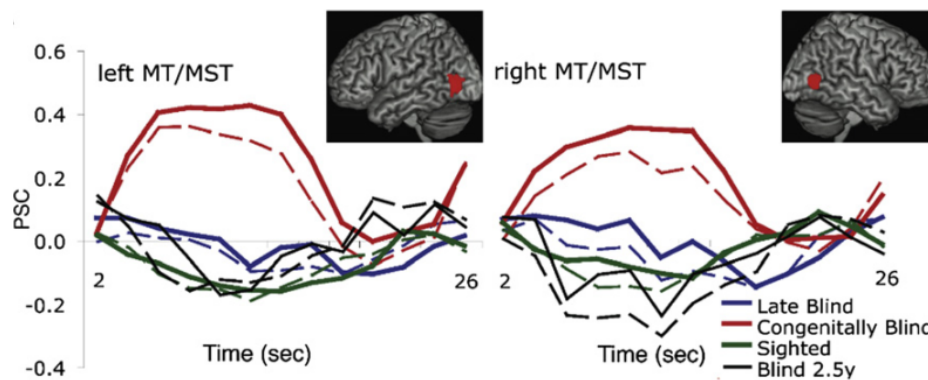
**Figure 4. Functional relevance of right dorsal occipital region for spatial localization in early blind individuals.** TMS applied to right dorsal extrastriate regions selectively disrupts sound localization only in early blinds. Pitch and intensity discriminations remain unaffected in both groups. Adapted from Collignon et al. (2007).

Importantly, the functional recruitment of occipital regions in blinds appears to have a functional role in task-dependent processing rather than an unspecific generalized gain of function.

### 1.4.2. Critical period of neural development

As mentioned above, non-visual tasks strongly activate the occipital cortex of congenitally blind and early blind groups. The extent to which crossmodal plasticity manifests in late blinds remains more elusive. One of the first neuroimaging studies in blind individuals demonstrated larger occipital activity in early blinds compared to the sighted controls with eyes closed and late blinds (Veraart et al., 1990, see Figure 3). Although both late and early blind groups showed higher activity in the visual areas than sighted peers in a tactile task, V1 activity was suppressed in the late blind group (Sadato et al. 2002). This suggests the existence of a critical period for crossmodal plasticity in the blind individuals.

Visually dominated motion responsive regions hMT+/V5 reveal significantly different activity in early and late blind individuals (Bedny et al. 2010). In early blind individuals, hMT+/V5 is activated for auditory motion. However, activity in late-blind adults for moving sounds is below baseline, like in sighted subjects (Figure 5). Interestingly, in a blind individual who lost his sight after the age of 2-3, the responsiveness of hMT+/V5 was more similar to sighted group rather early blind group (Bedny et al. 2010). Despite more than 50 years of visual deprivation, in this individual, visual motion area hMT+/V5 region were not recruited for auditory motion.



**Figure 5. Critical period for crossmodal plasticity in hMT+/V5 for auditory motion in early and late blind, and sighted individuals.** Responses to auditory looming with high (straight lines) and low motion (dashed lines) content are only seen in visual areas of the congenitally blind individuals, while late blind individuals show baseline activity as an early blind subject who lost sight at the age of 2.5 years old. Adapted from Bedny et al. (2010).

Similarly, while sound processing activates some occipital regions in both congenitally and late blind individuals, the cuneus is only activated by sound in congenitally but not late blinds (Collignon, Dormal, Albouy, et al. 2013). More importantly, spatial processing of sounds selectively activates the right dorsal stream only in congenitally blind individuals. Recent studies in cataract-reversal individuals demonstrated that a short period of visual deprivation triggers long-lasting occipital cortex reorganization, but not functional specialization (Collignon et al. 2015), and enhanced the salience of auditory inputs during audiovisual integration tasks (de Heering et al. 2016). Furthermore, no difference in auditory cortical responses was observed during an auditory motion task between cataract-reversal individuals and normally sighted participants (Collignon et al., 2015), suggesting that a brief and reversible period of visual deprivation does not have permanent effect on auditory cortex. Losing sight during a critical period of development may lead to the enhancement of functional specialization in visual cortex to a non-visual modality, while in late blind individuals, crossmodal plasticity shows no domain specific functional organization. In this thesis, only congenitally and early blind individuals will be included as participants since we

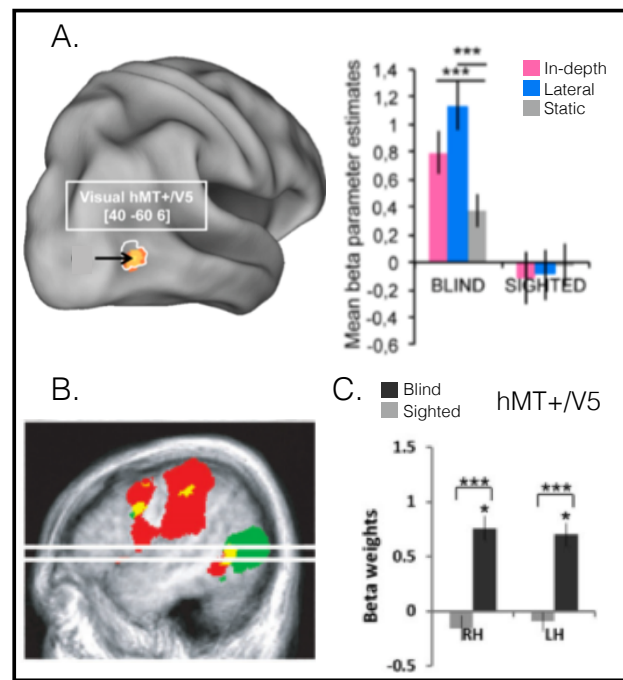
were mostly interested by the question of how an early and total absence of vision affects the neural network dedicated to motion processing.

### 1.4.3. Functional specialization – Crossmodal reorganization

The visual cortex in sighted individuals has two pathways to process information: the ventral stream is involved with object representation (*what* pathway) and dorsal stream processes spatial and sensorimotor information (*where* pathway) (Goodale 1992). Recent studies further suggested a more complex substream system including “how” pathway processing sensorimotor information (Kravitz et al., 2011; see for review Rauchkecker 2017).

Some studies question whether the rewired visually deprived occipital cortex also has a similar division of labor when processing non-visual input. In the congenitally blind, the ventral stream is selectively active for object representation (Pietrini et al. 2004) and shape recognition (Amedi et al. 2007). Furthermore, it shows preference for both living and nonliving stimuli (Mahon et al. 2009): the parahippocampal place area (PPA) is selective for large objects (He et al. 2013), the lateral occipitotemporal cortex (LOC) maintains its tool/shape selectivity (Peelen et al. 2013), and the visual word form area (VWFA) is recruited for Braille word processing (Büchel et al. 1998; Reich et al. 2011). Studies using sensory substitution devices (SSD) demonstrated that the visual number-form area is activated in the congenitally blind for number recognition (Abboud et al. 2015), letter strings trigger higher response in visual word-form area (Reich et al. 2011), shape information drives neural activity in tactile-visual area (Amedi et al. 2007) and body parts activate the extrastriate body area (Striem-Amit & Amedi 2014). Taken together, the ventral stream in blind individuals seems to maintain its functional organization for processing object identity.

The dorsal stream is selectively active for auditory localization in early blind individuals (Weeks et al. 2000; Collignon et al., 2007; Collignon et al. 2011). The functional specialization of the right dorsal occipital cortex for processing tactile and auditory spatial information could stem from being involved in visuo-spatial processing in the sighted (Collignon et al. 2011; Collignon et al. 2009; Collignon, Dormal, Albouy, et al. 2013). This suggests that right dorsal occipital cortex may maintain its functional architecture and might process non-visual spatial input in the absence of sight. In the dorsal stream, middle temporal gyrus, a region dedicated to support visual motion in the sighted individuals, developed to process auditory (Poirier et al. 2006; Bedny et al. 2010; Wolbers et al. 2011; Jiang et al. 2014; Dormal et al. 2016) and tactile (Ricciardi et al. 2007; Matteau et al. 2010) motion in case of early visual deprivation (Figure 6).



**Figure 6. Auditory motion selectivity in early blind individuals.** A. Auditory motion selectivity in the blind group was calculated with a conjunction analysis of Blind > Sighted x [In-depth Motion > Static] And Blind > Sighted x [Lateral Motion > Static]. The observed auditory activity overlaps with visual motion area, hMT+/V5 in sighted. *Left below panel:* The beta parameter estimates show that in blind group motion conditions activate hMT+/V5, while in sighted hMT+/V5 activation is suppressed during auditory motion. B. The activity map in red represents tactile motion activity in blind individuals, while the green indicates the visual motion area in sighted. In yellow is the overlap between tactile and visual motion. C. Beta parameter estimates of auditory motion responses within the visually defined hMT+/V5 region in both sighted (gray) and blind (black). Adapted from Dormal et al. (2016) (A), Ricciardi et al. (2007) (B), Jiang et al. (2014) (C).

In the case of early blindness, it therefore seems that the functional organization of occipital areas that are dedicated to process specific visual input in the sighted, is maintained but reoriented toward non-visual modalities. The organization of the visual cortex appears to be based on specific computational units that are dedicated to perform a particular function, rather than strictly sensory-dependent. However, when lacking input in the preferred modality, this cortex reorients itself towards auditory or tactile modalities to accomplish the required computation, at least when vision is lost early in life (see reviews Dormal & Collignon 2011; Voss & Zatorre 2012).

#### 1.3.4. Non visual activations in the visual cortex of sighted

Several studies have found evidence that, to some extent, the occipital cortex is recruited for nonvisual tasks even in the sighted individuals (Alink et al. 2008; Lewis & Noppeney 2010; Sadaghiani et al. 2009). For instance, when the visual information is unreliable, evoked BOLD responses in hMT+/V5 region for audio-visual stimuli increases (Sadaghiani et al., 2009). These results suggest that hMT+/V5 is sensitive to the other modalities in the absence of reliable visual input.

Auditory and tactile dynamic stimuli alone can also evoke crossmodal activation in



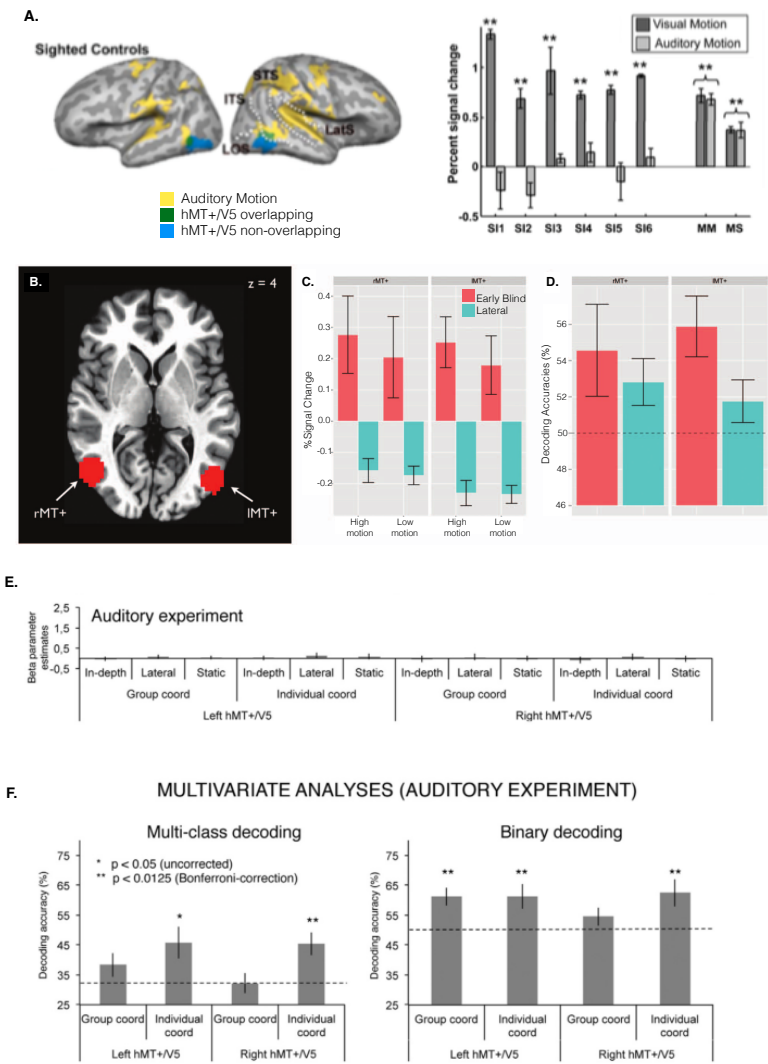
sighted individuals in the vicinity of hMT+/V5 (Pavani et al. 2002; Warren et al. 2002; Poirier et al. 2005; Strnad et al. 2013; Hagen et al. 2002; Matteau et al. 2010; Ricciardi et al. 2007; van Kemenade et al. 2013). Similarly, LOC region in the ventral stream, preferentially responsive to pictures of objects (Malach et al. 1995), shows activity for tactile object exploration (Amedi et al., 2001; Amedi et al. 2007; Amedi et al. 2010; Zhang et al., 2004) and auditory size judgments in living versus nonliving objects (Peelen et al., 2013), manipulable and non-manipulable objects (He et al., 2013) in sighted individuals. These studies raise an important question: is the functional recruitment of these occipital areas in blind individuals a consequence of visual deprivation? Or does it rely on pre-existing/innate organization of the brain in both blind and sighted individuals (Pascual-Leone & Hamilton 2001; Ricciardi et al. 2014; Hannagan et al. 2015)? The meta-modal theory of the brain suggests that areas typically known to be unisensory might be organized to compute a given function regardless of input modality (Pascual-Leone & Hamilton 2001). For instance, hMT+/V5 would prefer visual input due to the innate specialization of that region for computing motion/spatial information and the suitability of the visual modality to carry most informative cues for that function. One of the proposed explanations of remaining functional organization in early blinds is that, when a representation is shared across modalities, such as motion processing, multimodal functions or attributes have a greater potential to be recruited for crossmodal processing (Lomber & Malhorta 2008; Collignon et al., 2011). The computational mechanism of visual motion area might be recycled to process dynamic information when dominant sensory input is not available. Therefore, some researchers further argued that visual deprivation might not be compulsory for observing crossmodal responses in the “visual” cortex. However, the response could be enhanced in the lack of preferred modality by not having competitive visual input. For instance, in case of visual deprivation the observed recruitment of hMT+/V5 could result by the unmasking or the enhancement of a pre-existing supramodal nature of hMT+/V5 (Voss & Zatorre 2012; Pietrini et al., 2011; Ricciardi et al., 2014).

It is important to emphasize that similar activation in a given region could emerge from different processes/cognitive computations in blind and sighted populations. An alternative interpretation of observed crossmodal responses in area hMT+/V5 in sighted individuals is visual mental imagery (Goebel et al. 1998; Emmerling et al. 2016). Mental visual imagery evokes reliable activity in the sighted visual cortex (Kosslyn et al. 1993; Slotnick et al. 2005) and imagining apparent motion activates hMT+/V5 (Goebel et al., 1998). A recent high-field fMRI study demonstrated successful decoding of imagined motion

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directions in hMT+/V5 (Emmerling et al., 2015). Therefore, it could be argued that hMT+/V5 supports auditory motion processing in early blinds, whereas in sighted the corssmodal activity could reflect mental imagery. Ruling out such confound could be challenging, however, the reliance on visual imagery can be reduced by using low imagery content (noise).

In sighted individuals, however, several studies failed to showing univariate responses to auditory stimuli alone (Lewis et al., 2000; Bedny et al., 2010; Alink et al., 2012), and instead demonstrated deactivation for auditory motion (Saenz et al. 2008; Jiang et al., 2014; Dormal et al., 2016), spatial localization (Collignon et al., 2011; Renier et al. 2010), and tactile (Gougoux et al., 2005, Laurenti et al., 2002; Merabet et al., 2007) processing. Interestingly, when univariate activity showed deactivation or no response to auditory motion in sighted individuals; multivariate analysis provided significant results about the presence of auditory motion information in hMT+/V5 for sighted (Figure 7).



**Figure 7. Auditory motion representations in hMT+/V5 in sighted individuals.** **A.** Left panel: Yellow regions show auditory motion selective activity in the sighted group, blue indicates visual motion activity in hMT+/V5, and green is the overlap between visual and auditory motion. Right panel: Deactivation of auditory motion in sighted was demonstrated in comparison with two sight-recovery participants. **B-D.** Data was obtained from Bedny et al., (2010). **(C)** Univariate analysis based on hMT+/V5 ROI, percent signal change in early blind and sighted group. **(D).** Multivariate results showing no significant difference of classification performance for the decoding of high versus low motion conditions in early blind and sighted participants (for univariate analysis, see Figure 5, Bedny et al., 2010). **E-F.** Results of the univariate (top panel) and multivariate pattern (bottom panel) analyses in the auditory motion experiments. Bottom-Left-panel: multi-class decoding accuracy of the 3 auditory conditions (in-depth, lateral, static). Bottom-Right-panel: binary decoding accuracy of the 2 auditory motion conditions (in-depth vs. lateral motion). In the lack of univariate analysis, multivariate can provide information related to the auditory motion within hMT/V5. Adapted from Saenz et al. (2008) (A), Strnard et al. (2013) (B-D), and Dormal et al. (2016) (E-F).

It should be noted that deactivation by nonvisual tasks could be, nevertheless, task dependent (Merabet et al., 2007) and indicate the presence of nonvisual information in occipital cortex of sighted (Ghazanfar et al., 2007). Moreover, the deactivation in the occipital cortex due to crossmodal input could stem from inhibitory modulations to decrease influences from visual input (Laurienti et al., 2002).

Altogether, this section reviewed studies on cross-modal plasticity in occipital regions and, mainly focused on auditory motion responses in hMT+/V5 in both early blind and sighted individuals. Aforementioned studies support the notion that cross-modal reorganization of hMT+/V5 following visual deprivation maintains the computational role of the colonized area while redirecting the modality to non-visual input (Dormal et al., 2016; Jiang et al., 2014; Collignon et al., 2009, Bedny et al., 2010). To understand how visual deprivation affects hMT+/V5 responses, the empirical work in study 2 was dedicated to investigate if auditory motion direction can be decoded in hMT+/V5 in both sighted and blind individuals, or whether this is specific to early blind individuals. Addressing this question would clarify how (visual) experience affects the functional development of hMT+/V5, as well as the modality preferences of this region for motion processing. Furthermore, the enhancement of hMT+/V5 for auditory motion questions the computational role of regions within the auditory cortex that are typically involved in spatial/motion processing. We, therefore, investigated both crossmodal plasticity in visual motion area, and intramodal plasticity in auditory motion responsive area to deepen the understanding of computational roles of auditory and visual cortices in early blind and sighted individuals.

### 1.5. METHODS TO INVESTIGATE HOW THE BRAIN IMPLEMENTS AUDITORY MOTION DIRECTION AND SOUND-SOURCE LOCATION

In order to address how visual and auditory cortices code for auditory motion and localization, advanced sound system and state-of-art fMRI data analyses were used. In the following section, general information related to these methods is described.

### 1.5.1. Sound system

Our limited knowledge of the auditory space processing in the cortex might notably be related to the technical challenge of evoking vivid auditory experience while lying in the unwelcoming and noisy scanner environment. To create an externalized ecological sensation of sound location and motion, we relied on individual in-ear stereo recordings that were recorded from each participant in both horizontal and vertical axes. Then, these recordings were re-played to the participants when they were inside fMRI. By using in-ear recordings of external sounds, auditory stimuli automatically convolved with each individual's own pinna and head related transfer function to produce the auditory perception in external space (Wightman & Kistler 1989). Maintaining ecological properties of subject-specific binaural (interaural time and level differences) and spectral cues plays a crucial role in sharpening the auditory perception and increases the richness of the spatial cues (Hofman et al. 1998; Pavani et al. 2002) triggering more reliable brain response to the multiplexed aspect related to spatial hearing.

### 1.5.2. fMRI data analyses

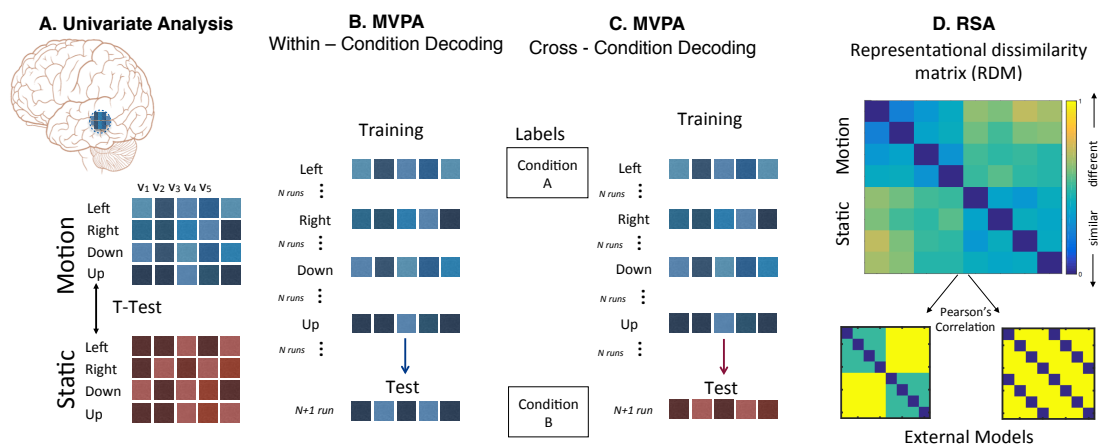
#### *MVPA*

In the last two decades, pattern classification techniques to analyze fMRI data brought new perspectives to cognitive neuroscience (see review Haxby 2012; Kriegeskorte et al. 2008; Haynes 2015). Unlike conventional univariate approach, multivariate pattern analysis allowed neuroscientists to investigate activity pattern of many voxels, rather than focusing solely on individual voxels (Cox & Savoy 2003). Conventional fMRI analysis reveals the voxels that show significant response to experimental conditions, therefore providing a measure of the overall responsiveness of a region (Figure 8A). Voxels with consistent but non-significant responses are discarded in univariate analyses, even if they carry information about the experimental condition (Norman et al. 2006; Haxby et al. 2001; Cox & Savoy 2003). These fine-scale spatial patterns that might carry information about the different experimental conditions are the bases of MVPA approach. In MVPA, classifiers (i.e., machine-learning algorithms such as support-vector-machines, SVMs) are trained with extracted pattern of activity from a brain region to differentiate between experimental conditions. Next, the classifiers are tested on unknown neural patterns (Figure 8B). Above chance-level decoding accuracy is a proxy that neural patterns contain information about the experimental conditions. In the present thesis, MVPA approach was used to reveal

auditory motion direction and sound source location information in both visual and auditory cortices.

### Cross-condition MVPA

To understand whether brain regions contain condition-specific (e.g. direction and location) and/or modality-specific (e.g. visual and auditory) information, several studies employed cross-condition (Formisano et al., 2008) or cross-modality decoding analysis (Man et al. 2012; Kaplan et al. 2015; Fairhall & Caramazza 2013). Cross-condition or cross-modality decoding analyses are based on classifiers that are trained and tested on the two different experimental conditions in order to reveal whether there is shared information across conditions or modalities (Figure 8C). In this way, the classifier detects the feature-specific information that is shared by both modalities/conditions.



**Figure 8. Univariate and Multivariate Analyses.** **A.** Univariate analyses model each voxel individually based on regressors/contrasts, and captures areas where all voxels show an effect in the same direction. **B.** Multivariate classification analysis extracts pattern of activity - patch of voxels, for instance from hMT+ region. On hMT+/V5 pattern, we used cross-validation method to train classifier on four motion directions (left, right, down and up) and test whether the classifier can predict unlabeled motion direction in a dataset, which was not used for training. **C.** Cross-decoding analysis relied on same technique, however the training and testing were performed on different conditions. Condition A was used for the training dataset, while testing performed on Condition B. Likewise, reverse analysis was performed, training on Condition B and testing on Condition A, then the accuracies were averaged. **D.** Representational Similarity Analysis (RSA) relies on correlation between dissimilarities in the neural patterns evoked by specific conditions and computational models that have assumptions on how dissimilar the conditions are.

Up to now, the cross-modal/condition classification has been considered as a technique to identify regions that show abstract representations of modality or conditions (Fairhall & Caramazza 2013; Hong et al. 2012; Higgins et al. 2017). In the present dissertation, we argue that even cross-MVPA can provide useful hints about shared information across conditions in a given region, results cannot be taken as evidence that the region implements abstract representation. In machine-learning algorithms the decision

boundary that classifiers rely on, splits the vector space depending on the number of stimuli. In cross-MVPA, the classifier learns the decision boundary according to the stimuli-features of condition A (e.g. four motion directions) and classifies the stimuli in condition B (e.g. four sound source locations) according to learned decision boundary. The successful cross-MVPA reveals there is shared information across conditions. However, it fails at conveying further information than stimuli-features in motion direction and sound source location can be differentiated with the same decision boundary. Anti-correlated neural patterns of two conditions could potentially lead to successful cross-MVPA (Rezk et al., 2018), therefore cross-condition decoding should be interpreted with caution.

### *Representational similarity analysis (RSA)*

RSA is another multivariate pattern approach that relates three major branches: brain activity measurement, behavioral measurement, and computational modeling (Kriegeskorte et al. 2008). To deepen the understandings of neural activity patterns, this approach compares the representational similarities between each experimental condition. The correlations between activity patterns and either behavioral measurement and/or computational models indicate how the information is represented in a given brain region. Abstracting the information from the neural pattern itself, allows us to make direct comparisons between represented similarities with computational models, different brain regions, and even across populations (Kriegeskorte et al., 2008).

Interestingly, RSA can detect the degrees of similarities between the two conditions, unlike cross-MVPA. The reason is that RSA relies on correlations between the patterns of activity, therefore can detect and differentiate positive and negative correlations. The idea of investigating abstract representations with both cross-MVPA and RSA is coming from results of an experiment performed in our lab. In sighted participants, visual motion selective area responds to both visual and auditory motion, and cross-MVPA (training on visual motion, testing on auditory motion) provided significant results (Rezk et. al, 2018). The cross-MVPA results could lead to the wrong assumption that hMT+/V5 computes motion independently of the modality. However, further multivariate analyses provided evidence that auditory and visual motion evokes de-correlated neural patterns in hMT+/V5. We can, therefore, conclude that this is a motion-specific region that contains shared information between modalities but it is not abstracted from the sensory input. In fact, the patterns of activity generated from visual and auditory modalities are still distinguishable. In the present thesis, we performed cross-condition decoding to reveal whether auditory

motion and sound-source location patterns share representations within the PT, and to further analyze their neural patterns implementing RSA.

We performed RSA to understand the similarities between the neural patterns generated by the auditory motion directions and the sound-source locations in the PT. We used Pearson's linear correlation as the similarity measure to compare each possible pair of activity patterns evoked by the four different motion directions and four different static locations (Figure 8D). This resulted in an 8 x 8 correlation matrix for each participant that was then converted into a representational dissimilarity matrix (RDMs). Each square of the RDM contains the dissimilarity index between the patterns of activity generated by two conditions, in other words the RDM represents how different is the neural representation of each condition from the neural representations of all the other condition in the selected region-of-interest. Then, we created multiple computational models ranging from a fully condition-distinct model to a fully condition-invariant model with intermediate gradients in between (Zabicki et al. 2016). Finally, we computed Pearson's correlation to compare neural RDMs and computational model RDMs. The resulting correlation captures which computational model better explains the neural dissimilarity patterns between motion direction and static location conditions.

### 1.6. SUMMARY AND CONCLUSION

Before going to the experimental part of this thesis, we briefly reviewed the studies on auditory spatial (e.g. motion and static) processing in auditory and visual motion responsive areas. We, then, described what we currently know about how blindness impacts on auditory motion processing. Up to our knowledge, very few studies investigated how the brain represents auditory motion in comparison to sound-source location. In our study 1, we aimed at understanding whether auditory motion perception and sound source location share, at least partially, a common neural representation in the auditory spatial processing region, in particular the planum temporale. Specifically, we asked whether neural patterns show selectivity for motion direction and spatial location. In study 2, we investigated how visual experience shapes the functional reorganization of motion responsive regions in visual and auditory cortices. Addressing this question aimed to clarify the interplay between both auditory and visual cortical regions typically involved in the processing of moving stimuli. We will then summarize the main findings of these empirical studies and describe how they help to bring new theoretical perspectives in the research field.

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## **Chapter 2**

### **Representation of auditory motion directions and sound source locations in the human planum temporale**

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### 2.1. ABSTRACT

The ability to precisely compute the location and direction of sounds in external space is a crucial perceptual process to efficiently interact with dynamic environments. Little is known, however, about how the human brain implements spatial hearing. In our study, we used fMRI to characterize the brain activity of humans listening to left, right, up and down moving as well as static sounds. Whole brain univariate results contrasting moving and static sounds varying in their location revealed a robust functional preference for auditory motion in bilateral human Planum Temporale (hPT). Importantly, multivariate pattern classification analysis showed that hPT contains information about both auditory motion directions and, to a lesser extent, sound source locations. More precisely, we observed that our classifier successfully decoded opposite axes of motion (vertical versus horizontal) but was less able to classify opposite within-axis direction (left versus right or up versus down); reminiscent of the axis of motion organization observed in the middle-temporal cortex for vision. Further multivariate analyses demonstrated that even if motion direction and location rely on partially shared pattern geometries in PT, the responses elicited by static and moving sounds were however distinct. Altogether our results demonstrate that human PT codes for auditory motion and location but that the underlying neural computation linked to motion processing is more reliable and partially distinct from the one supporting sound source location.

### 2.2.INTRODUCTION

The ability to precisely locate and track moving information is a crucial perceptual skill for efficient interaction with the environment. While the brain mechanisms underlying the processing of visual localization and visual motion have received considerable attention (Braddick et al., 2001; Britten et al., 1996; Movshon and Newsome, 1996; Newsome and Park, 1988), much less is known about how the brain implements spatial hearing. The representation of auditory space relies on the computations and comparison of intensity, temporal and spectral cues that arise at each ear (Blauert, 1982; Searle et al., 1976). In the auditory pathway, these cues are both processed and integrated in the thalamus, brainstem and cortex in order to create an integrated neural representation of auditory space (Boudreau and Tsuchitani, 1968; Goldberg and Brown, 1969; Imig et al., 2000; Ingham et al., 2001; Young et al., 1992; Yin and Chan, 1990). At the cortical level, the acoustic space lacks point-to-point spatial representation (Derey et al., 2016; Middlebrooks, 2002; Middlebrooks and Bremen, 2013; Middlebrooks and Pettigrew, 1981; Ortiz-Rios et al., 2017; Rajan et al., 1990). However, differences in spatial selectivity along anterior-posterior auditory areas suggest that specific regions within the auditory cortex might specialize in the processing of spatial hearing. Lesion studies have indeed demonstrated the critical role of the auditory cortex for spatial hearing in humans (Duffour-Nikolov et al., 2012; Sanchez-Longo and Forster, 1958; Zatorre and Belin, 2001). Similar to the visual cortex dual-stream processing model, partially distinct ventral “what” and dorsal “where” auditory processing streams have been proposed for auditory processing (Barrett and Hall, 2006; Lomber and Malhotra, 2008; Rauschecker and Tian, 2000; Recanzone, 2000; Romanski et al., 1999; Tian et al., 2001; Warren and Griffiths, 2003). However, it remains poorly understood how the human brain implements the processing of auditory motion and location, and how these two processes differ from each other.

One candidate region that might integrate spatial cues to compute motion and location information in the human auditory cortex is the planum temporale (hPT) (Barrett and Hall, 2006; Baumgart and Gaschler-Markefski, 1999; Warren et al., 2002). hPT is located in the superior temporal gyrus, posterior to Heschl’s gyrus, and is typically considered part of the dorsal auditory stream (Poirier et al., 2017; Rauschecker and Tian, 2000; Recanzone, 2000; Romanski et al., 1999; Tian et al., 2001). Interestingly, in macaque monkeys neurons in the caudal belt region demonstrate sharper spatial tuning and proportionally more neurons show spatial selectivity that correlated with the behavioral performance of auditory

localization compared to primary cortex neurons (Recanzone 2000b; Woods et al., 2006). Some authors have suggested that hPT equally engages in the processing of moving sounds and the location of static sound-sources (Barrett and Hall, 2006; Derey et al., 2016; Krumbholz et al., 2005; Smith et al., 2004, 2007, 2010; Zatorre et al., 2002). This proposition is supported by early animal electrophysiological studies suggesting the existence of neurons in the auditory cortex that are selective to sound source location and motion directions (Altman, 1968, 1994; Benson et al., 1981; Doan et al., 1999; Imig et al., 1990; Middlebrooks and Pettigrew, 1981; Poirier et al., 1997; Rajan et al., 1990), which display similar response profiles for moving and sound source locations (Ahissar et al., 1992; Doan et al., 1999; Poirier et al., 1997). In contrast, other studies in animals (Poirier et al., 2017) and humans (Baumgart and Gaschler-Markefski, 1999; Bremmer et al., 2001; Griffiths et al., 1998; Hall and Moore, 2003; Krumbholz et al., 2005; Lewis et al., 2000; Pavani et al., 2002; Poirier et al., 2005) pointed toward a more specific role of hPT for auditory motion processing. In addition to the shared or distinct nature of the neural representation of auditory motion and location in the hPT, the characteristic tuning of this region for separate direction or axis of motion/location remains unknown.

The main goals of the present study were threefold. First, using multivariate pattern analysis (MVPA), we investigated whether information about auditory motion direction and sound-source location can be retrieved from the pattern of activity in hPT. Further, we asked whether the spatial distribution of the neural representation is in the format of “preferred axis of motion” as observed in the visual motion selective regions (Albright et al., 1984; Zimmermann et al., 2011). Finally, we aimed at characterizing whether the processing of motion direction (e.g. going to the left) and sound-source location (e.g. being in the left) rely on common neural representations in the hPT.

### **2.3. MATERIALS AND METHODS**

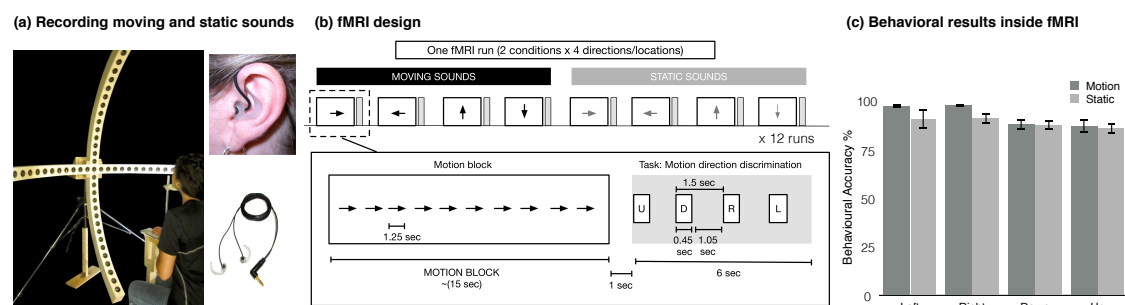
#### **2.3.1. Participants**

Eighteen participants with no reported auditory problems were recruited for the study. Two participants were excluded due to poor spatial hearing performance in the task. The final sample, therefore, included 16 right-handed participants (8 females, age range: 20 to 42, mean  $\pm$  SD = 31.7  $\pm$  5.6 years). Participants were blindfolded and instructed to keep their eyes closed throughout the experiments and practice runs. All the procedures were approved by the research ethics boards of the Centre for Mind/Brain Sciences (CIMEC) and

University of Trento. Experiments were undertaken with the understanding and written consent of each participant.

### 2.3.2. Auditory stimuli

Our limited knowledge of the auditory space processing in the cortex of humans might be a consequence of the technical challenge of evoking vivid perceptual experience of auditory space inside fMRI. To create an externalized ecological sensation of sound location and motion, we relied on individual in-ear stereo recordings that were recorded in a semi-anechoic room and from 30 loudspeakers on horizontal and vertical planes, mounted on two semicircular wooden structures with a radius of 1.1m (see Figure 1A). Participants were seated in the center of the apparatus with their head on a chin-rest, such that the speakers on the horizontal and vertical planes were equally distant from participants' ears. Then, these recordings were re-played to the participants when they were inside the functional MRI (fMRI). By using such sound system with in-ear recordings, auditory stimuli automatically convolved with each individuals' own pinna and head related transfer function to produce a salient auditory perception in external space.



**Figure 1. Stimuli and Experimental Design.** (A) The acoustic apparatus used to present auditory moving and static sounds while binaural recordings were carried out for each participant before the fMRI session. (B) Auditory stimuli presented inside the fMRI consisted of 8 conditions: leftward, rightward, downward and upward moving stimuli and left, right, down and up static stimuli. Each condition was presented for 15 s (12 repetition of 1250 ms sound, no ISI) and followed by 7 s gap for indicating the corresponding direction/location in space and 8 s of silence (total inter-block interval was 15 s). Sound presentation and response button press were pseudo-randomised. Subjects were asked to respond as accurately as possible during the gap period. (C) The behavioural performance inside the scanner.

#### 2.3.2.1. Sound Apparatus

The auditory stimuli were prepared using custom MATLAB scripts (r2013b; Matworks). Auditory stimuli were recorded using binaural in-ear omni-directional microphones (Sound Professionals-TFB-2; 'flat' frequency range 20–20,000 Hz) connected to a portable Zoom H4n digital wave recorder (16-bit, stereo, 44.1 kHz sampling rate). Microphones were positioned at the opening of participant's left and right auditory ear canals. While auditory stimuli were



played, participants were listening without performing any task with head fixed to the chin-rest in front of them. Binaural in-ear recordings allowed combining binaural properties such as interaural time and intensity differences, and participant specific monaural filtering cues to create reliable and ecological auditory space sensation (Pavani et al., 2002).

### 2.3.2.2. *Stimuli recordings*

Sound stimuli consisted of 1250 ms pink noise (50 ms rise/fall time). In the motion condition, the pink noise was presented moving in 4 directions: leftward, rightward, upward and downward. Moving stimuli covered 120° of space/visual field in horizontal and vertical axes. To create the perception of smooth motion, the 1250 ms of pink noise was fragmented into 15 equal length pieces with each 83.333 ms fragment being played every two speakers, and moved one speaker at a time, from outer left to outer right (rightward motion), or vice-versa for the leftward motion. For example, for the rightward sweep, sound was played through speakers located at -60° and -52° consecutively, followed by -44°, and so on. A similar design was used for the vertical axis. This resulted in participants perceiving moving sweeps covering an arc of 120° in 1250 ms (speed = 96°/s; 50 ms fade in/out) containing the same sounds for all four directions. The choice of the movement speed of the motion stimuli aimed to create listening experience relevant to everyday-life conditions. Moreover, at such velocity it has been demonstrated that human listeners are not able to make the differences between concatenated static stimuli from motion stimuli elicited by a single moving object (Poirier et al., 2005), supporting the subject's report that our stimuli were perceived as smoothly moving (no perception of successive snapshots). In the static condition, the same pink noise was presented separately at one of 4 locations: left, right, up, and down. Static sounds were presented at the second most outer speakers (-56° and +56° in the horizontal axis, and +56° and -56° in the vertical axis) in order to avoid possible reverberation difference at the outermost speakers. The static sounds were fixed at one location within experimental block instead of presented in multiple locations (Poirier et al., 2005; Krumbholz et al., 2005). This strategy was purposely adopted for three main reasons. First, randomly presented static sounds can evoke auditory apparent motion (Strybel & Neale 1994; Lakatos et al., 1997; see review Carlile 2016). Second, in the visual domain, incoherent moving (i.e. flickering) dots evoke higher activity compared to 100% coherent moving stimuli in hMT+/V5 region (McKeefry et al., 1997; Vachon et al., 2009). One possible explanation is that incoherent moving stimuli are actually difficult; therefore, require more attention compared to the 100% coherent moving directions. We avoided such confound by

presenting static sounds in a fixed location (Vachon et al., 2009). Lastly, presenting static sounds located on a given space and moving sounds directed toward the same space allows us to investigate a possible shared computation between moving and static sounds using cross-condition decoding (see below).

Before the recordings, the sound pressure levels (SPL) were measured from the subject's head position and ensured that each speaker conveys 65dB-A SPL. All participants reported strong sensation of auditory motion and were able to detect locations with high accuracy (see Fig 1C). Throughout the experiment, participants were blindfolded. Stimuli recordings were conducted in a session that lasted approximately 10 minutes, requiring the participant to remain still during this period.

### **2.3.3. Auditory experiment**

Auditory stimuli were presented via MR-compatible closed-ear headphones (Serene Sound, Resonance Technology; 500-10KHz frequency response) that provided average ambient noise cancellation of about 30 dB-A, and amplitude was adjusted according to each participant's comfort level. To familiarize the participants with the task, they completed a practice session outside of the scanner while lying down until they reached above 80% accuracy.

Each run consisted of the 8 conditions (4 motion and 4 static) randomly presented using a block-design. Each condition was presented for 15 s (12 repetition of 1250 ms sound, no ISI) and followed by 7 s gap for indicating the corresponding direction/location in space and 8 s of silence (total inter-block interval was 15 s). The ramp applied at the beginning and at the end of each sound creates static bursts and minimized adaptation to the static sounds. During the response gap, participants heard a voice saying "left", "right", "up", and "down" in pseudo-randomized order. Participants were asked to press a button with their right index finger when the auditory block's direction or location was matching with the auditory cue (Figure 1B). The number of targets and the order (position 1-4) of the correct button press were balanced across conditions. This procedure was adopted to ensure that the participants gave their response using equal motor command for each condition and to ensure the response is produced after the end of the stimulation period for each condition. Each scan consisted of one block of each condition, resulting in a total of 8 blocks per run, with each run lasting 4 m 10 s. Participants completed a total of 12 runs. The order of the blocks was pseudo-randomized within each run, and across participants.

Based on pilot experiments, we decided to not rely on a sparse-sampling design as sometimes done in the auditory literature in order to present the sounds without the scanner background noise (Hall et al., 1999). These pilot experiments showed that the increase in the signal to noise ratio potentially provided by sparse sampling did not compensate for the loss in the number of volume acquisitions. Indeed, pilot recordings on participants not included in the current sample showed that, given a similar acquisition time between sparse-sampling designs (several options tested) and continuous acquisition, the activity maps elicited by our spatial sounds contained higher and more reliable beta values using continuous acquisition.

### **2.3.4. fMRI data acquisition and analyses**

#### *2.3.4.1. Imaging parameters*

Functional and structural data were acquired with a 4T Bruker MedSpec Biospin MR scanner, equipped with an 8-channel head coil. Functional images were acquired with T2\*-weighted gradient echo-planar sequence. Acquisition parameters were: repetition time of 2500 ms, echo time of 26 ms, flip angle of 73°, a field of view of 192 mm, a matrix size of 64 x 64, and voxel size of 3 x 3 x 3 mm<sup>3</sup>. A total of 39 slices were acquired in ascending feet-to-head interleaved order with no gap. The three initial scans of each acquisition run were discarded to allow for steady-state magnetization. Before every two 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).

High-resolution anatomical scan was acquired for each subject using a T1-weighted 3D MP-RAGE sequence (176 sagittal slices, voxel size of 1x1x1 mm<sup>3</sup>; field of view 256 x 224 mm; repetition time = 2700 ms; TE = 4.18 ms; FA: 7°; inversion time: 1020 ms). Participants were blindfolded and instructed to lie still during acquisition and foam padding was used to minimize scanner noise and head movement.

#### *2.3.4.2 Univariate fMRI analysis*

##### *Whole brain*

Raw functional images were pre-processed and analysed with SPM8 (Wellcome Trust Centre for Neuroimaging London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm/>) implemented in MATLAB R2014b (MathWorks). Before the statistical analysis, our preprocessing steps included slice time correction with reference to the middle temporal

slice, realignment of functional time series, the coregistration of functional and anatomical data, spatial normalization to an echo planar imaging template conforming to the Montreal Neurological Institute space, and spatial smoothing (Gaussian kernel, 6 mm FWHM) were performed.

To obtain blood oxygen level-dependent (BOLD) activity related to auditory spatial processing, we computed single subject statistical comparisons with fixed-effect general linear model (GLM). In the GLM, we used eight regressors from each condition (four motion direction, four sound source location). The canonical double-gamma hemodynamic response function implemented in SPM8 was convolved with a box-car function to model the above mentioned regressors. Motion parameters derived from realignment of the functional volumes (3 translational motion and 3 rotational motion parameters), button press, and the four auditory response cue events were modeled as regressors of no interest. During the model estimation, the data were high-pass filtered with cut-off 128s to remove the slow drifts/ low-frequency fluctuations from the time series. To account for serial correlation due to noise in fMRI signal, autoregressive (AR (1)) was used.

In order to obtain activity related to auditory processing in the whole brain, the contrasts tested the main effect of each condition ([Left Motion], [Right Motion], [Up Motion], [Down Motion], [Left Static], [Right Static], [Up Static], [Down Static]). To find brain regions responding preferentially to the auditory motion and static, we combined all motion conditions [Motion] and all static conditions [Static]. The contrasts tested the main effect of each condition ([Motion], [Static]), and comparison between the conditions ([Motion > Static], and [Static > Motion]). These linear contrasts generated statistical parametric maps (SPM[T]) which were further spatially smoothed (Gaussian kernel 8 mm FWHM) and entered in a second-level analysis, corresponding to a random effects model, accounting for inter-subject variance. One-sample t-tests were run to characterize the main effect of each condition ([Motion], [Static]), and the main effect of motion processing ([Motion > Static]) and static location processing ([Static > Motion]). Statistical inferences were performed at a threshold of  $p < 0.05$  corrected for multiple comparisons (Family-Wise Error corrected; FWE) either over the entire brain volume or after correction for multiple comparisons over small spherical volumes (12 mm radius) located in regions of interest (SVC). Significant clusters were anatomically labeled using the xjView Matlab toolbox (<http://www.alivelearn.net/xjview>) or structural neuroanatomy information provided in the Anatomy Toolbox (Eickhoff et al., 2007).

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### *Region of interest analysis*

#### *ROI Definition*

Due to the hypothesis-driven nature of our study we defined hPT as an *a priori* region of interest for statistical comparisons and in order to define the volume in which we performed multivariate pattern classification analyses.

To avoid any form of double dipping that may arise when defining the ROI based on our own data, we decided to independently define hPT, using a meta-analysis method of quantitative reverse inference, implemented via the online tool Neurosynth (Yarkoni et al., 2011) using the term “Planum Temporale” query. Rather than showing which regions are disproportionately reported by studies where a certain term is dominant (forward inference;  $P(\text{activation} | \text{term})$ ), this method identifies regions whose report in a neuroimaging study is diagnostic of a certain term being dominant in the study (reverse inference;  $P(\text{term} | \text{activation})$ ). As such, the definition of this ROI was based on a set of 85 neuroimaging studies at the moment of the query (September 2017). This method provides an independent method to obtain masks for further region-of-interest analysis. The peak coordinate from the meta-analysis map was used to create a 6 mm spheres (117 voxels) around the peak z-values of hPT (peak MNI coordinates [-56 -28 8] and [60 -28 8]; lhPT and rhPT hereafter, respectively).

#### *ROI Analyses*

##### Univariate

The beta parameter estimates of the 4 motion directions and 4 sound source locations were extracted from lhPT and rhPT regions (Fig 2C). In order to investigate the presence of motion directions/sound source locations selectivity and condition effect in hPT regions, we performed a 2 Conditions (motion, static) x 4 Orientations (left, right, down, and up) repeated measures ANOVA in each hemisphere separately on these beta parameter estimates. Statistical results were then corrected for multiple comparisons (number of ROIs x number of tests) using the false discovery rate (FDR) method (Benjamini and Yekutieli, 2001). A Greenhouse–Geisser correction was applied to the degrees of freedom and significance levels whenever an assumption of sphericity was violated.

### 2.3.4.3. ROI - Multivariate pattern analyses

#### *Within Condition Decoding*

Four-class and binary classification analyses were conducted within the hPT region in order to investigate the presence of auditory motion direction and sound source location information in this area. To ensure that the number of voxels was identical across subjects an ANOVA-based feature selection was performed to select the 110 voxels within each ROI, which are most informative/discriminative across all motion and static conditions (Cox & Savoy 2003; Haxby et al., 2001; Norman et al., 2006).

Multivariate pattern analyses (MVPA) were performed in the lhPT and rhPT. Preprocessing steps were identical to the steps performed for univariate analyses, except for functional time series that were smoothed with a Gaussian kernel of 2 mm (FWHM). MVPA was performed in CoSMoMVPA (<http://www.cosmomvpa.org/>; (Oosterhof et al., 2016), which implements LIBSVM software (<http://www.csie.ntu.edu.tw/~cjlin/libsvm>). A general linear model was implemented in SPM8, where each block was defined as a regressor of interest. A beta map was calculated for each block separately. Two multi-class and six binary linear support vector machine (SVM) classifiers with a linear kernel with a fixed regularization parameter of  $C = 1$  were trained and tested for each participant separately. The two multi-class classifiers were trained and tested to discriminate between the response patterns of the 4 auditory motion directions and locations, respectively. Four binary classifiers were used to discriminate brain activity patterns for motion and location within axes (left vs. right motion, left vs. right static, up vs. down motion, up vs. down static, hereafter within axis classification). Four binary classifiers were used to discriminate brain activity patterns for motion and location within axes (left vs. right motion, left vs. right static, up vs. down motion, up vs. down static, hereafter within axis classification). We used 8 additional classifiers to discriminate across axes (Left vs. Up, Left vs. Down, Right vs. Up, and Right vs. Down motion directions, Left vs. Up, Left vs. Down, Right vs. Up, and Right vs. Down sound source locations, hereafter across axes classification).

For each participant, the classifier was trained using a cross-validation leave-one-out procedure where training was performed with  $n-1$  runs and testing was then applied to the remaining one run. In each cross-validation fold, the beta maps in the training set were normalized (z-scored) across conditions, and the estimated parameters were applied to the test set. To evaluate the performance of the classifier and its generalization across all the data, the previous step was repeated 12 times where in each fold a different run was used as the testing data and the classifier was trained on the other 11 runs. For each region per

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subject, a single classification accuracy was obtained by averaging the accuracies of all cross-validation folds.

### *Cross-condition Decoding*

To test whether motion directions and sound source locations share a similar neural representation in hPT region, we performed cross-condition classification. We carried out the same steps as for the within-condition classification as described above but trained the classifier on sound source locations and tested on motion directions, and vice versa. The accuracies from the two cross-condition classification analyses were averaged. For interpretability reasons, cross-condition classification was only interpreted on the stimuli categories that the classifiers discriminated reliably (above chance level) for both motion and static conditions (e.g. if discrimination of left vs. right was not successful in one condition, either static or motion, then the left vs. right cross-condition classification analysis was not carried out).

### *Across-condition Decoding*

To foreshadow our results, cross-condition classification analyses (see previous section) showed that motion directions and sound source locations share, at least partially, a similar neural representation in hPT region. To further investigate the similarities/differences between the neural patterns evoked by motion directions and sound source locations in the hPT, we performed 4 binary classifications: leftward motion vs. left static, rightward motion vs. right static, upward motion vs. up static, and downward motion vs. down static. The mean of the four binary classifications was computed to produce one accuracy score per ROI. Prior to performing the across-condition and cross-condition MVPA, each individual pattern was normalised separately across voxels so that any cross or across-condition classification could not be due to global univariate activation differences across the conditions.

### *Statistical significance*

Statistical significance in the multivariate classification analyses was assessed using non-parametric tests permuting condition labels and bootstrapping (Stelzer et al., 2013). Each permutation step included shuffling of the condition labels and re-running the classification 100 times on the single-subject level. Next, we applied bootstrapping procedure in order to obtain a group-level null distribution that is representative of whole group. From each

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subject's null distribution one value was randomly chosen and averaged across all the subjects. This step was repeated 100,000 times resulting in a group level null distribution of 100,000 values. The classification accuracies across subjects we considered as significant if the  $p < 0.05$  after corrections for multiple comparisons using the FDR method (Benjamini and Yekutieli, 2001).

Similar approach was adopted to assess significance difference between two auditory conditions (motion and static). We performed additional permutation tests (100000 iterations) by building a null distribution for t-stats after randomly shuffling the classification accuracy values across two conditions, and re-calculating the two-tail t-test between the classification accuracies of motion and static conditions. All p-values were corrected for multiple comparisons using the FDR method (Benjamini and Yekutieli, 2001).

### *2.3.4.4. Representation Similarity analysis*

#### *2.3.4.4.1 Neural Dissimilarity matrices*

We employed representation similarity analysis (RSA; Kriegeskorte et al., 2008) to characterize the degree of shared representation between motion directions and sound source locations in hPT region. The RSA was performed using CosmoMVPA toolbox (Oosterhof et al., 2016) implemented in MATLAB. To perform this analysis we first extracted in each subject the activity patterns associated with each condition (Edelman et al., 1998; Haxby et al., 2001). Then, we averaged individual subject statistical maps (i.e. activity patterns) in order to have a mean pattern of activity for each condition across runs. Finally, we used Pearson's linear correlation as the similarity measure to compare each possible pair of the activity patterns evoked by the four different motion directions and four different sound source locations. This resulted in an 8 x 8 correlation matrix for each participant that was then converted into a representational dissimilarity matrix (RDMs) by computing  $1 - \text{correlation}$ . Each square of the RDM contains the dissimilarity index between the patterns of activity generated by two conditions, in other words the RDM represents how different is the neural representation of each condition from the neural representations of all the other condition in the selected ROI. The 16 neural RDMs (1 per subject) for each of the 2 ROIs were used as neural input for RSA.

#### *2.3.4.4.2 Computational models*

To investigate shared representations between auditory motion directions and sound source locations, we created multiple computational models ranging from a fully condition-distinct



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model to a fully condition-invariant model with intermediate gradients in between (Zabicki et al., 2016).

### *Condition-Distinct model*

The condition-distinct models assume that dissimilarities between motion and static condition is 1 (i.e. highly dissimilar), meaning that neural responses/patterns generated by motion and static conditions are totally unrelated. For instance, there would be no similarity between any motion directions with any sound source location. The dissimilarity values in the diagonal were set to 0, simply reflecting that neural responses for the same direction/location are identical to themselves.

### *Condition-Invariant model*

The condition-invariant models assume a fully shared representation for specific/corresponding static and motion conditions. For example, the models consider the neural representation for the left sound source location and the left motion direction highly similar. All within-condition (left, right, up and down) comparisons are set to 0 (i.e. highly similar) regardless of their auditory condition. The dissimilarities between different directions/locations are set to 1 meaning that each within condition sound (motion or static) is different from all the other within conditions.

### *Intermediate models*

To detect the degree of similarity/shared representation between motion direction and sound source location patterns, we additionally tested 2 classes of 5 different intermediate models. The two classes were used to deepen the understanding of characteristic tuning of hPT for separate direction/location or axis of motion/location. The two model classes represent 2 different possibilities. The first scenario was labeled as Within-Axis Distinct, and these models assume that each of the 4 directions/locations (i.e. left, right, up, down) would generate a distinctive neural representation different from all of the other within-condition sounds (e.g. the patterns of activity produced by the left conditions are highly different from the patterns produced by right, up and down conditions) (see Figure 4C, upper panel). To foreshadow our results, we observed preference for axis of motion in MVP-classification, therefore we created another class of models to further investigate neural representations of within-axis and across-axes of auditory motion/space. The second scenario was labeled with Within-Axis Combined, and these models assume that opposite direction/locations

within the same axis would generate similar patterns of activity (e.g. the pattern of activity of horizontal (left and right) conditions are different from the patterns of activity of vertical conditions (up and down) (see Figure 4C, lower panel).

In all intermediate models, the values corresponding to the dissimilarity between same auditory spaces (e.g. left motion and left location) were gradually modified from 0.9 (motion and static conditions are mostly distinct) to 0.1 (motion and static conditions mostly similar). These models were labeled M9, 7, 5, 3, and 1 respectively.

In all condition-distinct and intermediate models, the dissimilarity of within-condition sounds was fixed to 0.5 and dissimilarity of across-condition sounds was fixed to 1. Across all models, the diagonal values were set to 0.

### 2.3.4.4.3. *Performing RSA*

We computed Pearson's correlation to compare neural RDMs and computational model RDMs. The resulting correlation captures which computational model better explains the neural dissimilarity patterns between motion direction and sound source location conditions. To visualize the distance between the patterns of the motion directions and sound source locations, we used multi-dimensional scaling (MDS) to project the high-dimensional RDM space onto 2 dimensions with the neural RDMs that were obtained from both lhPT and rhPT. Additionally, the single-subject 8 x 8 correlation matrices were used to calculate the reliability of the data considering the signal-to-noise ratio of the data (Kriegeskorte et al., 2007). For each participant and each ROI, the RDM was correlated with the averaged RDM of the rest of the group. The correlation values were then averaged across participants. This provided the maximum correlation that can be expected from the data.

## 2.4. RESULTS

### 2.4.1. Behavioral results

During the experiment, we collected target direction/location discrimination responses (see Figure 1C). The overall accuracy scores were entered into 2 x 4 (Condition, Orientation) repeated measures ANOVA. No main effect of Condition ( $F_{1,15} = 2.22$ ;  $p = 0.157$ ) was observed, indicating that the overall accuracy while detecting direction of motion or sound source location did not differ. There was a significant main effect of orientation ( $F_{1,15} = 11.688$ ;  $p < 0.001$ ), caused by greater accuracy in the horizontal orientations (left and right) as compared to the vertical orientations (up and down). Post-hoc two-tailed t-tests ( $p < 0.05$ , Bonferroni corrected) revealed that accuracies did not reveal significant difference within

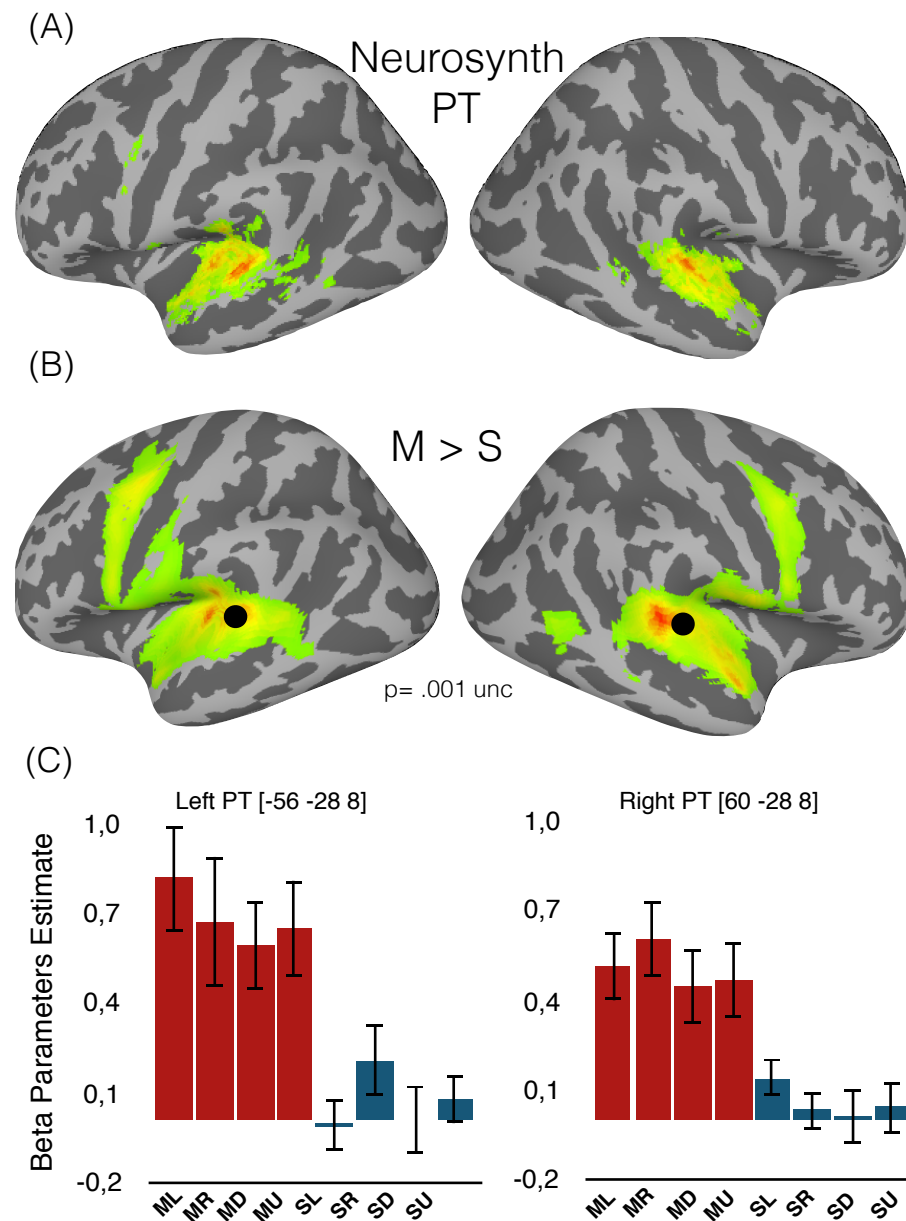
horizontal orientations (left vs right;  $t_{15} = -0.15$ ,  $p=1$ ), and vertical orientations (up vs down;  $t_{15} = 0.89$ ,  $p=1$ ). However, left orientation accuracy was greater as compared to down ( $t_{15} = 3.613$ ,  $p=0.005$ ), and up ( $t_{15} = 4.51$ ,  $p<0.001$ ) orientations and right orientation accuracy was greater as compared to the down ( $t_{15} = 3.76$ ,  $p=0.003$ ) and up ( $t_{15} = 4.66$ ,  $p<0.001$ ) orientation accuracies. No interaction between Condition x Orientation was observed, pointing out that differences between orientations in terms of performance expresses both for static and motion.

### 2.4.2. fMRI results – whole-brain univariate analyses

To identify brain regions that are preferentially recruited for auditory motion processing, we performed a univariate RFX- GLM contrast [Motion > Static] (Figure 2A). Consistent with previous studies (Dormal et al., 2016; Getzmann and Lewald, 2012; Pavani et al., 2002; Poirier et al., 2005; Warren et al., 2002), whole-brain univariate analysis revealed activation in the superior temporal gyri, bilateral hPT, precentral gyri, and anterior portion of middle temporal gyrus in both hemispheres (Figure 2A, Table 1). The most robust activation (resisting whole brain FWE correction,  $p<0.05$ ) was observed in the bilateral hPT (peak MNI coordinates  $[-46 -32 10]$  and  $[60 -32 12]$ ). We also observed significant activation in occipito-temporal regions (in the vicinity of hMT+/V5) as suggested by previous studies (Dormal et al., 2016; Poirier et al., 2005; Warren et al., 2002).

### 2.4.3. fMRI results – ROI univariate analyses

Beta parameter estimates were extracted from the pre-defined ROIs (see methods) for the four motion directions and four sound source locations from the auditory experiment (Figure 2C). We investigated the condition effect and the presence of direction/location selectivity in lhPT and rhPT regions separately by performing  $2 \times 4$  (Conditions, Orientations) repeated measures of ANOVA with beta parameter estimates. In lhPT, main effect of Conditions was significant ( $F_{1,15} = 37.28$ ,  $p < 0.001$ ), indicating that auditory motion evoked higher response compared to static sounds. There was no significant main effect of Orientations ( $F_{1.5,22.5} = 0.771$ ,  $p = 0.4$ ), and no interaction ( $F_{3,45} = 2.21$ ,  $p = 0.11$ ). Similarly, in rhPT, only main effect of Conditions was significant ( $F_{1,15} = 37.02$ ,  $p < 0.001$ ). No main effect of Orientation ( $F_{1.5,23.2} = 1.43$ ,  $p = 0.3$ ) or interaction ( $F_{3,45} = 1.73$ ,  $p = 0.19$ ) was observed. Overall, brain activity in the hPT as measured with beta parameter estimate extracted from univariate analysis did not provide evidence of motion direction or sound source location selectivity.



**Figure 2. Univariate whole brain results.** (A). Auditory motion processing [motion > static] at  $p < 0.001$  uncorrected. (B). Reverse inference map was obtained from the online tool Neurosynth using the term “Planum Temporale” (FDR corrected  $p < 0.05$ ). The black spheres are illustration of drawn mask (radius = 6mm, 117 voxels) around the peak coordinate from Neurosynth (search term “planum temporale”, meta-analysis of 85 studies). (C). Mean activity estimates (arbitrary units  $\pm$  SEM) associated with the perception of auditory motion direction (red) and sound-source location (blue). ML: motion left, MR: motion right, MD: motion down, MU: motion up, SL: static left, SR: static right, SD: static down, and SU: static up.

**Table 1.** Results of the univariate analyses for the main effect of auditory motion processing [motion > static], and auditory localization processing [static > motion]. Coordinates reported in this table are significant ( $p < 0.05$  FWE) after correction over small spherical volumes (SVC, 15 mm radius) of interest (#) or over the whole brain (\*). Coordinates used for correction over small spherical volumes are as follows (x, y, z, in MNI space): left middle temporal gyrus (hMT+/V5) [-42 -64 4] (Dormal et al., 2016), right middle temporal gyrus (hMT +/V5) [42 - 60 4] (Dormal et al., 2016), right superior frontal sulcus [32 0 48] (Collignon et al., 2011), right middle occipital gyrus [48 -76 6] (Collignon et al., 2011). K represents the number of voxels when displayed at  $p(\text{unc}) < 0.001$ . L: left, R: right, G: gyrus, S: sulcus.

Area	k	x (mm)	y (mm)	z (mm)	Z	p
<i>MOTION &gt; STATIC</i>						
L planum temporale	10506	-46	-32	10	6.63	0.000*
L Middle Temporal G		-56	-38	14	6.10	0.000*
L Precentral G		-46	-4	52	5.25	0.004*
L Putamen		-22	2	2	4.98	0.011*
L Middle Temporal G	43	-50	-52	8	3.79	0.01#
R Superior Temporal G	7074	66	-36	12	6.44	0.000*
R Superior Temporal G		62	-2	-4	5.73	0.000*
R Superior Temporal G		52	-14	0	5.56	0.001*
R Precentral G		50	2	50	4.70	0.032*
R Superior Frontal S	159	46	0	50	4.40	0.001#
R Middle Temporal G	136	42	-60	6	4.31	0.001#
R Middle Occipital G	24	44	-62	6	3.97	0.006#

#### 2.4.4. fMRI results – ROI multivariate pattern analyses

To further investigate the presence of information about auditory motion direction and sound source location in hPT, we ran multi-class and binary multivariate pattern classifications. Figure 3A-C shows the mean classification accuracy across categories in each ROI.

##### 2.4.4.1. MVPA – Within Condition

###### 2.4.4.1.1. Decoding auditory motion and static

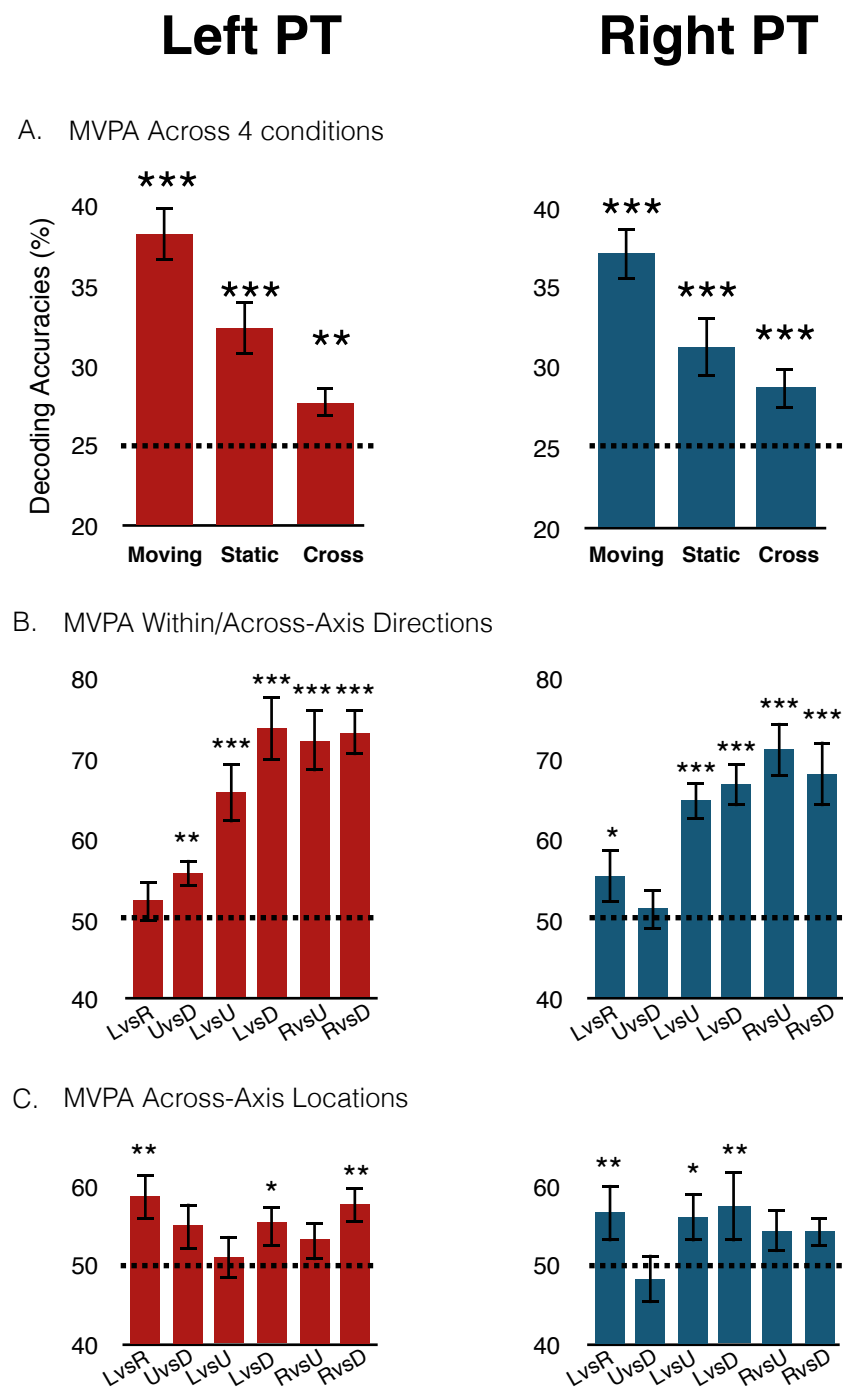
Multi-class across four conditions classification accuracy in the hPT was significantly above chance (chance level = 25%) in both hemispheres for motion direction (lhPT: mean  $\pm$  SD =  $38.4 \pm 7$ ,  $p < 0.001$ ; rhPT: mean  $\pm$  SD =  $37.1 \pm 6.5$ ,  $p < 0.001$ ), and sound source location (lhPT: mean  $\pm$  SD =  $32.4 \pm 6.7$ ,  $p < 0.001$ ; rhPT: mean  $\pm$  SD =  $31.2 \pm 7.5$ ,  $p < 0.001$ ). In addition, we assessed the differences between classification accuracies for motion and static stimuli by using permutation tests in lhPT ( $p = 0.0238$ ) and rhPT ( $p = 0.0236$ ), indicating greater accuracies for classifying motion direction than sound source location across all regions.

### 2.4.4.1.2. MVPA – “Axis of Motion” Preference

In order to test whether neural patterns within hPT contain information about opposite directions/locations within an axis, we performed two binary within-axis classifications (see Supplemental Analysis). The classification accuracies were plotted in Figure 3B-C.

We asked whether the spatial distribution of the neural representation is in the format of “preferred axis of motion” as observed in the visual motion selective regions (Albright et al., 1984; Zimmermann et al., 2011). In motion direction classifications, to assess the statistical difference between classification accuracies of across axes (left vs. up, left vs. down, and right vs. up, right vs. down) and within axes (left vs. right, and up vs. down) directions, we performed pairwise permutation tests and FDR-corrected for multiple comparisons. Across-axes classification accuracies in lhPT ([left vs. up] vs. [left vs. right]:  $p=0.006$ , [left vs. down] vs. [left vs. right]:  $p<0.001$ , [right vs. down] vs. [left vs. right]:  $p<0.001$ , [right vs. up] vs. [left vs. right]:  $p=0.001$ ), and rhPT ([left vs. up] vs. [left vs. right]:  $p=0.029$ , [left vs. down] vs. [left vs. right]:  $p=0.014$ , [right vs. down] vs. [left vs. right]:  $p=0.02$ , [right vs. up] vs. [left vs. right]:  $p=0.003$ ) were significantly higher compared to the horizontal within-axis classification accuracies. Similarly, across-axes classification accuracies were significantly higher when compared with vertical within-axis classification accuracies in lhPT ([up vs. down] vs. [left vs. up],  $p=0.02$ ; [up vs. down] vs. [left vs. down],  $p=0.001$ ; [up vs. down] vs. [right vs. up],  $p=0.001$ ; [up vs. down] vs. [right vs. down],  $p<0.001$ ) and rhPT ([up vs. down] vs. [left vs. up],  $p=0.001$ ; [up vs. down] vs. [left vs. down],  $p=0.001$ ; [up vs. down] vs. [right vs. up],  $p=0.001$ ; [up vs. down] vs. [right vs. down],  $p=0.002$ ). No significant difference was observed between the within-axis classifications in lhPT ([left vs. right] vs. [up vs. down],  $p=0.24$ ) and rhPT ([left vs. right] vs. [up vs. down],  $p=0.31$ ). Similarly, among the across-axes conditions, classification accuracies did not show significant difference in bilateral hPT. In static sound location classifications, no significant difference was observed between across-axes and within-axes classification accuracies, indicating that classifiers did not perform better when discriminating sound source locations across axes compared to the opposite locations.

To investigate the presence of information about aggregated opposite directions/location within an axis (across-planes) two additional binary classifications performed (see Supplemental Analysis).



**Figure 3. Within and cross-classification results. (A).** Classification results for the 4 conditions. Within-condition and cross-condition classification results are shown in the same bar plots. Moving: four motion direction; Static: four sound source location; and Cross: cross-condition classification accuracies. **(B).** Classification results of within (left vs. right, up vs. down) and across axes (left vs. up, left vs. down, right vs. up, right vs. down) motion directions. **(C).** Classification results of within (left vs. right, up vs. down) and across axes (left vs. up, left vs. down, right vs. up, right vs. down) sound source locations. LvsR: Left vs. Right, UvsD: Up vs. Down, LvsU: Left vs. Up, LvsD: Left vs. Down, RvsU: Right vs. Up, RvsD: Right vs. Down classifications. FDR corrected p-values: (\*)  $p < 0.05$ , (\*\*)  $p < 0.01$ , (\*\*\*)  $p < 0.001$  testing differences against chance level (dotted lines; see methods).

One may wonder whether the higher classification accuracy for across compared to within axes relates to the perceptual differences in discriminating sounds within the horizontal and vertical axes. Indeed, because we opted for an ecological design reflecting daily-life listening condition, we observed, as expected, that discriminating vertical directions was more difficult than discriminating horizontal ones (Middlebrooks and Green, 1991). However, it should be noted that, while accuracy differences between across- and within-axes classification was only observed in the motion condition, behavioral differences were observed in both static and motion conditions. This observation strengthens the notion that the higher classification accuracies for axes of motion do not simply stem from behavioral performance differences.

#### *2.4.4.2. MVPA – Cross-condition*

To investigate if motion direction and sound source locations rely on shared representation in hPT, we trained the classifier to distinguish neural patterns from the motion directions (e.g. going to the left) and then tested on the patterns elicited by static conditions (e.g. being in the left), and vice versa.

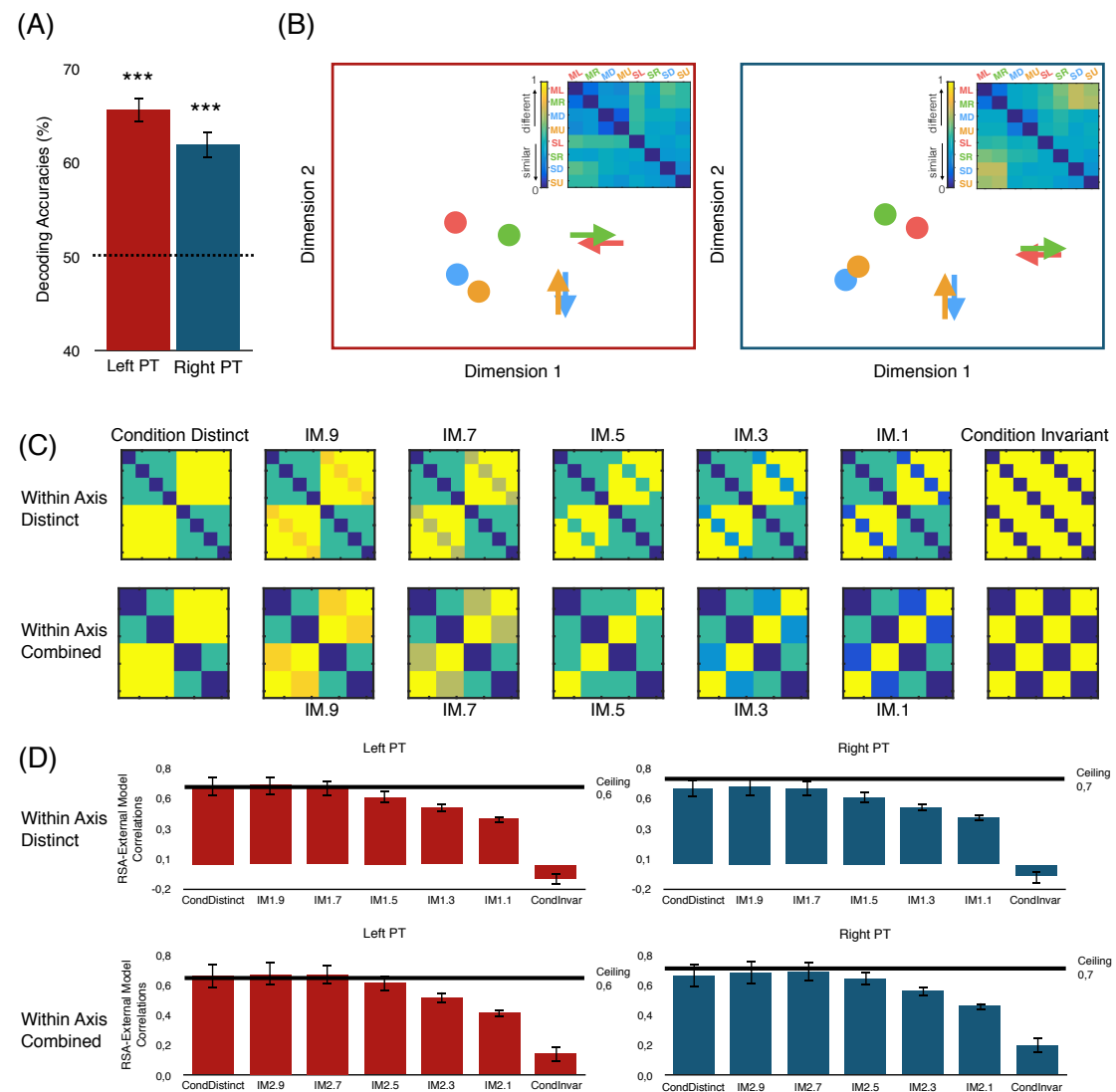
Cross-condition classification revealed significant results on across 4 conditions (lhPT: mean  $\pm$  SD =  $27.8 \pm 5.3$ ,  $p = 0.008$ , rhPT: mean  $\pm$  SD =  $28.7 \pm 3.8$ ,  $p < 0.001$ ) and across axes (lhPT: mean  $\pm$  SD =  $57.6 \pm 6.2$ ,  $p < 0.001$ ; mean  $\pm$  SD =  $58.8 \pm 6.2$ ,  $p < 0.001$ ). Within- axis categories did not reveal any significant cross-condition classification. These results suggest that a partial overlap between the neural patterns of moving and static stimuli in the hPT.

#### *2.4.4.3. MVPA – Across-condition Decoding*

Cross-condition classification results indicated a shared representation between motion directions and sound source locations. Previous studies argued that successful cross-condition classification reflects an abstract representation of stimuli conditions (Fairhall and Caramazza, 2013; Higgins et al., 2017; Hong et al., 2012). To test this hypothesis, patterns of the same orientation of motion and static conditions (e.g. leftward motion and left location) were involved in across-condition MVPA. The rationale was that if the hPT region carries fully abstract representation of space, across-condition classification would give results in favor of the null hypothesis (no differences across conditions). In the across-condition classification analysis, accuracies from the four across-condition classification analyses were averaged and survived FDR corrections in bilateral hPT (lhPT: mean  $\pm$  SD =  $65.6 \pm 5$ ,  $p < 0.001$ , rhPT: mean  $\pm$  SD =  $61.9 \pm 5.6$ ,  $p < 0.001$ ), indicating that the neural patterns of motion



direction can be reliably differentiated from sound-source location within hPT.



**Figure 4. Pattern dissimilarity between motion directions and sound source locations. (A).** Across-condition classification results of across 4 conditions are represented in each ROI (lhPT and rhPT). 4 binary classifications [leftward motion vs. left location], [rightward motion vs. right location], [upward motion vs. up location], and [downward motion vs. down location] were computed and averaged to produce one accuracy score per ROI. FDR corrected p-values: (\*\*\*)  $p < 0.001$ . Dotted lines represent chance level. **(B).** The embedded top panel shows neural RDMs extracted from left and right hPT, and multi-dimensional scaling (MDS) plot visualizes the similarities of the neural pattern elicited by 4 motion directions (arrows) and 4 sound source locations (dots). Color codes for arrow/dots are as follows: green indicates left direction/location, red indicates right direction/location, orange indicates up direction/location, and blue indicates down direction/location. ML: motion left, MR: motion right, MD: motion down, MU: motion up, SL: static left, SR: static right, SD: static down, and SU: static up. **(C-D).** The results of representational similarity analysis (RSA) in hPT are represented. **(C).** RDMs of the computational models that assume different similarities of the neural pattern based on auditory motion and static conditions. **(D).** RSA results for every model and each ROI. For each ROI, the black line represents the reliability of the data considering the signal-to-noise ratio (see Materials and Methods), which provides an estimate of the highest correlation we can expect in a given ROI when correlating computational models and neural RDMs. Error bars indicate SEM. IM1: Intermediate models with within-axis conditions distinct, IM2: Intermediate model with within-axis conditions combined.

### 2.4.4.4. RSA

#### *Multi-dimensional Scaling*

Visualization of the representational distance between the neural patterns evoked by motion directions and sound source locations further supported that within-axis directions show similar geometry compared to the across-axes directions, therefore, it is more difficult to differentiate the neural patterns of opposite directions in MVP-classification. MDS also showed that in both lhPT and rhPT, motion directions and sound source locations are separated into 2 clusters (Figure 4B).

#### *RSA with external models*

The correlation between model predictions and neural RDMs for the lhPT and rhPT is shown in Figure 4D. The cross-condition classification results indicated a shared representation within the neural patterns of hPT for motion and static sounds. We examined the correspondence between the response pattern dissimilarities elicited by our stimuli with 14 different model RDMs that included a fully condition distinct, fully condition-invariant models, and intermediate models with different degrees of shared representation.

First set of computational RDMs were modeled with the assumption that the neural patterns of within-axis sounds are fully distinct. The analysis revealed a negative correlation with the fully condition-invariant model in the bilateral hPT (lhPT: mean  $r \pm SD = -0.12 \pm 0.18$ , rhPT: mean  $r \pm SD = -0.01 \pm 0.2$ ) that increased gradually as the models progressed in the condition-distinct direction. The model that best fit the data was the M9 model in the bilateral hPT (lhPT: mean  $r \pm SD = 0.66 \pm 0.3$ , rhPT: mean  $r \pm SD = 0.65 \pm 0.3$ ). A similar trend was observed for the second set of models that have the assumption of within-axis sounds evoke similar neural patterns. Condition-invariant model provided the least explanation of the data (lhPT: mean  $r \pm SD = 0.14 \pm 0.25$ , rhPT: mean  $r \pm SD = 0.2 \pm 0.29$ ), and correlations gradually increased as the models progressed in the condition-distinct direction. The winner models in this set were the models M9 in lhPT and M7 in the rhPT (lhPT: mean  $r \pm SD = 0.67 \pm 0.22$ , rhPT: mean  $r \pm SD = 0.69 \pm 0.15$ ).

In addition, we assessed differences between correlation coefficients for computational models and sets using a 7 x 2 x 2 (Models, Classes, and Hemispheres) repeated measures ANOVA. This revealed a main effect of Models ( $F_{6,90} = 32.8$ ,  $p < 0.001$ ) indicating correlations gradually increased as the models progressed in the condition-distinct direction. The significant main effect of Classes was also observed ( $F_{1,15} = 7.66$ ,  $p = 0.014$ ) due to the higher correlation coefficients in Within-Axis Combined set. Within-Axis

Combined models explained our stimuli space better than Within-Axis Distinct models supporting similar pattern representation within planes. There were no differences in correlations for Hemispheres ( $F_{1,15} = 0.587$ ,  $p = 0.45$ ) and no significant interaction between Models x Hemispheres ( $F_{6,90} = 0.25$ ,  $p = 0.95$ ), and between Classes x Hemispheres ( $F_{1,15} = 0.749$ ,  $p = 0.4$ ).

In the lhPT, M9 and M7 model predictions reached the noise ceiling, indicating the model performed as well as possible given the variability of the pattern across subjects. These results indicate that separate auditory spatial conditions (motion or static) elicit massively different neural patterns in hPT.

### 2.5. DISCUSSION

In line with several studies investigating auditory motion processing, our univariate results demonstrated a preference for moving over static sounds in the superior temporal gyri, bilateral hPT, precentral gyri, and anterior portion of middle temporal gyrus in both hemispheres (Baumgart and Gaschler-Markefski, 1999; Krumbholz et al., 2005; Pavani et al., 2002; Poirier et al., 2005; Warren et al., 2002). The most robust cluster of activity was observed in the bilateral hPT (Figure 2B, Table 1). Moreover, activity estimates extracted from independently defined hPT (from neurosynth meta-analysis) also revealed higher activity for moving relative to static sounds. Both whole-brain and ROI analyses therefore clearly indicated a functional preference (expressed here as higher activity level estimates) for motion processing over sound-source location in bilateral hPT regions (Figure 2).

Does hPT contain information about specific motion directions and sound source locations? At the univariate level, our four (left, right, up and down) motion directions and sound source locations did not evoke differential univariate activity in hPT region (see Figure 2C). We then carried out multivariate pattern classification in order to investigate whether information related to motion directions and sound-source locations could be retrieved from the distributed activity reliably elicited by each separate condition across voxels of the hPT.

We observed that bilateral hPT contains reliable information about the four auditory motion directions (Figure 3A). Our results therefore demonstrate that despite no univariate differences, area hPT contains reliable distributed information about separate directions of motions (Alink et al., 2012; Dormal et al., 2016; Jiang et al., 2014, 2016). Our results are therefore similar to the observations made with fMRI in the human visual motion area hMT+/V5 showing reliable direction-selective information despite comparable voxel-wise

univariate activity levels across directions (Kamitani and Tong, 2006). To the best of our knowledge, this study is the first to investigate the differences between within- and across-axes of motion directions classification. Within-axis MVP-classification results revealed that both horizontal (left versus right), and vertical (up versus down) motion directions can be classified in the hPT region (see Figure 3B-C). However, the results showed lack of consistency across hemispheres. The lhPT contained decodable information about up versus down directions but not between left versus right; the opposite results were observed in the rhPT. Importantly, across axes direction classification revealed massively higher accuracies compared to within-axis classifications, indicating that classification motion direction information is much more reliable across axis of motion, rather than separate directions within horizontal (left versus right) or vertical (up versus down) axes. Such enhanced classification accuracy across axes versus within axis is reminiscent of observations made in MT+/V5 where the large-scale axis of motion selective organization was observed in non-human primates (Albright et al., 1984), and in human area MT+/V5 (Zimmermann et al., 2011). Further examination with RSA provided additional evidence that within-axis combined models (aggregating the opposite directions/location) explain better the neural representational space of hPT by showing higher correlations values compared to within-axis distinct models. These results strengthen the idea of representation of opposite directions/locations are similar in the neural patterns of hPT (see Figure 4D).

The resemblance between our findings with the conclusions reached in the hMT+/V5 for visual motion (Zimmermann et al., 2011) suggests that the topographic organization principle of hMT+/V5 and hPT shows similarities in representing motion directions. The functional organization of the middle occipito-temporal region hMT+/V5 is characterized by columns containing neurons that react specifically to a certain visual motion direction (Albright et al., 1984). Those columns vary smoothly for certain motion direction but are also found running side by side with their respective opposing motion direction counterparts (Albright et al., 1984; Born and Bradley, 2005; Diogo et al., 2003; Geesaman et al., 1997; Zimmermann et al., 2011). By aggregating opposing motion directions, larger axis of motion features can be constructed that are more easily detectable with fMRI than individual direction selective columns (Zimmermann et al., 2011). Moreover, neural responses to opposite directions were suggested to play a role in encoding visual motion direction by triggering excitatory/inhibitory mechanism within hMT+/V5 (Heeger et al., 1999). Due to this topographic organization principle of area hMT+/V5, and probably in combination with excitatory/inhibitory activity features of the opposing motion directions, it

has been suggested that the representation of preferred axis of motion is more systematic from the pattern of fMRI activity when compared to the opposite direction of motion (Zimmermann et al., 2011; but see below for alternative accounts). The observed motion opponent mechanism in visual motion area could also exist in hPT region and influence the reliable axis of motion classification. A number of electrophysiological studies have indeed demonstrated the existence of motion direction sensitive neurons in the auditory cortex of mammals (Ahissar et al., 1992; Doan et al., 1999; Poirier et al., 1997) and showed higher spatial selectivity (sharper spatial tuning) in the caudal fields (homologue to area hPT) (Woods et al., 2006; Zhou and Wang, 2012). Visual motion aftereffect (vMAE) is the most compelling psychophysical evidence that point towards the existence of direction specific mechanisms in vision. The effect relies on prolonged exposure to a particular motion direction, followed by the viewing of a stationary object, elicits the illusion of motion in the opposite direction, demonstrating an adaptation of specialized direction detecting mechanisms (Barlow and Hill, 1963). The effect of adaptation to a specific motion direction has been commonly observed in hMT+/V5 (He et al., 1998; Hogendoorn and Verstraten, 2013; Huk et al., 2001; Tootell et al., 1995; Van Wezel 2002). Similarly, behavioral studies have provided compelling evidence for motion selective (Deas et al., 2008; Guerreiro et al., 2016; Kitagawa and Ichihara, 2002; Reinhardt-Rutland and Anstis, 1982) and direction-sensitive auditory motion aftereffects (aMAEs) (Dong et al., 2000; Grantham, 1998; Grantham and Wightman, 1979; Neelon and Jenison, 2003). However, the existence of direction specific adaptation in the human auditory cortex remains controversial (Grzeschik et al., 2013; Magezi et al., 2013).

Even if it has been proposed that successful classification may potentially stem from the spatial biases within each voxel that relates to the underlying cortical columnar organization or other types of direction selective signals (Bartels et al., 2008; Haynes and Rees, 2006; Kamitani and Tong, 2005), alternative explanations have also been provided. Indeed, if fMRI signal within a voxel would exclusively reflect a sampling of cortical columns, smoothing of the data would substantially decrease the classification accuracies due to averaging out the random biases in the neighboring voxels (Kamitani and Sawahata, 2010). Contrary to that, evidence points to no influence of smoothing (Op de Beeck, 2010). Studies conducted on early visual cortex proposed that classifying orientation preference reflects much larger scale (e.g. retinotopy) rather than columnar organization (Op de Beeck, 2010; Freeman et al., 2011, 2013). Interestingly, high-field fMRI studies showed that the signal carries information related to both large- and fine-scale (columnar level) biases (Gardumi et

al., 2016; Pratte et al., 2016; Sengupta et al., 2017). A study that investigated the effect of spatial resolution and smoothing on the classification accuracies on two different auditory tasks, concluded that the influence of large- and fine-scale spatial biases depends on the specific task of interest (Gardumi et al., 2016). These studies support the notion that MVP-classification results could reflect the combination of both large- and fine-scale organization. The present study sheds important new lights on the coding mechanism of motion direction within the hPT and demonstrates that fMRI signal in the hPT contains direction specific information and point toward an “axis of motion” organization. However, further studies are needed to test the similarities between the coding mechanisms implemented in visual and auditory motion selective regions, and more particularly, to investigate whether directional information captured in fMRI emerges from columnar level or larger-scale spatiotopic organization.

Supporting univariate motion selectivity results in bilateral hPT, MVPA revealed that multi-class and across-axes classifications are higher for moving than for static sounds (Figure 3A-B). However, despite minimal univariate activity elicited by sound-source location in hPT, and the absence of reliable univariate differences in the activity elicited by each position (see Figure 2C), MVP-classification results showed that beside the vertical axis (up versus down), sound source location information can be reliably decoded bilaterally in hPT (Figure 3C). Our results are in line with previous studies showing that posterior regions in auditory cortex exhibit location sensitivity both in animals (Recanzone, 2000; Stecker et al., 2005; Tian et al., 2001) and humans (Ahveninen et al., 2006, 2013; Brunetti et al., 2005; Deouell et al., 2007; Derey et al., 2016; Krumbholz et al., 2005; Warren and Griffiths, 2003; Zatorre et al., 2002).

In contrast to what was observed for motion direction, sound source location patterns did not reveal “axis of location” preference in hPT. This indicates that auditory sound source locations might not follow similar topographic representations to motion directions.

The observed lack of axis of location preference in PT could be attributed to widespread/interspersed distribution of location selective neurons (Ahissar et al., 1992). One recent study has demonstrated that sound locations in the azimuth can be modeled with opponent channel coding based on the BOLD responses in bilateral hPT (Derey et al., 2016). Opponent channel coding model, which stems from electrophysiological recordings of mammalian auditory pathway (Day and Delgutte, 2013; Miller and Recanzone, 2009; Stecker et al., 2005), proposes that sound locations in the azimuth may be represented

through the combined activity of two neuronal subpopulations that are broadly tuned with an overall preference for opposite auditory hemifields (McAlpine et al. 2001; Stecker et al. 2005), and recent data in both monkeys and humans suggest that these broadly tuned neurons are distributed more widely across auditory cortex (Derey et al., 2016; Magezi and Krumbholz, 2010; Ortiz-Rios et al., 2017; Salminen et al., 2009; Werner-Reiss and Groh, 2008). In the horizontal within-condition classification, our findings are in line with previous observations from monkey and human fMRI studies that in the posterior auditory cortex (including PT), fMRI signals contain representations of sound location (Derey et al., 2016; Lewis et al., 2008; Ortiz-Rios et al., 2017). The widespread and spatially contralateral bias might provide information to the classifier to detect the neural pattern differences between sounds on the horizontal axis (see Figure 3C). In the vertical axis, MVP-classification was not significant for sound source locations (see Figure 3C). A recent electroencephalographic (EEG) study also showed that while horizontal sound source (left versus right) revealed successful classification in the scalp, less consistent classification results was observed for vertical sounds (Bednar et al. 2017). It should be noted that the lack of significant classification could simply indicate that the neural patterns evoked by up and down sounds, at our brain sampling level, cannot be differentiated by the classifier, which does not mean that hPT do not contain any information related to up vs down vertical sounds. Our results however demonstrate that information about the position of sounds is more easily decodable in the horizontal plane when compare to the vertical plane, using the patterned activity recorded in hPT.

To which extend the neural representation of motion directions and sound source locations overlaps has been debated extensively (Grantham, 1986; Kaas et al., 1999; Poirier et al., 2017; Romanski et al., 2000; Smith et al., 2004, 2007; Zatorre and Belin, 2001). Despite the fact that hPT preferentially represents directional motion (observed in our study by higher univariate responses and higher within-condition classification accuracies), the cross-condition classification results revealed that auditory motion (e.g. going to the left) and sound-source location (being on the left) share partial neural representations in hPT (Figure 3A). The idea of cross-condition classification between motion direction and sound-source location necessarily relies on whether there is a shared computation between sounds located on a given space and sounds directed towards this space. Low-level features of these two types of auditory stimuli vary in many ways and produce large difference at the univariate level in the cortex (see Figure 2B). However, perceiving, for instance, a sound going toward the left side or located on the left side evoke a sensation of location/direction

in the external space that is common across conditions. Our significant cross-condition classification may therefore relate to the evoked sensation/perception of an object being/going to a common external spatial location. Electrophysiological studies in animals demonstrated that motion-selective neurons in the auditory cortex displayed similar response profile to sounds located or moving toward the same position in external space, suggesting that the processing of sound-source locations may contribute to the perception of moving sounds (Ahissar et al., 1992; Doan et al., 1999; Poirier et al., 1997). Results from human psychophysiological and auditory evoked potential studies also strengthen the notion that sound source location contributes to motion perception (Getzmann and Lewald, 2011; Strybel and Neale, 1994). Our cross-condition MVPA results therefore extend the notion that motion directions and sound source locations might have common features that are shared for encoding spatial sounds.

Significant cross-condition classification has typically been considered as a demonstration that the region implements a partly common and abstracted representation of the tested conditions (Fairhall and Caramazza, 2013; Higgins et al., 2017; Hong et al., 2012). For instance, a recent study elegantly demonstrated that the human auditory cortex at least partly integrates interaural time and level differences (ITD and ILD) into a higher-order representation of auditory space based on significant for cross-cue classification (training on ITD and classifying ILD, and reversely). In the present study, we argue that even if cross- condition MVP-classification can provide useful hints about shared information across conditions in a given region; successful cross-MVPA results cannot be taken as evidence that the region implements abstract representation. Our successful across-condition classification (see Figure 4A) demonstrated that, even though there are shared representations for moving and static sounds within hPT, classifiers are able to easily distinguish motion directions from sound source locations (e.g. leftward versus left location). RSA analyses further supported the idea that moving and static sounds elicit distinct patterns in hPT (see Figure 4B-D). Altogether, our results suggest that hPT contains both motion direction and sound-source location information but that the neural patterns related to these two conditions are only partially overlapping. Our observation of significant cross-condition classification based on highly distinct pattern of activity between static and moving sounds may support the notion that even if location information could serve as a substrate for movement detection, motion encoding does not solely rely on location information (Ducommun et al., 2002; Getzmann, 2011; Poirier et al., 2017).



### 2.6. CONCLUSION

The present study demonstrates that information related to both horizontal and vertical moving and static sounds can be detected in the PT. Despite the shared information between the neural patterns evoked by auditory motion and static sounds, we show that motion directions and static locations generate highly distinct patterns of activity in the independently defined PT. Importantly, using multivariate decoding of different motion directions, we show evidences that direction-related information within PT displays axis-of motion coding features, reminiscent to the known organization of visual motion selective area.

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## Supplemental Information

To further investigate the presence of information about auditory motion direction and sound source location in opposite directions/location within an axis and across-planes, we ran four binary MVP-classifications in the left and right hPT. Figure 3B-C in the main text shows the mean classification accuracy across categories in each ROI.

### *MVPA –Binary Across-planes*

We used 2 additional classifiers to discriminate across planes (horizontal vs. vertical motion, horizontal vs. vertical static, hereafter across planes classification). Binary across-planes (horizontal vs. vertical) classification was significantly above chance level in the lhPT and rhPT both for moving (lhPT: mean  $\pm$  SD = 74.5  $\pm$  10.5,  $p < 0.001$ ; rhPT: mean  $\pm$  SD = 65.6  $\pm$  10.6,  $p < 0.001$ ), and static sounds (lhPT: mean  $\pm$  SD = 55.6  $\pm$  8.6,  $p < 0.001$ ; rhPT: mean  $\pm$  SD = 57.8  $\pm$  8.9,  $p < 0.001$ ). For multiple-comparisons, FDR-correction performed on p values.

### *MVPA – Binary Within-Axis*

Binary horizontal (left vs. right) within-axis classification showed significant results in both lhPT and rhPT for static sounds (lhPT: mean  $\pm$  SD = 58.6  $\pm$  14.5,  $p < 0.001$ ; rhPT: mean  $\pm$  SD = 56.5  $\pm$  11.9,  $p = 0.008$ ), while motion classification was significant only in the rhPT (mean  $\pm$  SD = 55.5  $\pm$  13.9,  $p = 0.018$ ). Moreover, binary vertical (up vs down) within-axis classification was significant only in the lhPT for both motion (mean  $\pm$  SD = 55.7  $\pm$  7.1,  $p = 0.01$ ), and static (mean  $\pm$  SD = 54.9  $\pm$  11.9,  $p = 0.03$ ) conditions. For multiple-comparisons, FDR-correction performed on p values.



## **Chapter 3**

### **Decoding auditory motion direction and location in hMT+/V5 and planum temporale of sighted and blind individuals**

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(final stage for submission).

### 3.1. ABSTRACT

In sighted individuals, a portion of the middle occipito-temporal cortex (hMT+/V5) responds preferentially to visual motion whereas the planum temporale (PT) responds preferentially to auditory motion. In case of early visual deprivation, hMT+/V5 enhances its response tuning toward moving sounds. However, the impact of early blindness on the PT remains poorly understood. Moreover, whether hMT+/V5 contains sound direction selectivity and whether the functional enhancement observed in the blind is motion specific or also involves auditory localization is equivocal. We used fMRI to characterize the brain activity of sighted and early blind individuals listening to left, right, up and down moving and static sounds. Whole-brain univariate analysis revealed preferential response to auditory motion in both sighted and blind participants in a dorsal fronto-temporo-parietal network including PT, as well as in the most anterior portion of hMT+/V5. Blind participants showed additional preferential response to auditory motion in the more posterior region of hMT+/V5. Multivariate pattern analysis revealed significant decoding of auditory motion direction in independently localized PT and hMT+/V5 in blind and sighted participants. However, decoding accuracies in the blind were significantly higher in hMT+/V5 and lower in PT when compared to sighted participants. Interestingly, decoding sound location showed a similar pattern of results even if the decoding accuracies were in general lower than those obtained from motion directions. Together, these results suggest that early visual deprivation triggers a network-level reorganization that enhances the recruitment of occipital areas in conjunction with a release in the computational workload of temporal regions typically dedicated to spatial hearing.

### 3.2.INTRODUCTION

The human region hMT+/V5 has long been considered hard-wired for the processing of visual motion (Tootell et al. 1995; Zeki et al. 1991; Watson et al. 1993). Its location in the ascending limb of the inferior temporal sulcus is relatively consistent across individuals (Dumoulin et al. 2000), its functional preference for visual motion is observed very early in development (Braddick et al. 2005; Gilmore et al. 2007; Hou et al. 2009) and the organization of this region shares striking similarities across species (Albright et al. 1984; Newsome & Park 1988; Mikami et al. 1986; Saito et al. 1986; Tanaka & Saito 1989; Duffy & Wurtz 1991). Examining how a visual region like hMT+/V5 develops in congenitally blind individuals presents an opportunity to assess how genetic and experience-dependent constraints functionally tune specialized computational/cognitive brain units.

In case of early visual deprivation, hMT+/V5 shows a reliable and preferential response to auditory (Poirier et al. 2006; Dormal et al. 2016; Jiang et al. 2014) and tactile motion (Ricciardi et al. 2007; Matteau et al. 2010), highlighting that while the driving modality input might change without developmental vision, the computational preference toward motion processing remains. But is the processing of non-visual motion in hMT+/V5 a unique consequence of early blindness? Some studies in sighted have shown that at least some part of this extended region (e.g. MST) may also respond to auditory (Saenz et al. 2008; Poirier et al. 2005; Collignon et al. 2015) and tactile motion (Hagen et al. 2002; Beauchamp et al. 2007; van Kemenade et al. 2013; Ricciardi et al. 2007), even if to a lower extent than in the early blind (Jiang et al. 2016; Dormal et al. 2016; Jiang et al. 2014). These observations suggest that the enhanced non-visual responses for moving stimuli observed in early blinds may build on pre-existing connections between auditory, tactile and visual motion processing centers (Konkle et al. 2009; Dormal et al. 2012; Berger & Ehrsson 2016). However, the involvement of hMT+/V5 for non-visual motion processing in the sighted remains controversial (Lewis et al. 2000; Bedny et al. 2010; Alink et al. 2012; Jiang et al. 2014).

In non-human primates, MT+ displays a columnar organization supporting visual direction selectivity (Dubner & Zeki 1971; Albright et al. 1984; Movshon & Newsome 1986; Born & Bradley 2005). Even if the presence of such columnar organization for motion direction remains to be demonstrated in the human homologue region hMT+/V5 (Bartels et al. 2008; Zimmermann et al., 2011), fMRI studies have shown that visual motion direction can also be successfully decoded in this region (Kamitani & Tong 2006; Seymour et al.

2009<sup>1</sup>). If the visually deprived occipital cortex reorganizes to process non-visual inputs by maintaining a similar functional organization as the one observed in the sighted (Amedi et al. 2007; Ricciardi et al. 2007; Dormal & Collignon 2011; Collignon, Dormal & Lepore 2013; Wang et al. 2017), it might be hypothesized that auditory motion direction can be decoded in hMT+/V5 regions in early blinds. To date, only few studies have investigated the decoding of different auditory motion direction in hMT+/V5 of sighted and early blind people, providing mixed results (Wolbers et al. 2011; Alink et al. 2012; Jiang et al. 2016; Dormal et al. 2016). Discrepancies could at least partially be attributed to the variety of auditory stimuli used across studies and the challenge of creating a vivid and ecological sensation of auditory motion while the subject is inside the scanner.

The recruitment of the hMT+/V5 region for auditory motion in blind and, to a lesser extent, in sighted individuals may reflect a more general involvement of this region for spatial hearing. In blind individuals, enhanced selectivity for auditory spatial processing has been observed in the middle/superior occipital gyrus – a region in close proximity to hMT+/V5 (Collignon et al. 2011; Weeks et al. 2000; Gougoux et al. 2005). A study using transcranial magnetic stimulation (TMS) found that focally and transiently disrupting the activity of this region significantly altered auditory spatial localization abilities in the early blind but not in sighted participants, while leaving pitch and intensity perception unaffected in both groups (Collignon et al. 2007). However, most previous studies (Collignon et al. 2011; Collignon et al. 2007; Gougoux et al. 2005) investigated sound location abilities asking to compare the position of a target relative to a probe sound (e.g. is the target on the left or right side of the probe), a condition that can trigger induced motion perception (Lakatos & Shepard 1997). Therefore, whether hMT+/V5 shows selective response to moving sounds or also contributes computing sound-source location remains unknown (see review Dormal et al. 2012).

What is the impact of the enhanced involvement of hMT+/V5 for auditory motion (and potentially location) on regions of the auditory system that typically involve in this process? The planum temporale (PT), a region in the superior temporal cortex that is posterior to Heschl's gyrus, has been suggested to engage in auditory spatial processing in general, including the processing of moving sounds and the location of static sound-sources (Zatorre et al. 2002; Smith et al. 2004; Smith et al. 2007; Smith et al. 2010). However, other studies in animals (Poirier et al. 2017) and humans (Baumgart & Gaschler-Markefski 1999;

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<sup>1</sup> The observation of significant decoding of visual motion direction does not however prove the presence of the underlying columnar organization for directionality since successful decoding may emerge from more macroscopic organizational principles (e.g. retinotopy; Dukelow 2001; Huk 2002; Amano 2009; Kolster 2010).



Bremmer et al. 2001; Hall & Moore 2003; Pavani et al. 2002; Krumbholz et al. 2005; Rees et al. 1998; Lewis et al. 2000; Poirier et al. 2005) pointed toward a specific role of PT for auditory motion processing. Human studies using multivariate pattern analyses support the notion that PT contains directional auditory motion information (Alink et al. 2012; Jiang et al. 2014; Jiang et al. 2016). In case of early blindness, some evidence points to an interplay between hMT+/V5 and PT for processing auditory motion, with enhanced auditory motion information in hMT+/V5 but reduced information in PT when compared to sighted controls (Jiang et al. 2014; Dormal et al. 2016). However, whether the re-distributed “workload” in between hMT+/V5 and PT can also be observed for multiple motion planes, and whether re-distribution can occur also for computing spatial positions remains unknown.

The present study aimed to address three questions that have previously received equivocal answers in the literature. First, we asked if auditory motion direction can be decoded in hMT+/V5 region in both sighted and blind individuals. Second, we investigated whether hMT+/V5 and PT regions only codes for motion direction information or also contain information about sound-source location in both the blind and the sighted. Lastly, we asked how early blindness affects auditory representation in PT.

### 3.3. MATERIALS AND METHODS

#### 3.3.1. Participants

Sixteen early blind (EB) and 18 sighted control participants (SC) were recruited for the study. Participants were matched for age and gender. Sighted participants also participated in an independent visual motion localiser task. Two SC participants were excluded due to poor performance on the task within the scanner. This resulted in a total of 32 participants included in the analyses: 16 early blind participants (8 female, age range: 20 to 46, mean  $\pm$  SD =  $33.7 \pm 7.2$  years) and 16 sighted participants (8 female, age range: 20 to 42, mean  $\pm$  SD =  $31.8 \pm 5.7$  years). An additional 17 sighted participants (10 females, age range: 20 to 41, mean  $\pm$  SD =  $28 \pm 5.3$  years) participated in an independent auditory motion localizer experiment.

In all cases, blindness was attributed to peripheral deficits with no additional neurological problems (see Supplementary Table 1). All the blind participants lost sight since birth or had visual problems since birth that evolved toward complete blindness before 4

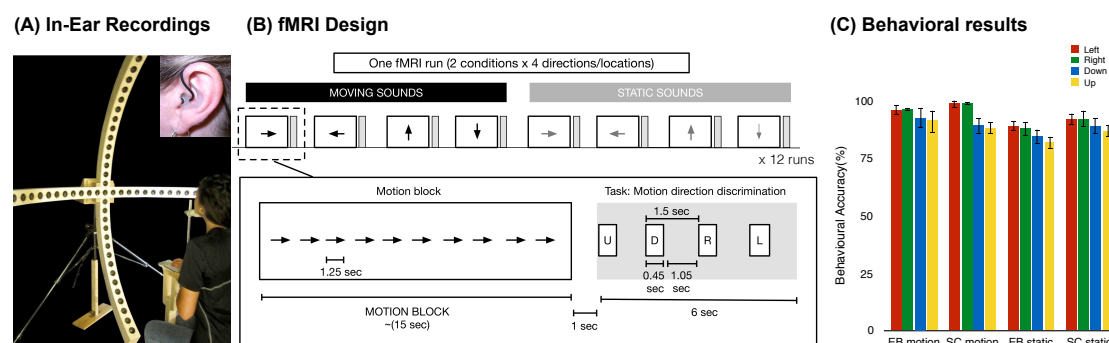
years of age. Seven blind participants had faint light perception but could not recognise colors or shapes.

Sighted participants had normal or corrected-to-normal vision. Experiments were undertaken with the understanding and written consent of each subject. All the procedures were approved by the research ethics boards of the Centre for Mind/Brain Sciences (CIMEC) and the University of Trento, and in accordance with The Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickham 1964).

## 3.3.2. Auditory stimuli

To induce a reliable perception of auditory space for each participant in the MRI scanner, auditory stimuli were recorded in a semi-anechoic room using binaural in-ear microphones from each participant independently. Binaural in-ear recordings allow binaural properties such as interaural time and intensity differences, as well as participant-specific monaural filtering cues, and serve to create reliable and ecological auditory space (Pavani et al. 2002).

To create an externalized ecological sensation of sound location and motion, we relied on individual in-ear stereo recordings that were recorded in a semi-anechoic room and from 30 loudspeakers on horizontal and vertical planes, mounted on two semicircular wooden structures with a radius of 1.1m (see Figure 1A). Participants were seated in the center of the apparatus with their head on a chin-rest, such that the speakers on the horizontal plane were at the participant's ear level and those on the vertical plane were aligned with the participant's mid-sagittal plane.



**Figure 1. Stimuli and Experimental Design.** (A). Acoustic apparatus used to present auditory moving and static sounds while binaural recordings were carried out from each participant's ear before the fMRI session. (B). Auditory stimuli presented inside the fMRI consisted of 8 conditions: leftward, rightward, downward and upward moving sounds and left, right, down and up static sounds. (C). The behavioral performance recorded inside the scanner.

Auditory stimuli were prepared using a custom-designed MATLAB scripts (R2013b, MathWorks). During the presentation of stimuli, the audio was recorded using binaural in-ear omni-directional microphones (Sound Professionals-TFB-2; 'flat' frequency range 20–20,000 Hz) attached to a portable Zoom H4n digital wave recorder (16-bit, stereo, 44.1 kHz sampling rate). Microphones were positioned at the opening of participant's left and right auditory ear canals. Then, these recordings were re-played to the participants when they were inside the functional MRI (fMRI). By using in-ear recordings, auditory stimuli automatically convolved with each individuals' own pinna and head related transfer function to produce a salient auditory perception in external space. The recorded auditory stimuli were used in both the main auditory experiment and the auditory motion localizer. All participants were blindfolded throughout the experiment. Prior to the recordings, the sound pressure level (SPL) were measured from the subject's head position and ensured that each speaker conveys 65dB-A SPL.

### *Stimuli recordings*

Sound stimuli consisted of 1250 ms pink noise (50 ms rise/fall time). In the static condition, the pink noise was presented separately at one of 4 locations: left, right, up, and down. Static sounds were presented at the third most outer speakers ( $-52^\circ$  and  $+52^\circ$  in the horizontal axis, and  $+52^\circ$  and  $-52^\circ$  in the vertical axis) in order to avoid possible reverberation difference at the outermost speakers. In the motion condition, the same pink noise was presented moving in 4 directions: leftward, rightward, upward and downward. Moving stimuli covered  $120^\circ$  of space/visual field in horizontal and vertical axes. To create the perception of smooth motion, the 1250 ms of pink noise was fragmented into 15 equal length pieces with each 83.333 ms fragment being played every two speakers, and moved one speaker at a time, from the outer left to the outer right (rightward motion), or vice-versa for the leftward motion. For example, for the rightward sweep, sound was played through speakers located at  $-60^\circ$  and  $-52^\circ$  consecutively, followed by  $-44^\circ$ , and so on. A similar design was used for the vertical axis. This resulted in participants perceiving moving sweeps covering an arc of  $120^\circ$  in 1250 ms (speed =  $96^\circ/\text{s}$ ) for four different directions. Participants were instructed to listen to the stimuli, without performing any task. Stimuli recordings were conducted in a session that lasted approximately 10 minutes, requiring the participant to remain still during this period. All participants reported strong sensation of auditory motion and were able to detect directions and locations with high accuracy (see Fig 1C).

### 3.3.3 Auditory experiment

Auditory stimuli were presented via MR-compatible closed-ear headphones (Serene Sound, Resonance Technology), and amplitude was adjusted according to each participant's comfort level. To familiarize participants with the task, participants completed a practice outside of the scanner while lying down until they reached above 80% of accuracy. Participants were blindfolded and instructed to keep their eyes closed.

Each run consisted of the 8 conditions (4 motion and 4 static) randomly presented using a block-design. Each condition was presented for 15 s block (12 repetitions of each event of 1250 ms sound, no ISI) and followed by 7 s gap for indicating the corresponding direction/location in space and 8s of silence (total inter-block interval was 15 s). The ramp applied at the beginning and at the end of each sound creates static bursts, and prevented adaptation to the static sounds. During the response gap, participants heard a voice saying "left", "right", "up", and "down" in pseudo-randomized order. Participants were asked to press a button with their right index finger when the auditory block's direction or location was matching with the auditory cue (Figure 1B). The number of targets and the order (position 1-4) of the correct button press were balanced across conditions. This procedure was adopted to ensure that the participants gave their response using equal motor command for each condition and to ensure the response is produced after the end of the stimulation period for each condition. Each scan consisted of one block of each condition, resulting in a total of 8 blocks per run, with each run lasting 4 m 10 s (100 volumes). Participants completed a total of 12 runs. The order of the blocks was pseudo-randomized within each run, and across participants.

### 3.3.4 Auditory localizer

To localize regions responding to auditory motion, an independent group of sighted participants ( $n = 17$ ) undertook an auditory motion localizer scan. Individual in-ear recordings of moving and static stimuli were presented in a blocked design. Each block contained 12 repetitions of 1200 ms sounds from one of 8 conditions: 4 motion directions, and 4 static locations. Stimuli within a block were separate by 100 ms ISIs, and each block was followed by a 6 s rest period. The localizer had one run and consisted of 13 repetitions of each condition block in a pseudorandom order. The scan lasted a total of 9 m and 48 s (235 volumes). Participants were instructed to indicate via button press with their right index finger when they detected a stimulus with a shorter duration (targets = 600 ms). The

number of targets in each block was varied between 1 and 3 targets, with the location in the block randomized and balanced across conditions. Participants were familiarized with the task before the fMRI session, and were blindfolded throughout the scan.

### **3.3.5 Visual hMT+/V5 localizer**

To identify hMT+/V5 in sighted individuals, participants undertook an independent visual motion localizer scan. Visual stimuli were back-projected onto a screen (width: 42 cm, frame rate: 60 Hz, screen resolution: 1024 x 768 pixels; mean luminance: 109 cd/m<sup>2</sup> via a liquid crystal projector (OC EMP 7900, Epson Nagano) positioned at the back of the scanner and viewed via mirror mounted on the head coil at a distance of 134 cm. Stimuli were 16 s of random-dot patterns, consisting of circular aperture (radius 4°) of radial moving and static dots (moving and static conditions, respectively) with a central fixation cross (Huk et al. 2002). One hundred and twenty white dots (diameter of each dot was 0.1 visual degree) were displayed on a gray background, moving 4° per second. In all conditions, each dot had a limited lifetime of 0.2 s. Limited lifetime dots were used in order to ensure that the global direction of motion could only be determined by integrating local signals over a larger summation field rather than by following a single dot (Bex et al. 2003). Additionally, limited lifetime dots allowed the use of control flickering (as opposed to purely static) stimuli that were matched to the moving stimuli in terms of temporal resolution. Stimuli were presented for 16 s followed by a 6 s rest period. Stimuli within motion blocks alternated between inward and outward motion (expanding and contracting) once per second. Because the localizer aimed to localize the global hMT+/V5 complex (e.g. MT and MST regions) the static block was composed of dots maintaining their position throughout the block in order to prevent flicker-like motion (Smith 2006). The localizer consisted of 14 alternating blocks of moving and static dots (7 each) and lasting a total of 6 m 40 s (160 volumes). In order to maintain the participant's attention and to minimize eye-movement during acquisition during the localizer's run, participants were instructed to detect a color change (from black to red) of a central fixation cross (0.03°) by pressing the response button with the right index finger.

### **3.3.6. Imaging parameters**

Functional and structural data were acquired with 4T Bruker MedSpec Biospin MR scanner, equipped with 8-channel head coil. Functional images were acquired with T2\*-weighted gradient echo-planar sequence with fat suppression. Acquisition parameters were:

repetition time of 2500 ms, echo time of 26 ms, flip angle of 73°, a field of view of 192 mm, a matrix size of 64 x 64, and voxel size of 3 x 3 x 3 mm<sup>3</sup>. A total of 39 slices were acquired in ascending feet-to-head interleaved order with no gap. The three initial scans of each acquisition run 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 (Zeng & Constable 2002).

High-resolution anatomical scan was acquired using a T1-weighted 3D MP-RAGE sequence (176 sagittal slices, voxel size of 1 × 1 × 1mm; field of view 256 x 224 mm; repetition time = 2700 ms; TE = 4.18 ms; FA: 7°; inversion time: 1020 ms). Participants were blindfolded and instructed to lie still during acquisition and foam padding was used to minimize scanner noise and head movement.

### **3.3.7. Univariate fMRI analysis**

Raw functional images were pre-processed and analyzed with SPM8 (Wellcome Trust Centre for Neuroimaging London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm/>) implemented in MATLAB R2014b (MathWorks). Before the statistical analysis, our preprocessing steps included slice time correction with reference to the middle temporal slice, realignment of functional time series, the coregistration of functional and anatomical data, spatial normalization to an echo planar imaging template conforming to the Montreal Neurological Institute space, and spatial smoothing (Gaussian kernel, 6 mm FWHM) were performed.

#### **3.3.7.1. Auditory experiment**

To obtain blood oxygen level-dependent (BOLD) activity related to auditory spatial processing, we computed single subject statistical comparisons with fixed-effect general linear model (GLM). In the GLM, we used eight regressors from each condition (four motion direction, four sound source location). The canonical double-gamma hemodynamic response function implemented in SPM8 was convolved with a box-car function to model the above mentioned regressors. Motion parameters derived from realignment of the functional volumes (3 translational motion and 3 rotational motion parameters), button press, and four auditory response cue events were modeled as regressors of no interest. During the model estimation, the data were high-pass filtered with cut-off 128 s to remove the scanner drift

and low-frequency fluctuations from the time series. To account for serial correlation due to noise in fMRI signal, autoregressive (AR (1)) was used.

At the fixed-effect individual subject level (FFX), to obtain activity related to auditory processing in the whole brain, the contrasts tested the main effect of each condition: Left Motion, Right Motion, Up Motion, Down Motion, Left Static, Right Static, Up Static, and Down Static. Next, to identify regions responding preferentially to the auditory motion and static stimuli, we compared the response of all motion conditions to all static conditions (Motion > Static, and Static > Motion). These linear contrasts generated statistical parametric maps (SPM[T]) that were further spatially smoothed (Gaussian kernel 8 mm FWHM) before being entered in a second-level group analysis, using a random effect model (RFX), accounting for inter-subjects variance.

At the group level, a series of one-sample t-tests was implemented to examine the main effects of each condition (Motion, Static), general auditory processing (Motion + Static), and motion processing (Motion > Static) for each participant group. A conjunction analysis characterized brain areas jointly activated for the contrast Motion > Static in both groups (EB and SC). Two-sample t-tests were then performed to compare these effects between groups (SC > EB, EB > SC).

Statistical inferences were done using family-wise error (FWE) correction for multiple comparisons using  $p < 0.05$  over the entire brain volume or over small spherical volumes (15 mm radius) located around regions of interest (see Table 1) using a minimal cluster size threshold of 20 contiguous voxels (Worsley et al. 1996). Significant clusters were anatomically labeled using the xjView Matlab toolbox (<http://www.alivelearn.net/xjview>) or structural neuroanatomy information provided in the Anatomy Toolbox (Eickhoff et al. 2007).

### 3.3.7.2 Region of interest definition

We used independent auditory and visual motion localizers to functionally defined PT and hMT+/V5 regions. Preprocessing steps were similar to whole-brain univariate analysis (see section *Univariate fMRI Analysis*). Single subject statistical comparisons were made using a fixed-effect GLM for each participant with two regressors (motion, static), and motion parameters (6 regressors of no interest). The canonical double-gamma hemodynamic response function implemented in SPM8 was convolved with a box-car function for each regressor. Motion parameters derived from realignment of the functional volumes (3 translational motion and 3 rotational motion parameters), button press was modeled as

regressor of no interest. During the model estimation, the data were high-pass filtered with cut-off 128 s to remove the scanner drift and low-frequency fluctuations from the time series. To account for serial correlation due to noise in fMRI signal, autoregressive (AR (1)) was used.

One-sample t-tests were conducted to characterize the main effect of motion processing (Motion > Static). This linear contrast generated statistical parametric maps that were further spatially smoothed (Gaussian kernel 8 mm FWHM) and entered into a second-level group analysis using a random effects GLM. Group-level peak coordinates of bilateral hMT+/V5 and PT were defined by contrasting the main effects of localizer scan (Motion vs Static), surviving a whole-brain family-wise-error correction ( $p < 0.05$ ). Peak coordinates from the auditory and visual motion localizers were used to create a sphere of 6 mm radius (117 voxels) around 4 region-of-interests (ROIs): left hMT+/V5, right hMT+/V5, left PT, and right PT. The 4 ROIs were defined functionally but constrained by anatomical landmarks of the regions. PT was selected within the triangular region lying caudal to the Heschl's gyrus on the supratemporal plane, whilst hMT+/V5 was constrained with the ascending limb of the inferior temporal sulcus (Zeki et al. 1991; Watson et al. 1993).

### 3.3.8. Multivariate pattern analyses

In order to investigate the presence of auditory motion direction and sound source location information, multivariate pattern analyses (MVPA) were conducted within the independently defined hMT+/V5 and PT regions. To ensure that the number of voxels was identical across subjects an ANOVA-based feature selection was performed to select the 110 voxels within each ROI, which are most informative/discriminative across all motion and static conditions (Cox & Savoy 2003; Haxby et al., 2001; Norman et al., 2006). All further analysis was conducted on these regions for all sighted and blind participants.

Preprocessing steps were identical to the steps performed for univariate analyses, with the exception of functional volumes that were smoothed with a Gaussian kernel of 2 mm (FWHM). MVPA were performed in CoSMoMVPA (<http://www.cosmomvpa.org/>; (Oosterhof et al. 2016, which implements LIBSVM software (<http://www.csie.ntu.edu.tw/~cjlin/libsvm>). A general linear model was implemented in SPM8, where each block was defined as a regressor of interest. A beta map was calculated for each block separately. Two multi-class linear support vector machine (SVM) classifiers with a linear kernel with a fixed regularization parameter of  $C = 1$  was trained and tested for each participant separately within each group. The two multi-class classifiers were trained



and tested to discriminate between the response patterns of the 4 auditory motion directions and locations, respectively.

For each participant, the classifier was trained using a cross-validation leave-one-out procedure where training was performed with  $n-1$  runs and testing was then applied to the remaining one run. In each cross-validation fold, the beta maps in the training set were normalized (z-scored) across conditions, and the estimated parameters were applied to the test set. To evaluate the performance of the classifier and its generalization across all the data, the previous step was repeated 12 times where in each fold a different run was used as the testing data and the classifier was trained on the other 11 runs. For each region per subject, a single classification accuracy was obtained by averaging the accuracies of all cross-validation folds.

### *3.3.8.1. Within Condition Decoding*

To investigate motion direction and static location information in areas hMT+/V5 and PT in sighted and blind participants, 4-class classifiers were trained and tested to discriminate between the response patterns of the 4 auditory motion directions and 4 sound source locations, respectively (hereafter across-planes decoding). The order of the 4 motion conditions and 4 static conditions were randomized across runs in order to avoid biasing the classifier, and to prevent the classifier to learn and decode an alternative rule (i.e. the order, rather direction and location information).

### *3.3.8.2. Cross-condition Decoding*

To test whether neural patterns of auditory motion within hMT+/V5 and PT reflect neuronal computations purely dedicated to motion or that can be shared with static locations, we performed cross-condition classification in the areas that showed successful within-condition decoding with both motion and static stimuli. Specifically, the classifier was trained to discriminate static locations, and was then tested to distinguish between motion directions, and vice versa. Accuracies from the two cross-condition decoding analyses (static to motion, motion to static) were then averaged. For interpretability reasons, cross-condition classification was only interpreted on the stimuli categories that the classifiers discriminated reliably (above chance level) for both motion and static conditions (e.g. if discrimination of left vs. right was not successful in one condition, either static or motion, then the left vs. right cross-condition classification analysis was not carried out).

Prior to performing the cross-condition MVPA, each individual pattern was normalized separately across voxels so that any cross-condition classification could not be due to global univariate activation differences across the conditions.

### *3.3.8.3. Statistical Significance*

Statistical significance in the multivariate classification analyses was assessed using non-parametric tests permuting condition labels and bootstrapping (Stelzer et al. 2013). Each permutation step included shuffling of condition labels and re-running the classification, which was repeated 100 times on the single-subject level. Next, we applied a bootstrapping procedure in order to a group-level null distribution that is representative of each group. For each group, from each subject's null distribution one value was randomly chosen and averaged across all the subjects. This step was repeated 100,000 times resulting in a group level null distribution of 100,000 values. The classification accuracies across subjects we considered as significant if the  $p < 0.05$  after corrections for multiple comparisons using the FDR method (Benjamini & Yekutieli 2001). The group comparison was also tested for significance by using permutation (100,000 iterations).

Classification accuracies were entered into a  $2 \times 2 \times 2 \times 2$  repeated measures ANOVA to test the interaction between Group (EB, SC; between-subject factor), Condition (motion, static; within-subject factor), Region (hMT+/V5, PT; within-subject factor), and Hemisphere (left, right; within-subject factor).

### **3.3.9. Brain-Behavior Correlation Analysis**

We investigated the link between behavioral performance and neural activity of hMT+/V5 and PT regions by performing between-subject Pearson's correlation on behavioral performance with (1) extracted beta parameter estimates, and (2) extracted decoding accuracies in both EB and SC groups. Behavioral performance was measured as the accuracy of detecting motion directions and sound source locations during the fMRI session. We extracted beta parameter estimates from peak voxel of each ROI (left and right hemispheres in hMT+/V5 and PT) from each subject, and for each of the 8 auditory conditions (leftward, rightward, upward, downward, left, right, up, and down), and performed between-subject correlation.

Classification accuracies obtained from multi-class classification from each ROI of each subject was correlated with overall performance of motion direction and sound source

location discrimination. Statistical results were corrected for multiple comparisons using the FDR method (Benjamini & Yekutieli 2001).

### 3.4. RESULTS

#### 3.4.1. Behavioral

Behavioral performances in all the 8 conditions in both groups were above 80% of correct responses, demonstrating that we were able to trigger salient and reliable auditory percepts while the subjects were inside the scanner. To determine if there were any differences between groups or conditions in the target detection task performed during the auditory experiment, accuracy scores were entered into a 2 x 2 x 4 repeated measure ANOVA to test the interaction between Group (EB, SC; between-subject factor), Condition (motion, static; within-subject factor), and Orientation (left, right, up, and down; within-subject factor). Importantly, this showed no main effect of Group ( $F_{1,30} = 0.401$ ;  $p = 0.5$ ), indicating that the overall accuracy while detecting direction of motion or location of sound source did not differ between the blind and sighted groups. There was a significant main effect of Condition ( $F_{1,30} = 11.49$ ;  $p = 0.002$ ), which was caused by higher accuracy in the motion condition as compared to the static condition. There was a significant main effect of Orientation ( $F_{1.6,48.3} = 14.24$ ;  $p < 0.001$ ), caused by greater accuracy in the horizontal orientations (left and right) as compared to the vertical orientations (up and down). Post-hoc two-tailed t-tests ( $p < 0.05$ , Bonferroni corrected for multiple comparisons) showed that this main effect was due to significant difference between left orientation with up ( $t_{15} = 5.22$ ,  $p < 0.001$ ) and down ( $t_{15} = 3.87$ ,  $p = 0.001$ ) orientations, and between right orientation with up ( $t_{15} = 5.17$ ,  $p < 0.001$ ) and down ( $t_{15} = 3.81$ ,  $p = 0.001$ ) orientations. No interaction between Condition x Orientation was observed.

#### 3.4.2. Whole brain analyses

Figure 2 shows the response to motion and static auditory stimuli in EB and SC participants. Consistent with previous studies (Warren et al. 2002; Pavani et al. 2002; Poirier et al. 2005), a preferential response to auditory moving stimuli (Motion > Static) was observed for SC participants in the superior temporal gyri, bilateral planum temporale, precentral gyri, and anterior portion of middle temporal gyrus in both hemispheres (Figure 2A). A similar response was observed in EB participants (Figure 2B), with a reliable extension toward the occipital cortex.

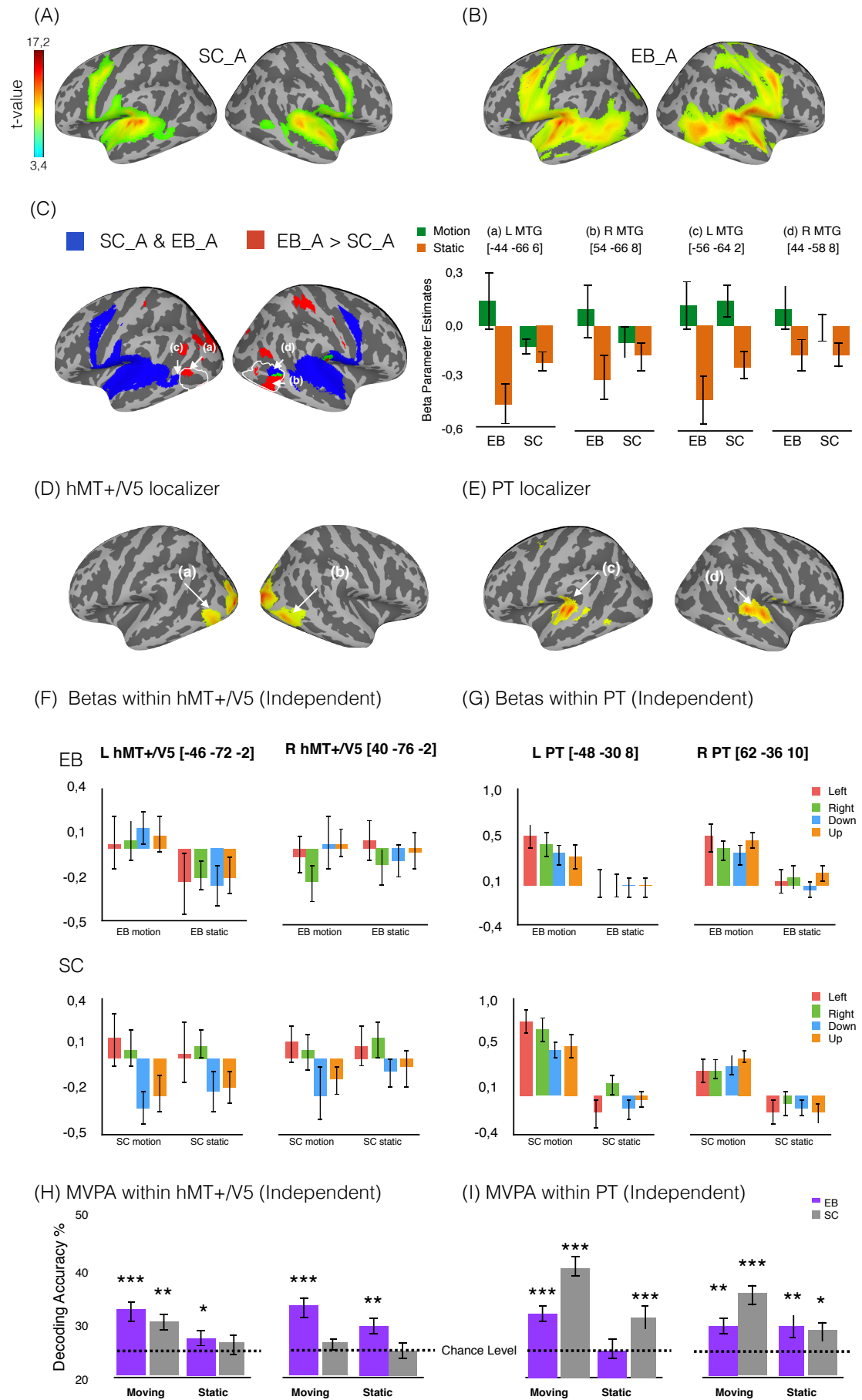
To identify regions responding more to moving than static sounds in both EB and SC

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participants, we ran a conjunction (AND; Nichols et al. 2005) analysis (SC [motion > static]  $\cap$  EB [motion > static]). This showed that both groups activated the superior temporal gyrus, bilateral planum temporale and the anterior portion of middle temporal gyrus bilaterally. The right middle temporal gyrus (MTG) region partially overlapped with the functionally defined hMT+/V5 identified visually (motion > static) in SC participants (white outline, Figure 2C).

To identify which regions activated more for moving than static sound in EB versus SC participants, we performed a two-sample t-test ((EB [motion > static] > SC [motion > static])). This revealed enhanced activity for EB participants in regions including the precuneus, the cuneus extending into the intraparietal sulci, planum temporale, and bilateral posterior middle temporal gyrus (see Table 1.).

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**Figure 2. Univariate whole brain results. A-B.** Activations obtained from the contrast testing which regions preferentially activated for auditory motion processing in sighted and early blind participants: (A) Sighted [Motion > Static], (B) Blind [Motion > Static]. **C.** Activation in blue indicates auditory motion selectivity in both of the groups [Sighted conj, Blind] x [Motion > Static]. Activation in red indicates enhanced responses to moving compared to static sounds in the early blind compared to the sighted group [Blind > Sighted] x [Motion > Static]. Activation in green indicates the overlap between the conjunction and group comparison analyses. The arrows indicate the peak coordinates of middle temporal gyrus (MTG) in the conjunction and group comparison analyses. All the maps are thresholded with  $p < 0.001$  (uncorrected) for illustration purpose only (see methods for statistical significance assessment). Right panel: Beta parameter estimates (arbitrary units  $\pm$  SEM; illustration purpose only) associated with the perception of motion (green), and static sounds (yellow) are plotted for blind and sighted at significant peak coordinates from the group comparison ((a) and (b)) and conjunction ((c) and (d)) analyses. **D-E.** Motion selective results from the visual and auditory motion localizers (FWE corrected  $p < 0.05$ ). **F-G.** From the peak coordinate of the motion localizers, mean activity estimates (arbitrary units  $\pm$  SEM) associated with auditory motion and static sounds are plotted. **H-I.** Decoding accuracies of 4 auditory motion directions and 4 static locations in independently localized hMT+/V5 and PT. Error bars indicate the SEM.

### 3.4.3. Independent visual and auditory motion localizer

In order to avoid circularity that can arise from selection of ROIs, more particularly “double dipping” (Kriegeskorte et al., 2009) – the use of the same dataset for selection and specific analysis – we independently localized visual and auditory motion responsive areas. Whole-brain univariate analyses for independent visual and auditory motion localizers were performed to acquire the peak coordinates of hMT+/V5 and PT, selective to visual and auditory motion respectively (Figure 2D-E). The obtained stereotactic MNI coordinates were as follows: L hMT+/V5: [-46 -72 -2]; R hMT+/V5: [40 -76 -2], and L PT: [-48 -30 8], R PT: [62 -36 10].

#### 3.4.3.1. Region of interest analyses

Beta parameters extracted from PT and hMT+/V5 ROIs were entered in a  $2 \times 2 \times 2 \times 2$  repeated measure ANOVA, Group (EB, SC) as between subjects factor and Hemisphere (left, right), Region (hMT+/V5, PT) and Condition (motion, static) as within-subjects factors. We observed a main effect of Condition ( $F_{1,30} = 69.2$ ,  $p < 0.001$ ) and Region ( $F_{1,30} = 10.8$ ,  $p < 0.001$ ). The main effect of Condition was caused by a greater response to motion > static stimuli across all regions. There was no interaction between Condition x Region x Hemisphere ( $F_{1,30} = 2.02$ ,  $p = 0.16$ ). There was a significant interaction between Group x Region x Condition ( $F_{1,30} = 12.63$ ,  $p < 0.001$ ). Post-hoc two-tailed t-tests ( $p < 0.05$ , Bonferroni corrected) showed that the interaction was caused by greater responses to motion > static stimuli for EB in hMT+/V5 ( $t_{15} = 3.82$ ,  $p < 0.001$ ) and PT ( $t_{15} = 7.9$ ,  $p < 0.001$ ) regions, whereas the SC participants only showed a greater response to motion > static in PT ( $t_{15} = 10.2$ ,  $p < 0.001$ , hMT+/V5:  $t_{15} = 0.06$ ,  $p = 0.9$ ) region (see Figure 2F-G).

To investigate motion direction and sound source location selectivity in each ROI, we performed 8 repeated measures of ANOVA. For motion direction, in left PT region, a 2 x 4 (Group: between subjects factor, Direction: within-subject factor) ANOVA revealed a main effect of Direction ( $F_{3,90} = 5.29$ ,  $p = 0.002$ ), that was caused by higher response to leftward sounds compared to downward ( $t_{3,30} = 3.35$ ,  $p = 0.006$ ) and upward ( $t_{3,30} = 3.23$ ,  $p = 0.009$ ) sounds ( $p < 0.05$ , Bonferroni corrected for multiple comparisons) across groups. However, no main effect of Group and no interaction were observed. In the right PT and the left hMT+/V5 regions, 2 x 4 (Group, Direction) ANOVA did not reveal any significant results. In right hMT+/V5, despite no main effects, Direction x Group revealed significant interaction ( $F_{2,2,66.3} = 4.43$ ,  $p = 0.013$ ). The interaction was driven by higher activity to horizontal motion direction and lower activity to vertical motion directions in the SC compared to the EB. These results indicated that no clear evidence of motion direction selective activity across groups.

Among the four 2 x 4 (Group: between subjects factor, Location: within-subject factor) ANOVAs to investigate sound source location selectivity, we observed significant results only in the left PT region. The main effect of Location was mainly driven by right location evoking higher activity in left PT compared to left location ( $t_{3,30} = 3.21$ ,  $p = 0.01$ ) and down location ( $t_{3,30} = 2.99$ ,  $p = 0.019$ ) sounds. Moreover, Location x Group interaction revealed that differential location activity was due to the SC group (stats).

Overall, beta parameter estimates did not show clear evidence for motion direction or sound-source location specific activity.

### 3.4.4. Multivariate pattern analyses

#### 3.4.4.1. Within-Condition: multi-class decoding

We ran multi-class MVP-decoding in four ROIs identified using the independent auditory and visual motion localizers (bilateral hMT+/V5, bilateral PT) in order to determine whether there were significant differences in the response patterns to the four motion directions (leftward, rightward, upward, downward) and four static locations (left, right, up, down).

Figure 2H-I shows decoding accuracies for motion and static stimuli in the four regions of interest for EB and SC participants. For motion stimuli, permutation testing (FDR-corrected) revealed that classification accuracies in hMT+/V5 were significantly above chance for EB participants in both the hemispheres (left: mean  $\pm$  SD =  $32.4 \pm 0.8$ ,  $p < 0.001$ ; right: mean  $\pm$  SD =  $33.1 \pm 0.7$ ,  $p < 0.001$ ). In SC participants, decoding accuracy was only significantly above chance in the left hMT+/V5 but not in the right hMT/V5 (left: mean  $\pm$  SD

=  $30.5 \pm 0.6$ ,  $p=0.002$ ; right: mean  $\pm$  SD =  $26.4 \pm 0.4$ ,  $p=0.184$ ). In PT, decoding accuracy was significantly above chance in both hemispheres in both groups (EB left: mean  $\pm$  SD =  $32 \pm 0.6$ ,  $p<0.001$ ; EB right: mean  $\pm$  SD =  $29.7 \pm 0.7$ ,  $p=0.003$ ; SC left: mean  $\pm$  SD =  $40.6 \pm 0.8$ ,  $p<0.001$ ; SC right: mean  $\pm$  SD =  $35.3 \pm 0.9$ ,  $p<0.001$ ). Permutation of two-sample t-tests revealed that decoding accuracy was higher for EB as compared to SC in the right hMT+/V5 ( $p=0.02$ ) but not in the left hMT+/V5 ( $p=0.62$ ). In contrast, decoding accuracy was greater in SC than in EB in the left PT ( $p=0.016$ ) but not in the right PT ( $p=0.101$ ) (Figure 2I).

For static location stimuli, decoding accuracies were significant within hMT+/V5 in the right (mean  $\pm$  SD =  $29.7 \pm 0.9$ ,  $p=0.003$ ) and very close to the cut-off significance value in the left hemisphere (mean  $\pm$  SD =  $27.6 \pm 0.6$ ,  $p=0.054$ ) of EB participants, while decoding was not significantly greater than chance in either the left or right hMT+/V5 for SC participants (left hMT+/V5: mean  $\pm$  SD =  $26.3 \pm 0.7$ ,  $p=0.2$ ; right hMT+/V5: mean  $\pm$  SD =  $25 \pm 0.5$ ,  $p=0.458$ ). In the PT, classification accuracy was significantly above chance in both hemispheres in SC participants (left PT: mean  $\pm$  SD =  $31.3 \pm 0.9$ ,  $p<0.001$ ; right PT: mean  $\pm$  SD =  $28.7 \pm 0.7$ ,  $p=0.023$ ), but only in the right hemisphere of EB (right PT: mean  $\pm$  SD =  $29.4 \pm 0.8$ ,  $p=0.007$ ; left PT: mean  $\pm$  SD =  $25.3 \pm 0.7$ ,  $p=0.458$ ).

Finally, we assessed differences between decoding accuracies using a  $2 \times 2 \times 2 \times 2$  (Group, Region, Condition, Hemisphere) repeated measures ANOVA. This revealed a main effect of Condition ( $F_{1,30} = 17.2$ ,  $p < 0.001$ ) due to greater accuracies for motion over static stimuli across all regions. We also observed a main effect of Region ( $F_{1,30} = 10.5$ ,  $p = 0.003$ ) showing overall higher decoding in PT than hMT+/V5. Crucially, we observed a significant interaction between Group  $\times$  Region ( $F_{1,30} = 26.54$ ,  $p < 0.001$ ). Post-hoc two-tailed t-tests ( $p<0.05$ ; Bonferroni corrected for multiple comparisons) showed that decoding accuracy in hMT+/V5 was significantly greater for EB over SC ( $p = 0.003$ ). In contrast, decoding accuracy in PT was significantly greater for SC over EB ( $p = 0.004$ ). The lack of significant interaction between Group  $\times$  Region  $\times$  Condition indicates that differences in the decoding accuracies between groups and regions are not specific to motion condition.

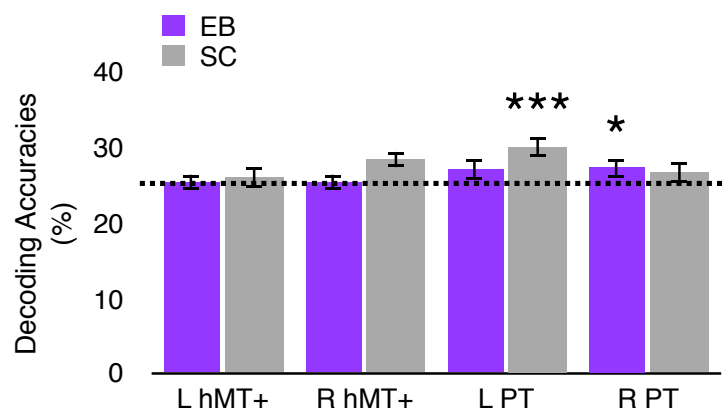
#### 3.4.4.4. Cross-condition decoding

Within-condition classification results provide evidence that both motion direction and location can be decoded in bilateral PT for SC, and the right PT and right hMT+/V5 of EB. However, these data do not address whether the patterns are shared across the spatial conditions – for example, whether the representations of leftward motion and left static are similar. To investigate the shared representation of motion direction and sound-source



location, we trained our classifiers on neural patterns extracted from motion directions and tested on patterns underlying sound-source location, and vice versa. For interpretability reasons, cross-condition classification was only carried out in ROIs that decoded significantly above chance for both motion and sound-source conditions in the within-condition decoding analysis (In sighted group, left and right PT, in early blind group right hMT+/V5).

Cross-condition classification in the four regions of interest revealed significant results in the left PT (mean  $\pm$  SD =  $27.8 \pm 5.3$ ,  $p < 0.001$ ) and a trend in the right PT (mean  $\pm$  SD =  $26.7 \pm 5.1$ ,  $p = 0.085$ ) in the SC group; while significant cross-condition decoding was observed in the right PT (mean  $\pm$  SD =  $28.7 \pm 3.8$ ,  $p = 0.03$ ), but not in right hMT+/V5 (mean  $\pm$  SD =  $25.4 \pm 5.7$ ,  $p = 0.341$ ) in the EB group (see Figure 3).



**Figure 3. Cross-classification results.** The cross-condition MVP-decoding was performed on four ROIs. The classifiers were trained on 4 motion condition and tested on 4 static condition (and vice versa). FDR corrected p-values: (\*) is  $p < 0.05$ , (\*\*) is  $p < 0.01$ , (\*\*\*)  $p < 0.001$ . Dotted lines represent chance level.

### 3.4.5. Brain-Behavior correlation analyses

In order to explore whether the brain activity elicited by our moving and static sounds in hMT+/V5 and PT links to the ability of the listener to discriminate the direction and location of these sounds, we conducted between-subject correlations analyses. The multi-class decoding accuracies and beta parameter estimates were extracted from the peak coordinates of independently defined hMT+/V5 and PT regions. Behavioral accuracies of discrimination motion directions (motion condition) and sound source locations (static condition) were correlated with decoding accuracies and beta parameter estimates separately. No correlation was observed between behavioral performance and the neural activity of hMT+/V5 and PT across groups (see Supplemental Fig. 1).

### 3.5. DISCUSSION

In this study, we comprehensively investigated the role of hMT+/V5 and PT regions in auditory motion direction and sound-source location in sighted and early blind individuals. Both groups showed auditory motion selective response in the classical auditory network, as well as a region overlapping with the most anterior portion of hMT+/V5. Moreover, early blinds showed additional preferential response in the more posterior region of hMT+/V5.

Our analysis showed no differences between the four sound locations or directions at the univariate level. However, we found that motion direction and sound-source location can be decoded in both hMT+/V5 and PT regions in both the sighted and the blind. Importantly, we observed that visual experience had a major impact on the coding profile of these regions. Overall, our results demonstrated enhanced tuning for auditory motion direction and sound-source location in hMT+/V5 regions in EB when compared to SC. This enhanced auditory tuning in hMT+/V5 in the blind co-occurs with a reduced computational involvement of PT regions. Early visual deprivation therefore triggers a network-level reorganization between occipital and temporal regions typically dedicated to spatial hearing. Whole-brain univariate analyses revealed preferential response to auditory motion for both sighted and blind participants in a dorsal fronto-temporo-parietal network, including PT as well as a region overlapping with the most anterior portion of the right hMT+/V5 (Figure 2C; Table 1). These univariate results therefore support and extend a growing body of evidence suggesting that moving auditory (Warren et al. 2002; Poirier et al. 2005) and tactile (Beauchamp et al. 2007; Ricciardi et al. 2007; Matteau et al. 2010; van Kemenade et al. 2013) stimuli can evoke preferential responses in a portion of the hMT+/V5 in sighted individuals. The observation of motion selective activity in both of the groups was used to support the idea that this region may implement, at least partially, abstracted motion computation that is independent of sensory input and/or experience (Ricciardi & Pietrini 2011; Strnad et al. 2013). It is, however, important to note that an overlap of functional preference for auditory motion between the sighted and the blind individuals does not guarantee similar underlying computation. For instance, hMT+/V5 could activate due to visual imagery in sighted people (Goebel et al. 1998; Sathian 2005; Vetter et al. 2014; Emmerling et al. 2016) but instead relies on crossmodal reorganization of occipital regions in case of early visual deprivation (Poirier et al. 2006; Dormal et al. 2016; Jiang et al. 2014). Actually, a study using TMS found that focally and transiently disrupting the activity of hMT+/V5 significantly altered auditory spatial localization abilities only in the early blind and

not in sighted participants, suggesting that non-visual processing could be mediated by different mechanisms in blind and sighted populations (Collignon et al. 2007).

Blind participants showed additional preferential response to moving over static sounds in the more posterior region of hMT+/V5. Our finding is in line with previous studies showing that hMT+/V5 responds to auditory (Poirier, Collignon, Scheiber, L. Renier, et al. 2006; Bedny et al. 2010; Wolbers et al. 2011; Jiang et al. 2014; Dormal et al. 2016) and tactile (Ricciardi et al. 2007; Matteau et al. 2010) motion stimuli in early blind individuals. These results support the notion that cross-modal reorganization of hMT+/V5 following visual deprivation maintains the computational role of the colonized area while redirecting the modality to non-visual input (Collignon et al. 2009; Dormal et al. 2016; Collignon et al. 2011; Ricciardi et al. 2014; Amedi et al. 2017). Similarly, studies involving early deaf animals suggested that regions normally sensitive to auditory motion processing in the “auditory” cortex specifically reorganize to support visual motion processing (Lomber et al. 2010; Meredith et al. 2011).

Overall, the four motion directions and four sound source locations did not evoke differential univariate activity in the hMT+/V5 region in both groups (see section *Region of interest analyses*). Our results demonstrate that information pertaining to multiple axes of motion can be decoded within hMT+/V5 in EB and SC groups. In congruency with the univariate analyses, the right hMT+/V5 showed enhanced decoding accuracy in the blind relative to the sighted group (Figure 2H), suggesting again that early visual deprivation increases the functional involvement of the hMT+/V5 for the processing of auditory motion.

Our findings contrast with previous studies that did not find information about auditory motion direction in hMT+/V5 of the sighted (Jiang et al. 2014; Jiang et al. 2016; Alink et al. 2012). The contradiction could emerge from the differences in experimental design and auditory stimuli. In those studies, the directional selectivity was investigated exclusively in the horizontal axis, while the present study contained both horizontal and vertical auditory stimuli. It is possible that activity patterns elicited in hMT+/V5 for the cardinal motion directions differ to a larger extent from activity patterns elicited by sounds provided only in the horizontal axis (Alink et al. 2012; Jiang et al. 2014; Jiang et al. 2016). Here, we propose a mechanistic framework to explain the differences across above mentioned studies and our results. In the visual domain, the functional organization of the middle occipito-temporal region hMT+/V5 is characterized by columns containing neurons that react specifically to a certain visual motion direction (Albright et al. 1984). Those columns vary smoothly for certain motion direction but are also found running side by side

with their respective opposing motion direction counterparts (Albright et al. 1984; Diogo et al. 2003; Born & Bradley 2005; Zimmermann et al. 2011). By aggregating opposing motion directions, larger axis of motion features can be constructed that are more easily detectable with fMRI than individual direction selective columns (Zimmermann et al. 2011). In the present study, axis of motion (horizontal versus vertical) classification provided more reliable results compared to within-axis direction (e.g. left versus right or up versus down) classifications, indicating that axis of motion directions is more easily detectable also in the auditory domain in hMT+/V5 (see Supplementary Analysis). Our results are consistent with the results of Dormal et al., (2016) showing that radial and vertical motion can be decoded in hMT+/V5 in early blind and, to a lower extent, sighted individuals. Our study extends these results by showing enhanced decoding across-axes when compared to within-axes of motion. This brings the resemblance between the coding of hMT+/V5 in vision and audition to an additional and finer-grained level of resemblance (Kamitani & Tong 2006), further suggesting that topographic organization principle of hMT+/V5 might be maintained/recycled for representing auditory motion directions in sighted and blind people.

Previous studies highlighted that group-averaged responses for localization of hMT+/V5 in the sighted individuals can lead to deceptive BOLD activity to non-visual motion (Jiang et al., 2015; Saenz et al., 2008) due to the overlapping responses from neighboring areas. The misleading activity could stem from the location of visual hMT+/V5 varies widely across individuals (Dumoulin et al., 2000; Huk et al., 2002). We conducted additional analysis to test auditory motion direction in individually defined hMT+/V5 in sighted participants (see Supplemental Information). Our results confirmed the group-averaged hMT+/V5 that auditory spatial information can be detected in hMT+/V5 of sighted people.

It is however important to note that the observation of significant motion direction decoding in the visual (Kamitani & Tong 2006; Beckett et al. 2012; Wang et al. 2014) and auditory domain does not however prove the presence of an underlying columnar organization for directionality since successful decoding may emerge from more macroscopic organizational principles (e.g. retinotopy; Amano et al., 2009; Dukelow et al., 2001; Huk et al., 2002; Kolster et al., 2010). High-field fMRI studies have recently suggested that both large-scale (retinotopic organization) and fine-scale (e.g. columnar organization) seem to play a critical role in decoding performance based on fMRI data (Beckett et al. 2012; Wang et al. 2014; Sengupta et al. 2017; Gardumi et al. 2016; Pratte et al. 2016).

We have seen that a region corresponding to hMT+/V5 contains information about motion direction in the blind and, to a lesser extent, in sighted individuals. Does hMT+/V5 also contain information about sound-source locations? In sighted individuals, hMT+/V5 contains location selective representations of visual stimuli (Dukelow 2001; Huk 2002; Amano 2009; Kolster 2010; Fisher 2010). For instance, a recent fMRI study has found evidence that hMT+/V5 plays a role in the processing of visual localization of briefly flashed stimuli (Bonkhoff et al. 2017). These studies suggest an active processing of visual location information in hMT+/V5 in sighted individuals.

If auditory information is being processed in hMT+/V5 in a computationally analog structure as the one observed in vision, one may expect to find traces of sound source location in this region. In our study, we observed sound source location information in bilateral hMT+/V5 in EB, but not in SC group. Our results therefore confirm and extend previous studies demonstrating that the right dorsal extrastriate occipital cortex in blind individuals contributes to spatial processing of sounds (Collignon et al. 2007; Collignon et al. 2009; Collignon et al. 2011; Collignon et al. 2009b). However, in contrast to what was observed for the directions of motion, we did not observe “axis of position” preference in either group. Moreover, the cross-condition classification results showed that the classifiers trained on motion directions failed at classifying sound source locations (and vice-versa), therefore demonstrating separate pattern geometries between auditory motion and location processing in hMT+/V5 for both of the groups. This pattern of results contrast with the one observed in PT where axis of motion preference is observed for both motion directions and sound source location and where cross-conditions decoding shows significant results. These results suggest separate computational structure between PT and hMT+/V5. It therefore appears that hMT+/V5 in the blind is not a full replica of what is observed in sighted in vision and neither a duplicate of the functional organization observed in PT. Using electrophysiological measurements to investigate at what time point after stimulus presentation do the occipital and temporal regions participate in the auditory spatial processing would potentially help in addressing such question.

**What are the mechanisms that could drive such extension of the crossmodal recruitment of hMT+/V5 for auditory motion in the blind?** Large-scale connectivity patterns between separate sensory regions that are involved in related function could be a determining factor for the expression of crossmodal plasticity (Hannagan et al. 2015; Dormal & Collignon 2011). According to a biased connectivity framework, enhanced non-visual responses for moving stimuli observed in early blinds may build on pre-existing connections between auditory,

tactile and visual motion processing areas (Johnson 2011). This idea of shared computational structure between the senses may find support in the numerous studies showing strong multisensory interaction between visual and auditory motion processing (Soto-Faraco et al. 2004; Soto-Faraco et al. 2004; Soto-Faraco et al. 2002; Kitagawa & Ichihara 2002). For instance, it has been reported that adapting to visual motion induces an auditory aftereffect (Soto-Faraco et al. 2003; Soto-Faraco et al. 2005; Kitagawa & Ichihara 2002), strongly suggesting that the processing of visual and auditory motion relies on shared neural representations (see also Konkle et al. (2009) for a link between vision and touch for motion processing). Moreover, coherent audiovisual motion direction results in enhanced activity in hMT+/V5 compared to only visual motion or incoherent audiovisual motion stimuli (Scheef et al., 2009) and enhanced functional connectivity between hMT+/V5 and superior temporal gyrus (vicinity of area PT) has been observed during the processing of sound induced visual motion (Hidaka 2017).

During brain development, sensory experience impacts on synaptic pruning in cortical connections between regions (Innocenti & Price 2005; Innocenti 1995). Visually deprived cats show maintenance of partially pruned cortico-cortical and thalamic-cortical projections to the visual cortex (Berman 1991; Karlen 2006; Kingsbury 2002). It is therefore possible visual loss triggers the stabilization and/or strengthening of connections between PT and hMT+/V5. Furthermore, evidence from dynamic causal modeling of fMRI datasets suggests that early blindness triggers stronger cortico-cortical (functional) connections between auditory and occipital areas, together with the enhanced recruitment of occipital areas by auditory modality (Klinge et al. 2010; Collignon, Dormal, Albouy, et al. 2013). Intrinsic anatomical and functional connections between visual and auditory areas could therefore play a crucial role in re-distributing the auditory information between computationally analog units.

The decreased computational role of the PT suggests that the absence of visual experience since birth not only influences the response properties of “visual” areas but also alters the functioning of the regions supporting the remaining senses. In line with previous studies, both univariate and multivariate results showed that PT maintains its features to process auditory motion in early blind individuals, however, its fine-scale computational role – containing motion direction information - is reduced compared to sighted individuals (Dormal et al. 2016; Jiang et al. 2014; Jiang et al. 2016). Our results demonstrated not only the existence of auditory motion direction information in the two motion responsive regions across groups, but also a significant interaction between groups and regions showing that

early blindness triggers a workload re-distribution between these two motion responsive regions. Moreover, this re-distribution is not limited to auditory motion direction but also observed for static sound location. In other words, early blindness may trigger a large-scale reorganization in the division of computational labor across sensory regions.

**What are the behavioral consequences of such large-scale interplay between sensory cortices on auditory motion processing?** A limited number of studies have shown that enhanced occipital recruitment in EB may support compensatory behaviors in the remaining senses (Gougoux et al. 2005; Amedi et al. 2003; see Lomber & Malhotra 2008; Benetti et al. 2017 for similar reasoning with auditory deprivation). For instance, superior auditory localization abilities of blind individuals correlate with the enhanced recruitment of the occipital cortex (Gougoux et al. 2005). Moreover, TMS on right dorsal occipital regions specifically disrupts auditory localization in the blind (Collignon et al. 2007). In our study we did not observe significant correlation between neural activity or decoding accuracy and behavior. A possible explanation could be that, even if both the occipital and the temporal areas are functionally involved in processing auditory spatial tasks in both groups, there may not be a straightforward relation between brain activity in discrete regions and behavior. One more direct measure of the causal effects of the brain reorganization observed in EB can be obtained by using TMS to focally and transiently alter the activity of a specific brain region, like hMT+/V5 or PT. Previous studies seem to support this hypothesis showing that TMS applied over the right dorsal occipital regions causes selective impairment on sound localization only in blind individuals (Collignon et al. 2007). Moreover, stimulating hMT+/V5 in EB impairs accuracy, precision and speed perception of tactile motion (Ricciardi et al. 2011; Basso et al., 2012).

### 3.6. CONCLUSION

Our results clearly demonstrate not only the existence of auditory spatial information in the two motion responsive regions across groups, but also significant interaction between groups and regions showing that early blindness triggers a workload re-distribution between these two motion responsive regions. More specifically, auditory information is concomitantly enhanced in the hMT+/V5 and diminished in the PT of early blind when compared to sighted individuals. We propose that the enhanced crossmodal recruitment observed in hMT+/V5 of EB builds upon the typical directional and spatial tuning properties of this region in vision (Kolster et al. 2010; Amano et al. 2009; Bonkho et al. 2017; Albright et

al. 1984; Mikami et al. 1986; Kamitani & Tong 2006; Zimmermann et al. 2011). We believe that the computational structure of motion and location processing in vision and audition is sufficiently close to (1) find trace of auditory processing in hMT+/V5 of the sighted and (2) observe a massive extension of auditory computations in this region in the absence of visual inputs since birth.

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## Supplemental Information

**Supplemental Table 1.** Results of the univariate analyses for the main effect of auditory motion processing [motion > static] in the blind and the sighted, Coordinates reported in this table are significant ( $p < 0,05$  FWE) after correction over small spherical volumes (SVC) or over the entire brain volume (\*). Coordinates used for correction over small spherical volumes were extracted from four papers investigating auditory motion processing in the sighted only (Alink et al., 2012, Pavani et al., 2002) or comparing sighted and blinds (Dormal et al., 2016; Collignon et al., 2009) and are as follows (x, y, z, in MNI space): left superior temporal gyrus [-54 -36 14] (Pavani et al., 2002); right superior temporal gyrus [64 -26 10] (Pavani et al., 2002); left superior parietal lobule [-30 -54 64] (Pavani et al., 2002); right intraparietal sulcus [36 -40 40] (Collignon et al., 2011); right superior frontal sulcus [32 0 48] (Collignon et al., 2011); left precentral gyrus [-40 -6 60] (Pavani et al., 2002); right precentral gyrus [46 4 36] (Pavani et al., 2002); right middle occipital gyrus [48 -76 6] (Collignon et al., 2011); left middle temporal gyrus (hMT +/V5) [-42 -64 4] (Dormal 2016); right middle temporal gyrus (hMT +/V5) [42 -60 4] (Dormal et al., 2016); left superior occipital gyrus [-20 -80 30] (Collignon et al., 2011); right superior occipital gyrus (V3A) [22 -80 28] (Dormal et al., 2016); left planum temporal (PT) [-50 -31 14] (Alink et al., 2012); right plane temporale [54 -26 20] (Dormal et al., 2016), K represents the number of voxels when displayed at  $p(\text{unc}) < 0,001$ , L: left, R: right, G: gyrus, S: sulcus.

## Chapter 3

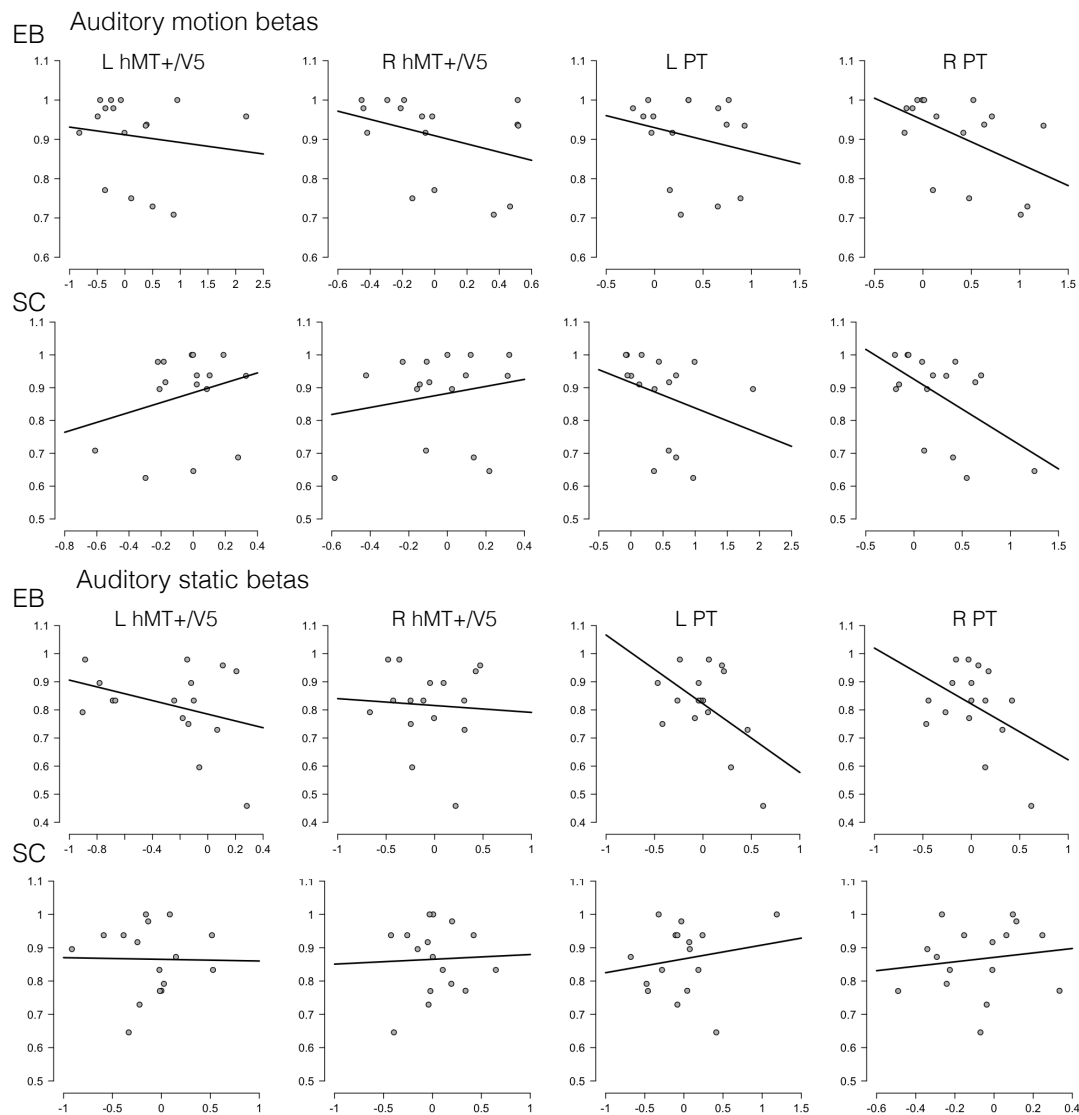
Area	k	x (mm)	y (mm)	z (mm)	Z	p
<i>BLIND &gt; SIGHTED [MOTION &gt; STATIC]</i>						
L middle temporal G	40	-44	-66	6	3,29	0,033
L superior occipital G	1065	-26	-84	28	4,68	0,02*
L superior parietal lobule	3	-32	-40	60	3,15	0,046
R middle temporal G	373	56	-64	6	3,95	0,004
R superior occipital G (V3A)	252	18	-80	30	4,16	0,002
R middle occipital G	355	56	-66	8	4,02	0,002
R intraparietal S	19	30	-34	52	3,25	0,036
R superior temporal G	24	54	-24	20	3,69	0,01
R planum temporale		54	-26	20	3,67	0,011
<i>BLIND <math>\cap</math> SIGHTED [MOTION &gt; STATIC]</i>						
L superior temporal G/ PT	1614	-44	-32	10	6,98	0,000*
L precentral G	432	-44	-8	52	5,69	0,000*
L planum temporale		-54	-38	14	5,69	0,000*
L superior G		-54	-18	6	5,46	0,001*
L precentral G	31	-58	0	28	4,89	0,008*
L middle temporal G	101	-56	-64	4	3,59	0,014
R posterior-medial frontal	42	6	-8	64	4,71	0,017*
R rolandic operculum	3	62	4	20	4,54	0,034*
R superior temporal G/ PT	1967	64	-36	16	6,50	0,000*
R superior G		60	-6	0	5,98	0,000*
R precentral G	208	52	-6	48	5,73	0,000*
R superior frontal S		46	-4	50	5,14	0,000*
R middle temporal G	162	44	-58	8	3,71	0,01
R middle occipital G	11	44	-62	8	3,35	0,027

## Chapter 3

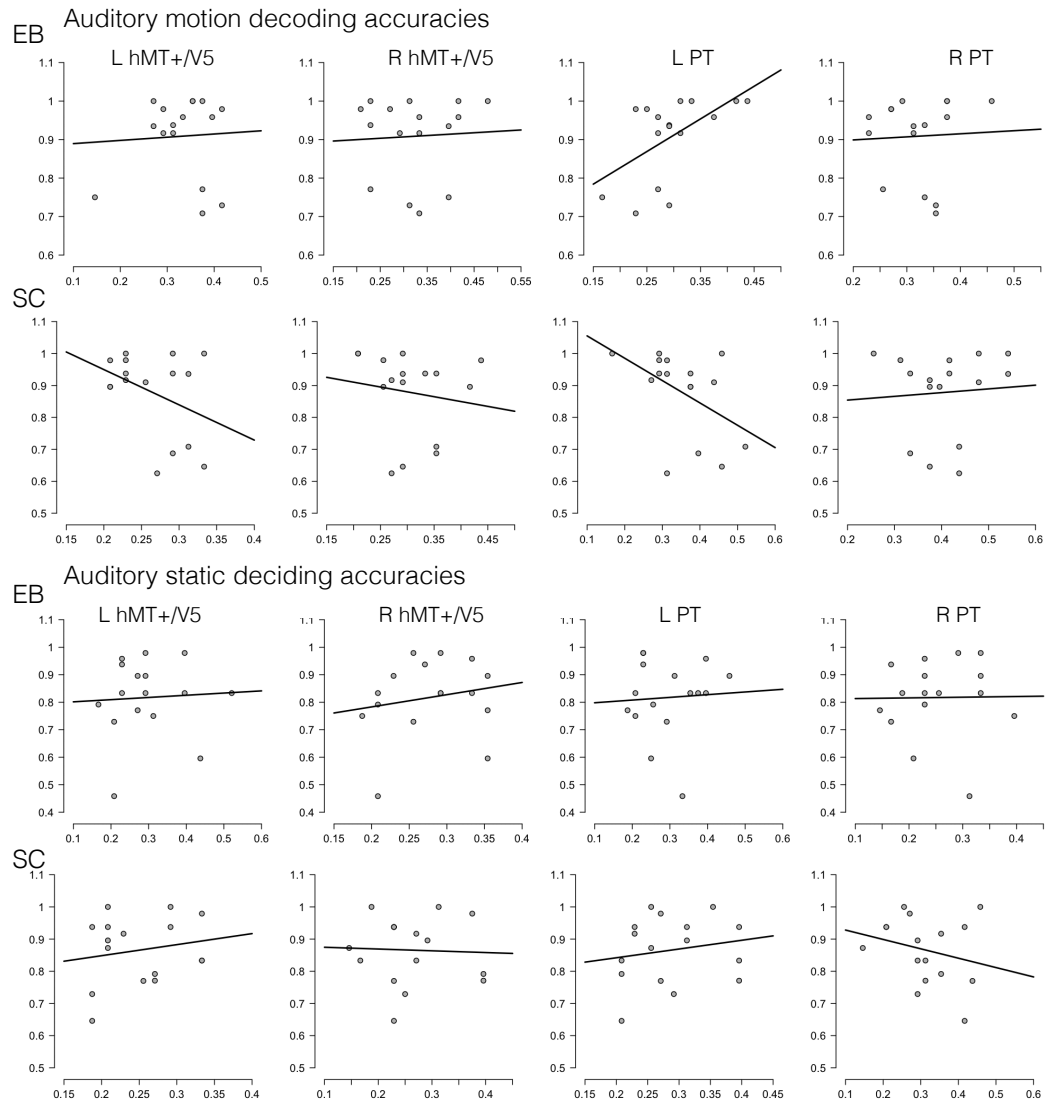
Area	k	x (mm)	y (mm)	z (mm)	Z	p
<i>BLIND [MOTION &gt; STATIC]</i>						
L superior temporal G	2458	-44	-32	10	6,98	0,000*
L planum temporale		-54	-38	14	5,69	0,000*
L precentral G	501	-44	-8	52	5,69	0,000*
L middle temporal gyrus	1143	-48	-64	6	5,13	0,000
L superior occipital gyrus	73	-4	-76	20	4,80	0,012*
L superior parietal lobule	87	-32	-40	60	3,90	0,005
R superior temporal G	3431	54	-30	18	6,79	0,000*
R planum temporale		64	-36	16	6,50	0,000*
R precentral G	557	54	-8	46	5,88	0,000*
R middle temporal gyrus	1118	54	-62	6	5,90	0,000
R middle occipital gyrus	509	54	-64	8	5,87	0,000
R superior frontal sulcus	187	46	-4	50	5,14	0,000
R intraparietal sulcus	152	28	-36	52	4,07	0,013
R superior occipital gyrus	143	18	-78	28	3,98	0,004
<i>SIGHTED [MOTION &gt; STATIC]</i>						
L superior temporal G	2873	-46	-32	10	Inf	0,000*
L planum temporale		-54	-38	14	7,66	0,000*
L precentral Gyrus	650	-46	-4	54	6,4	0,000*
L Putamen	462	-24	0	-2	5,97	0,000*
R Superior Temporal Gyrus	2683	66	-36	10	7,1	0,000*
R Precentral G	280	54	-4	48	5,81	0,000*
R Putamen	177	22	6	8	5,18	0,002*

Participant	Age	Gender	Handness	Residual Vision	Onset	Etiology	Educational Level	Musical Exp
EB1	28	M	R	Light	3y	Retinopathy of prematurity	High school	No
EB2	36	M	ambidextrous	None	0	Retinopathy of prematurity	High school	Yes
EB3	35	F	R	Light	0	Retinopathy of prematurity	High school	No
EB4	27	F	R	Light	0	Retinitis pigmentosa	University (Bachelor)	Yes
EB5	46	M	R	Light	0	Atrophy optic nerve	Junior high school	Yes
EB6	44	M	R	Light	0	Congenital retinopathy	University (Master)	Yes
EB7	34	F	R	Light	0	Retinopathy of prematurity	University (Master)	Yes
EB8	40	M	R	Light	0	Leber's congenital amaurosis	High school	Yes
EB9	27	F	R	None	0	Bilateral agenesis optic nerve	University(Master)	Yes
EB10	29	F	R	Light	0	Retinopathy of prematurity	High school	No
EB11	33	M	R	None	0	Retinopathy of prematurity	University (Bachelor)	Yes
EB12	20	F	R	Light	0	Leber's congenital amaurosis	High school	Yes
EB13	44	M	R	Light	0	Dystrophy optic nerve	High school	Yes
EB14	31	M	R	Light	0	Iplopasia optic nerve	University (Master)	Yes
EB15	35	F	R	None	0	Bilateral congenital microphthalmia	University (Master)	Yes
EB16	26	F	R	Light	0	Bilateral congenital microphthalmia	University (Master)	Yes

**Supplementary Table 2. Characteristics of the blind participants.** Handedness was evaluated using an adapted version of the Edinburgh inventory, Blind and sighted participants were classified as musicians if they had practiced a musical instrument or had vocal training for at least 2 years on a regular basis (at least 2 hours a week), A: Ambidextrous, M: male, F: female, y: years

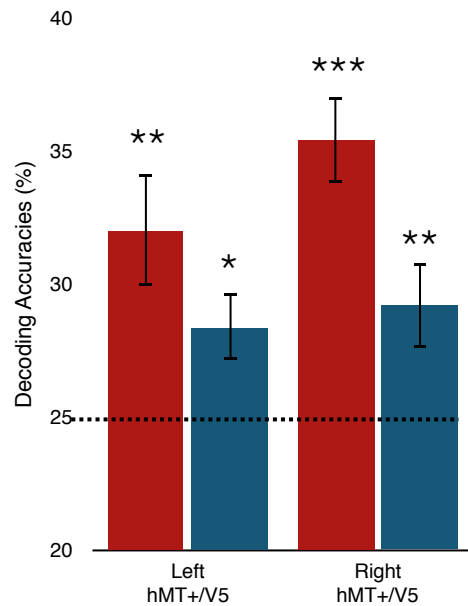


**Supplementary Figure 1. Univariate brain-behavioral correlation results.** Between-subject correlations was performed between behavioural performance and motion and static activity (beta parameter estimates) of 4 visual auditory localizer ROIs (left hMT+/V5, right hMT+/V5, left PT, and right PT). FDR-corrections were performed for multiple comparisons.



**Supplementary Figure 2. Multivariate brain-behavioral correlation results.** Between-subject correlations was performed between behavioural performance and multi-class decoding accuracies (four motion directions, and four sound source locations) extracted from 4 visual auditory localizer ROIs (left hMT+/V5, right hMT+/V5, left PT, and right PT). FDR-corrections were performed for multiple comparisons.





**Supplementary Figure 3. MVP-decoding results of the individually localised left and right hMT+/V5 in sighted participants.** Multi-class decoding results of 4 motion directions (red) and 4 sound source locations (blue) are represented in individually localised 6-mm sphere radius ROIs (left hMT+/V5 and right hMT+/V5). All p-values reflect differences between observed decoding accuracy against chance level (1000 permutations). Results were FDR-corrected for multiple comparisons (number of ROIs x number of tests), p-values: (\*) is  $p < 0.05$ , (\*\*)  $p < 0.01$ , (\*\*\*)  $p < 0.001$ . Error bars indicate the SEM. Dotted line indicates chance level (25%).

### Supplementary Analysis

#### Axis of Motion Preference

To investigate the preference of “axis of motion/space” in both hMT+/V5 and PT, binary classifiers were used to discriminate brain activity patterns for motion direction within axes (leftward vs. rightward, left vs. right position, upward vs. downward, up vs. down position hereafter within-axis classification), and 2 additional classifiers was used to discriminate across axes (horizontal vs. vertical motion, horizontal vs. vertical position, hereafter across-axes classification). We compared binary decoding accuracies of across-axes, horizontal and vertical within-axes to assess whether hMT+/V5 and PT regions demonstrate axis of motion characteristic tuning for auditory motion. We performed  $2 \times 3 \times 2$  repeated measures of ANOVA on 2 Groups (EB, SC; between-subject factor), 3 Axes (across axes, horizontal within-axis, and vertical within axis; within-subject factor), and 2 Hemispheres (left, right; within-subject factor) by entering **motion direction** accuracies

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extracted from hMT+/V5. The observed main effect of Axes ( $F_{1.9,59.7} = 7.05$ ,  $p = 0.002$ ) indicated across-axes direction classification are more reliable compared to horizontal ( $t = 3.14$ ,  $p = 0.01$ ) and vertical ( $t = 3.27$ ,  $p = 0.007$ ) within-axis classification. ANOVA on **sound source location** decoding accuracies did not reveal significant results.  $2 \times 3 \times 2$  (Group, Axes, Hemisphere) repeated measures of ANOVA on **motion direction** accuracies extracted from PT region revealed significant main effect of Axes ( $F_{1.9,56} = 21.07$ ,  $p < 0.001$ ), and Hemisphere ( $F_{1,30} = 4.88$ ,  $p = 0.035$ ), indicating similar results to hMT+/V5, across-axes direction classification are more reliable compared to horizontal and vertical within-axis classification. Surprisingly, **sound source location** also provides significant main effect of Axes ( $F_{1.7,52} = 3.8$ ,  $p = 0.034$ ), and Axes x Group interaction ( $F_{1.7,52} = 3.9$ ,  $p = 0.029$ ), and Axes x Hemisphere interaction ( $F_{1.9,57} = 11.2$ ,  $p < 0.001$ ).



## **Chapter 4**

### **General Discussion**

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### 4. GENERAL DISCUSSION

The main objective of this thesis was twofold: (1) to better understand how the human brain processes auditory motion and sound-source locations; (2) to investigate how the total absence of sight since birth impacts the neural architecture typically supporting auditory and visual motion processing.

#### 4.1. Auditory spatial information in PT

##### 4.1.1. Auditory motion direction decoding in PT

In chapter 2, we investigated the coding of auditory motion direction and sound source location in the human planum temporale (PT), and their level of shared representation. Our results demonstrated that independently defined PT regions contain information about both auditory motion direction and sound source location. Furthermore, cross-condition decoding analysis revealed a partially shared representation between motion and static conditions.

Consistent with previous studies (Warren et al. 2002; Pavani et al. 2002; Poirier et al. 2005; Getzmann & Lewald 2012; Dormal et al. 2016), whole-brain univariate analyses revealed preferential response to auditory motion in a dorsal fronto-temporo-parietal network, including PT (Chapter 2 Fig. 2A, Table 1). Both whole-brain and ROI analyses clearly indicated a functional preference (expressed as higher activity level estimates) for motion processing over sound-source location in bilateral PT regions (Chapter 2 Fig. 2). MVP-decoding results demonstrated that despite no univariate differences across separate motion directions, PT contains spatially distributed direction-selective features. Despite minimal univariate activity elicited by sound-source location in PT, and the absence of reliable univariate differences in the activity elicited by each position (Chapter 2 Fig. 2), MVP-decoding results showed that PT also spatially distributed sound source location information (Chapter 2 Fig. 3). Supporting univariate motion selectivity results in bilateral PT, MVPA revealed that multi-class and across-axes classifications are higher for moving than for static sounds (Chapter 2 Fig. 3A-B).

Neuroimaging studies debated on whether PT engages in spatial hearing in general (Zatorre et al. 2002; Smith et al. 2004; Smith et al. 2007; Smith et al. 2010) or contains motion-specific processing mechanisms (Poirier et al. 2017). In our study, univariate analyses showed that PT responds more to motion compared to static sounds, and multivariate-decoding analysis showed that in the PT information on motion direction is more robust than information on sound source location.

One may wonder whether the higher classification accuracy for motion directions compared to sound source locations relates to the spectro-temporal differences between motion and static stimuli. The auditory motion directions consisted of sounds moving in multiple spatial locations (from  $-60^\circ$  to  $+60^\circ$  or vice versa), however, the sound source locations were fixed in one spatial location throughout the one experimental block (Poirier et al., 2005; Krumbholz et al., 2005). We purposely adopted the strategy of presenting static sounds in fixed locations rather than presenting in multiple locations due to three main reasons. First, randomly presented static sounds can evoke auditory apparent motion (Strybel & Neale 1994; Lakatos et al., 1997; see review Carlile 2016). Second, in the visual domain, incoherent moving (i.e. flickering) dots evoke higher activity compared to 100% coherent moving stimuli in hMT+/V5 region (McKeefry et al., 1997; Vachon et al., 2009). Vachon and colleagues suggested that incoherent moving stimuli are actually difficult; therefore, require more attention compared to the 100% coherent moving directions (2009). We avoided such confounds by presenting static sounds in a fixed location. Furthermore, fMRI study in macaque clearly demonstrated that posterior region of superior temporal cortex (vicinity of hPT) has auditory motion-specific mechanism when motion stimuli contrasted with both static and spatially rich but non-dynamic stimuli (Poirier et al., 2017). Lastly, presenting static sounds located on a given space and moving sounds directed toward the same space allows us to investigate a possible shared computation between moving and static sounds using cross-condition decoding (see below).

Both univariate and multivariate results indicated a motion-specific mechanism in PT. Interestingly, significant cross-conditions classification in PT region suggested that the two spatial (motion and static) conditions rely on partially shared pattern geometries in PT.

Psychophysiological study that manipulated auditory apparent motion varying sound source location and inter-stimulus onset intervals, showed that localization cues were important for the determination of the direction of motion (Strybel & Neale 1994). However, the crucial factor of the perceiving of apparent motion was the inter-stimulus onset intervals instead of localization cues, suggesting that auditory motion perception does not solely rely on or stem from localization cues (Strybel & Neale 1994). Auditory evoked potentials to static and moving sounds have shown that, while the initial analysis of spatial sound features is being processed in a common auditory network with a strong contralateral effect (Ducommun et al. 2002; Getzmann 2011), the later stage of motion direction encoding varies according to the sound source processing (Getzmann 2011). A recent study, relying on

auditory adaptation paradigm, showed that when horizontal motion directions were preceded by contralateral static sounds, motion-onset response lowered, indicating that location induced adaptation to moving sounds (Getzmann & Lewald 2011). Due to the temporal resolution of fMRI, we cannot target early and late stages of auditory evoked potentials. However, our cross-condition classification results confirm and extend the idea that motion direction and sound source location might rely on partially common features that are shared for encoding spatial sounds.

Does the observation of significant cross-condition decoding demonstrate that sound-source locations and motion directions share similar and abstracted coding strategies? Cross-MVPA has been employed to investigate whether in a given region, generalized/common information can be observed across modalities/conditions (Fairhall & Caramazza 2013; Jung et al. 2017; Man et al. 2012; Formisano et al., 2008). The analysis is performed on evoked patterns of corresponding stimuli in two different modalities/conditions. To investigate whether conditions share common computational principles, the classifier is trained on one condition and test on the subsequent condition. The cross-trained-tested classifier could reveal the presence of category-specific information that is shared between conditions. Therefore, regions that demonstrate successful cross-condition MVP-decoding has been suggested to carry abstract features that are independent of the conditions (Fairhall & Caramazza 2013). For instance, successful cross-condition MVP-decoding was performed to investigate abstract representation in the neural patterns of two auditory spatial conditions (Higgins et al. 2017; Hong et al. 2012). A recent study investigated the processing of spatial cues in the auditory cortex and tested whether neural representations evoked by interaural time- (ITD) and interaural level- (ILD) differences share informative features (Higgins et al., 2017). Authors suggested integrated processing of ITD and ILD, and these spatial cues might integrate to form a cue independent representation of space due to the successful within-condition and cross-condition MVP-decoding. In another study, classifiers were trained on neural patterns evoked by one type of motion (e.g. first-order motion), and tested on neural patterns evoked by second-order direction of motion (Hong et al., 2012). The successful cross-MVPA results suggested that direction-selective responses in two different motion types are based on shared neural substrate.

In our studies, we trained classifiers to learn to distinguish motion directions. According to the neural patterns of training conditions (leftward, rightward, upward, and downward), the classifier sets a decision boundary to differentiate the four motion directions. If the set decision boundary were informative for the classifier to differentiate

the four sound source locations (left, right, up and down), then cross-condition MVP-decoding would be significantly higher compared to the chance level. The idea of cross-condition MVP-decoding on auditory neural patterns stem from possible shared representation between sounds going toward a given direction or located on the same location. Perceiving sounds going toward left or located on the left could evoke a sense of location/direction in the external space. The evoked sensation/perception of an object being/going to an external spatial location could be reflected in the auditory cortex with a shared neural representation. Early animal electrophysiological studies suggested a common mechanism between moving and static sounds for processing specific locations arising in space (Ahissar et al. 1992; Benson et al. 1981; Imig et al. 1990; Middlebrooks & Pettigrew 1981; Poirier et al. 1997; Rajan et al. 1990; Doan & Saunders 1999) and demonstrated the existence of neurons in the auditory cortex that are selective to sound source locations and motion directions (Ahissar et al., 1992; Doan and Saunders, 1999; Poirier et al., 1997; Rajan et al., 1990). More recent studies in humans have shown the existence of motion direction (Alink et al., 2012; Dormal et al., 2016; Jiang et al., 2014, 2016) and sound source location information (Derey et al., 2016) within PT region. Our results of successful within-condition and cross-condition classifications for directions and locations also confirmed the existence and the partially shared representations of direction and location information within the auditory cortex.

Our further analysis with across-condition classifications (going to left versus being on the left) provided strong evidences that neural patterns evoked by motion directions and sound source locations can be differentiated from each other (see Chapter 2 Fig. 4A), indicating that neural patterns carry condition specific information. Moreover, representational similarity analysis showed that neural representations of moving and static sounds are mostly distinct in PT (see Chapter 2 Fig. 4D). Importantly, the lowest correlation was observed between the neural patterns and the condition-invariant external model, indicating that motion and static conditions evoked highly differentiable patterns.

Altogether, these results suggest that PT contains information about both motion direction and sound-source location and that the neural patterns related to these two spatial conditions are only partially overlapping. In line with the results of fMRI study on non-human primates demonstrating motion-specific computation in the caudal belt and parabelt (i.e. homolog areas of PT) (Poirier et al., 2017), our study shows similar motion specific mechanisms in the human PT.



### 4.1.2. Axis of motion preference in PT

The activity patterns in the PT showed that horizontal and vertical moving sounds generate patterns that could successfully be differentiated from each other. However, within the horizontal axis (left versus right) and the vertical axis (up versus down) the classification revealed inconsistent results across hemispheres. Furthermore, across-axes motion direction classification consistently provided more robust information compared to the results of within-axis classifications. In the left hemisphere, we observed only vertical axis motion information; while in the right hemisphere we observed only horizontal axis information (see Chapter 2, Figure 3B). This lack of consistency across different hemispheres and less reliable direction information in the classification of opposite directions, points towards a similarity between the PT and the visual motion area hMT+/V5. In the visual domain, the functional organization of the hMT+/V5 is characterized by columns containing neurons that react specifically to a certain visual motion direction (Albright et al. 1984). Those columns vary smoothly for certain motion direction but are also found running side by side with their respective opposing motion direction counterparts (Albright et al. 1984; Diogo et al. 2003; Born & Bradley 2005; Zimmermann et al. 2011). By aggregating opposing motion directions, larger axis of motion features can be constructed that are more easily detectable with fMRI than individual direction selective columns (Zimmermann et al. 2011). In the Chapter 2, across-axis classifications provided more reliable results compared to within-axis direction (e.g. left versus right or up versus down) classifications, indicating that opposite motion directions are harder to detect also in the PT region for auditory motion.

It should be noted that, up to our knowledge, reports on the auditory cortex often indicate lack of topographic organization, specifically for spatial locations. Neurons that process spatial properties of sounds show non-uniform (non-systematic) distribution across the auditory cortex (Ahissar et al., 1992; Stecker et al., 2005). While a temporal modulation preference suggests a common columnar functional organization, spectral modulation preference rather indicates a laminar diversity or specialization that does not follow point-to-point topographic organization (Atencio & Schreiner 2010). The layers in the auditory cortex that show modulation preferences might play a distinct role in the extraction of dynamic sound information in addition to the cortical columns (Linden & Schreiner 2003; Atencio & Schreiner 2010). Despite the fact that previous studies of laminar differences and columnar processing have failed to reach a consensus on the organizational principles of auditory cortex (Dear et al. 1993; Eggermont 1996; Noreña & Eggermont 2002; Sugimoto et al. 1997; Abeles & Goldstein Jr. 1970; Clarey et al. 1994; Foeller et al. 2001; Phillips & Irvine

1981). Our observations from MVP-decoding could at least show a possible spatial distribution of motion direction selective neurons that allow the preference of the axis of motion in the PT region. The proportion of direction or motion selective neurons in PT is lower compared to hMT+/V5 area, and these neurons are typically interspersed with non motion-selective neurons (Ahissar et al., 1992). This might potentially result in difficulties in detecting an organized spatial distribution in PT such as the one observed in hMT+/V5.

Does our observation of significant decoding of motion directions support the existence of a columnar organization of sound source location or motion direction? Although our significant decoding indicates that direction specific information is more reliable compared to classification of opposite directions, classification may not refer to the existence of direction selective columns in the PT. Successful classification may stem from the (spatial) biases within each voxel emerged at the cortical columnar level or other types of direction selective signals (Kamitani & Tong 2005; Haynes & Rees 2006; Bartels et al. 2008). If fMRI signal within a voxel reflects exclusively a sampling of cortical columns, smoothing of the data would substantially decrease the decoding accuracies due to averaging out the random biases in the neighboring voxels (Kamitani & Sawahata 2010). Contrary to that, evidence points to no influence of smoothing (Op de Beeck 2010). Studies conducted on early visual cortex proposed that decoding orientations reflects much larger scale (e.g. retinotopy) rather than columnar organization (Freeman et al. 2011; Freeman et al. 2013; Op de Beeck 2010), and similarly, motion directions decoding in hMT+/V5 was suggested to emerge from large-scale systematic biases at the level of retinotopic maps, instead of relying on the functional organization of motion selectivity (Beckett et al. 2012; H. X. Wang et al. 2014). Interestingly, recent high-field fMRI studies showed that the fMRI BOLD signal carries information related to both large- and fine-scale (columnar level) biases (Sengupta et al. 2017; Gardumi et al. 2016; Pratte et al. 2016). Sengupta and colleagues demonstrated that orientation decoding is affected by both high spatial frequency components (fine-scale), as well as large-scale biases (2017). The effect of high spatial frequency also depends on the task. For instance, using the same auditory stimuli, Gardumi and colleagues showed that the decoding accuracy of different vowels increased with higher spatial resolution. However, when classifying the speaker identity on the same stimuli, no enhancement in decoding was observed with higher spatial resolution (Gardumi 2016). These results suggest that both high spatial frequency information and coarse large-scale information contribute to the classification process.

Our results demonstrate that PT contains direction specific information, and in particular that “axis of motion” representation are more easily accessible than within-axis representations. However, whether the information emerges from columnar level or larger-scale spatiotopic organization within PT remains to be addressed.

### **4.1.3. Sound source location decoding in PT**

At the univariate level, we observed a tendency of contralateral effect for sound source locations in the azimuth (see Chapter 2, Fig. 2). In addition, the multivariate results showed successful decoding for multi-class locations (left, right, up and down) and successful binary decoding only in the horizontal (left versus right) axis, in the bilateral PT. Our findings are in line with previous observations from monkey and human fMRI studies that in the posterior auditory cortex (including PT), fMRI signals contain representations of sound location (Ortiz-Rios et al., 2017; Derey et al., 2016). The widespread and spatially contralateral bias might provide information to the classifier to detect the neural pattern differences between sounds on the horizontal axis.

The information related to the horizontal sound source locations could stem from a heterogeneously spread population of neurons that are responsive to contralateral fields (Stecker et al., 2005; Derey et al., 2016; Ortiz-Rios et al., 2017). Recent fMRI studies investigated the topographic maps for preferred location in both auditory cortex and subcortical structures, and demonstrated a contralateral tuning but lacked point-to-point topographic map in the auditory cortex (Derey et al. 2016; Moerel et al. 2015). Derey et al. investigated the opponent coding model in the human auditory cortex reporting that human auditory cortex (including bilateral PT) also shows a broad contralateral spatial tuning for static sounds in the azimuth (2016). Similar results of broad contralateral tuning have been also observed in non-human primates (Ortiz-Rios et al. 2017) and cats (Stecker et al. 2005). Lack of (systematic) spatial selectivity emerged also at the level of sub-cortical structures. High-resolution fMRI studies, indicating that similarly to the auditory cortex, sub-cortical structures also do not show point-to-point spatiotopy, rather selectivity is limited to the contralateral locations in azimuth (Moerel et al., 2015). These results point out that the preference of location does not follow a topographic map across species, even if location specific information exists in earlier stages of the auditory pathway, as well as in the auditory cortex.

In the vertical within-condition classification, we do not observe information related to up and down sound source locations. It should be noted that lack of significant

classification could simply indicate that the neural patterns evoked by up and by down sounds cannot be differentiated by the classifier, instead of indicating no information related to the presented sounds. Recent electroencephalographic (EEG) study demonstrated that evoked event-related potentials across the scalp differ for horizontal and vertical static sounds, suggesting that topographic distributions of spatial cues underlying horizontal and vertical sounds could be different. While horizontal sound source (left versus right) revealed successful decoding in the scalp, less consistent decoding results was observed for vertical sounds (Bednar et al. 2017). Our results showing lack of significant classification indicated that spatially distributed neural patterns generated by sounds in the vertical axis cannot be differentiated from each other.

Unlike for motion direction, neural patterns of static sounds showed no preference of axis of location in the PT. Classification accuracies for opposite static sound locations within an axis were similar to the accuracies for aggregated locations across axes, indicating that lack of characteristic tuning to “axis of space” in the PT. Nonetheless, overall successful classifications of static locations suggest that PT contains information about the sound source location.

Considering the successful across-axes (horizontal versus vertical) classification both in motion directions and sound source locations, we further speculate that horizontal and vertical sounds might rely on different mechanisms. Our univariate results are in line with previous study showing that horizontal and vertical sounds rely on a common auditory network (Pavani et al., 2002), however, the multivariate classification results in the present study suggests that neural patterns carry distinctive information for the sounds arriving from different axes. Sounds presented horizontally and vertically contain distinct spatial cues (i.e. binaural and spectral cues, respectively), and these cues are processed in different subcortical structures (Goldberg & Brown 1969; Yin & Chan 1990; Boudreau & Tsuchitani 1968; Young et al. 1992; Imig et al. 2000)(Goldberg & Brown 1969; Yin & Chan 1990; Boudreau & Tsuchitani 1968; Young et al. 1992; Imig et al. 2000). The different spatial cue properties of horizontal and vertical sounds may potentially lead to the involvement of separate auditory networks/mechanisms. Future studies could target the possible influence of behavioral performance in the spatially distributed patterns of auditory cortex.

### **4.2. Functional reorganization of auditory motion processing in blind individuals**

The empirical work presented in Chapter 3 was dedicated to investigate the impact of visual deprivation in shaping the functional specialization of brain regions that are

typically supporting visual and auditory motion processing. First, we focused on cross-modal plasticity in visual areas during auditory motion processing. More specifically, we asked whether the cross-modal responses observed in visually deprived hMT+/V5 could respect the (intrinsic) fine-scale organization that typically emerges in sighted individuals. We further extended our question to understand whether such cross-modal responses to auditory motion stimuli can be observed even in sighted individuals, or whether this is specific to early blind individuals. Second, we investigated whether hMT+/V5 and PT regions only code for the motion direction information or also contain information about the sound-source location in both the blind and the sighted. Lastly, we asked how early blindness affects auditory representation in PT.

Whole-brain univariate analysis revealed preferential response to auditory motion for both sighted and blind participants in a dorsal fronto-temporo-parietal network including PT, as well as a region overlapping with the most anterior portion of hMT+/V5 (see Chapter 3 Fig. 2C). Blind participants showed additional preferential response in a more posterior portion of hMT+/V5. Multivariate pattern analyses revealed that classification accuracies in the early blind group were significantly higher in hMT+/V5 and lower in PT when compared to sighted participants. Furthermore, classification of sound source locations showed a similar pattern of results even if the accuracies were lower than those obtained from motion directions.

Previous studies have investigated auditory motion content (high versus low), motion planes (lateral versus radial), and horizontal directions (left versus right) in sighted and blind individuals (Strnad et al. 2013; Dormal et al. 2016; Jiang et al., 2014; Jiang et al. 2016). However, up to our knowledge, we are the first to show motion direction classification in multiple axes of sound motion, similar to the pioneering study showing direction selectivity in visual modality (Kamitani & Tong 2006). Previous work on classification of horizontal motion directions showed no significant results in the hMT+/V5 in sighted individuals (Jiang et al. 2014; Jiang et al. 2016; Alink et al. 2012). In the present study, specific information about auditory directions emerges in the visual motion area in both groups. This result, in contrast with previous studies, could be explained by the differences in experimental design and in the set of auditory stimuli. In those studies, in fact, the directional selectivity was investigated exclusively in the horizontal axis, while the present study contained both horizontal and vertical auditory stimuli. It is possible that activity patterns elicited in hMT+/V5 for four motion directions differ to a larger extent from

activity patterns elicited by sounds only in the horizontal axis (Alink et al. 2012; Jiang et al. 2014; Jiang et al. 2016).

In PT, in line with previous researches, both univariate and multivariate results showed that this region maintains its features to process auditory motion in early blind individuals, however, its fine-scale computational role – containing motion direction information - is reduced compared to sighted individuals (Dormal et al. 2016; Jiang et al. 2014; Jiang et al. 2016). Our results demonstrated not only the existence of auditory motion direction information in the two motion responsive regions across groups, but also a significant interaction between groups and regions showing that early blindness triggers a workload re-distribution between these two motion responsive regions.

While PT region showed significant sound source location information in both of the groups, hMT+/V5 revealed sound source information only in the early blinds. These results point towards a sensory experience dependent re-distribution of the workload between visual and auditory areas. Moreover, this re-distribution is not limited to motion direction information but also observed for static location information. The presence of static information in hMT+/V5 in the early blind group confirms and extends previous studies demonstrating that the dorsal extrastriate occipital cortex in blind individuals contributes to spatial processing of sounds (Collignon et al. 2007; Collignon et al. 2009; Collignon et al. 2011). Interestingly, even if hMT+/V5 contains both motion direction and sound source location information in the early blinds, cross-condition decoding was not significant. This result suggests that auditory motion evoked distinct neural patterns compared to static sounds. The region hMT+/V5 is highly specialized for processing visual motion (Tootell et al. 1995; Zeki et al. 1991; Watson et al. 1993) and its functional preference for visual motion is observed very early in development (Braddick et al. 2005; Gilmore et al. 2007; Hou et al. 2009). In line with hard-wired motion specificity of hMT+/V5 in sighted, in the lack of visual input, the functional specialization toward the processing of motion information is maintained while the modality tuning is redirected toward sounds. The results of cross-condition decoding support the notion that cross-modal plasticity colonizes the visual regions while maintains the specific computation of the colonized region (Collignon et al. 2009; Dormal et al. 2016; Collignon et al. 2011; Ricciardi et al. 2014; Amedi et al. 2017).

Investigating the possible spatiotopic organization of occipital regions in blind individuals is an interesting venue for future works. Recent evidences from resting-state fMRI studies have shown that functional connectivity of early visual areas follows retinotopic organizational principles (Striem-Amit et al. 2015; Bock et al. 2015). Striem-Amit and

colleagues investigated the functional connectivity patterns in the visual cortex in the absence of a task in sighted and blind individuals (2015). While resting-state functional connectivity in three retinotopic maps (eccentricity, laterality, and elevation) in the occipital regions shows similar patterns between blind and sighted populations, in blinds altered functional connectivity patterns were observed between portions of V1 and non-visual (somatosensory and auditory) cortices (Striem-Amit et al., 2015). If functional organization of occipital cortex in blinds follows principles similar to the ones by the occipital cortex for visual locations (retinotopy) in sighted, the observed sound source location information in the occipital areas of the blind group could stem from maintained retinotopic organization.

Overall, our findings expand upon previous knowledge about auditory motion and static location processing, and the functional specializations of cross-modal plasticity. Future studies could investigate the causal role of such re-distribution of computational roles between motion areas, and whether the interplay between intra- and cross-modal plasticity could shed lights on effective processing of auditory input (Stevens et al. 2007; Gougoux et al. 2005; Amedi et al. 2003; Voss et al. 2008; Voss et al. 2011; Lewald 2013). One way of investigating the causal role of the re-distributed workload would be to stimulate cortical areas with transcranial magnetic stimulation (TMS) to temporarily disrupt the auditory motion processing in these regions. Studies using TMS found that stimulating right dorsal occipital regions caused impairment on sound localization only in blind individuals (Collignon et al., 2007), and stimulating hMT+/V5 during tactile motion impaired accuracy, precision and speed perception only in the blind participants (Ricciardi et al. 2011; Basso et al. 2012). If the recruitment of occipital areas has a causal effect to the auditory motion perception in the early blind population, TMS applied over hMT+/V5 area could potentially reduce their performance on discriminating auditory motion direction. Moreover, investigating the contribution of hMT+/V5 activity to auditory motion perception in the sighted could reveal if the activation we observed in anterior hMT+/V5 for moving sounds also in the sighted plays a functional role in supporting auditory localization behavior. Based on our findings and on previous TMS studies in the tactile (Ricciardi et al. 2011) and auditory (Collignon et al. 2007) domains, we expect a decrease in auditory motion perception in the sighted group as well. However, this decrease would be enhanced in the early blind population.

A limited number of studies have shown that occipital recruitment in EB may support compensatory behaviors in the remaining senses (Gougoux et al. 2005; Amedi et al. 2003; Lomber & Malhotra 2008; Benetti et al. 2017 for similar reasoning with auditory deprivation). For instance, superior auditory localization abilities of blind individuals

correlate with the enhanced recruitment of occipital cortex (Gougoux et al. 2005). Interestingly, some studies have also shown that reduced auditory cortex activity was associated with efficient auditory processing in early blind individuals (Stevens & Weaver 2009; Watkins et al. 2013). It might, therefore, be hypothesized that a re-distribution of the computational role of PT and hMT+/V5 to implement spatial hearing and auditory motion may underlie the superior abilities that are reported in early blinds for auditory localization and motion discrimination (Lessard et al. 1998; Roeder et al. 1999; Gougoux et al. 2005; Voss et al. 2011; Lewald 2013; Voss & Zatorre 2015). In the present study we did not observe a direct link between the recruitment of auditory and occipital areas and behavioral performance in none of the groups (see Chapter 3 Supplementary Fig. 1). A possible explanation for this lack of correlation could be that, even if both occipital and temporal areas are functionally involved in processing auditory spatial tasks in both of the groups, there may not be a straightforward relation between brain and behavior. The brain is a highly interconnected organ and asking a direct link between the behavioral performance and the neural activity of certain region during complex tasks may be considered as an ill-posed question to investigate the functional relevance of a brain region. Instead of solely correlating one region's activity in isolation from its interconnected network, correlating a distributed pattern of activity of occipital and temporal regions could provide insights on the large-scale interplay between the two motion responsive regions. In a study from our laboratory, we observed that during processing sounds from different categories, the similarity between neural patterns of occipital and temporal regions did not differ between early blind and sighted participants. In line with our results from Chapter 3, the authors demonstrated that occipital regions contain more auditory information in the blind and a reduced role of the temporal cortex compared to the sighted individuals. Despite both occipital and temporal areas of early blinds are involved in processing auditory stimuli, these areas might be processing different aspects of the stimuli (Mattioni et al., 2018). Redistribution of workload by processing different aspect of the stimuli, could be a more efficient way to reorganize a highly interconnected system rather than relying on a duplication of the same computational process. Investigating neural pattern similarities of hMT+/V5 and PT during auditory motion processing could bring additional support to this notion. We therefore make the hypothesis that distributed patterns of activity of hMT+/V5 and PT would be highly dissimilar.



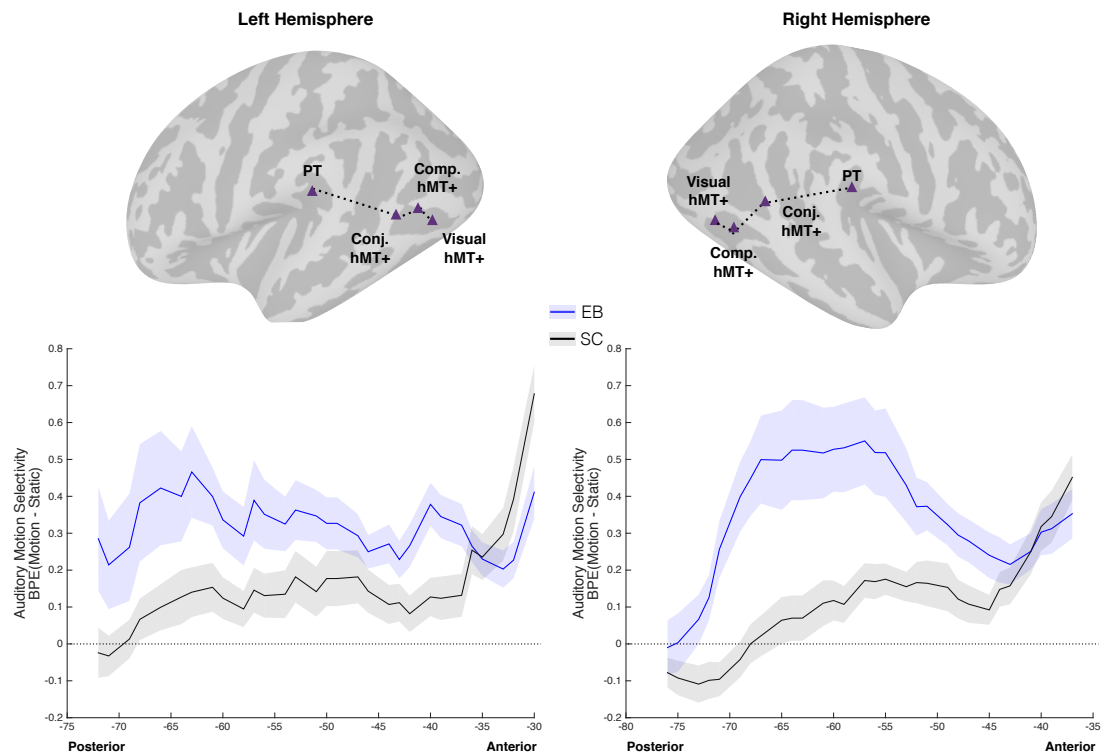
### 4.3. Cross-modal responses in visual cortex of sighted individuals

A growing body of evidence suggested that moving auditory (Warren et al. 2002; Poirier et al. 2005) and tactile (Beauchamp et al. 2007; Ricciardi et al. 2007; Matteau et al. 2010; van Kemenade et al. 2013) stimuli can also evoke preferential responses in a portion of the hMT+/V5 complex in sighted individuals. One of the possibilities for the observed activity of hMT+/V5 in response to auditory motion stimuli in sighted is visual imagery (Goebel et al. 1998; Sathian 2005; Vetter et al. 2014; Emmerling et al. 2016). Nonetheless, the observed hMT+/V5 activation in early blind individuals cannot be explained by visual imagery, as they have never received visual input (Strnad et al. 2013). Therefore, the observation that early blind individuals also preferentially activate hMT+/V5 for the processing of moving stimuli was used to support the idea that this region may implement, at least partially, an abstracted motion computation that is independent of sensory input and/or experience (Ricciardi & Pietrini 2011; Strnad et al. 2013). Our results on auditory motion processing do not fully support this supramodal brain assumption. First, auditory motion selectivity extended from temporal areas to middle temporal gyrus (MTG) in sighted, and showed no overlap with visual motion areas in the left hemisphere, while only the most anterior portions of hMT+/V5 overlapped with the activity in the right MTG (see Figure 1 and Chapter 3 Fig. 2C). Second, we observed in the univariate results that the hMT+/V5 region of sighted individuals showed deactivation or no response. Despite that deactivation, hMT+/V5 region showed significant auditory motion direction classification in sighted. It should be noted that successful MVPA (see *Section 4.1.1.*) indicates that the four motion directions evoke distinct neural patterns in hMT+/V5 and that the classifier can differentiate among them. However, the observed multivariate information about motion directions in hMT+/V5 could stem from task-dependent deactivation in sighted group. A recent study conducted in our lab demonstrated that neural patterns evoked by visual and auditory motion directions in hMT+/V5 of sighted individuals are anti-correlated (Rezk et al., 2018). We speculate that the existence of fine-scale auditory motion direction information in sighted hMT+/V5 does not provide clear evidence of the supramodality of hMT+/V5. An overlap of functional preference between the sighted and the blind, or significant MVP-decoding in both groups for non-visual motion in the visual areas should be interpreted with caution. For instance, hMT+/V5 could activate due to visual imagery in sighted people (Goebel et al. 1998; Sathian 2005; Vetter et al. 2014; Emmerling et al. 2016) and instead rely on crossmodal reorganization of occipital regions in case of early visual deprivation (Poirier et al. 2006; Dormal et al. 2016; Jiang et al. 2014). Actually, a study using TMS found that focally and

transiently disrupting of hMT+/V5 activity significantly altered auditory spatial localization abilities only in the early blind and not in sighted participants, suggesting that non-visual processing could be mediated by different mechanisms in blind and sighted populations (Collignon et al. 2007).

Returning briefly to the topic of cross-modal responses in both of the groups, the following section discusses the possible underlying mechanisms in the hMT+/V5 for processing auditory motion.

In our results, the anterior portion of hMT+/V5, that is in closer vicinity of the temporal areas, showed auditory motion selectivity in both of the populations, while posterior regions show auditory motion selective recruitment only in the early blind individuals. Previous studies showed that the anterior portion of visually defined hMT+/V5 is being recruited for both tactile and visual motion in sighted and blind people (Ricciardi et al. 2007). It was suggested that visual experience could lead to functional segregation within hMT+/V5, with the anterior portion recruited by tactile motion in both groups and carrying supramodal representations of motion; while the recruitment of the more posterior portion of hMT+/V5 would be sensory-specific and experience dependent. The posterior hMT+/V5 that is solely visual in the sighted could be recruited for non-visual motion processing in case of early blindness. Another study in sighted individuals showed that MST, the anterior part of hMT+/V5, responds to both visual and tactile motion, while MT (posterior regions within hMT+/V5) only responds to visual motion (Beauchamp et al., 2007). Taken together, the activity in the posterior hMT+/V5 seems to be highly driven by visual input in the sighted but extends its functional tuning toward non-visual inputs in early blind individuals. To explore further the auditory motion selectivity, we calculated the geodesic path (minimum distance) between the peaks of visually localized hMT+/V5, posterior portions of hMT+/V5 (EB>SC group comparison analysis), anterior portion of hMT+/V5 (group conjunction analysis) and auditory localized PT (see Chapter 3 Fig. 2C-E). Then, we extracted the activity estimates of auditory motion and static sounds across the posterior-anterior axis. Figure 1 represents the auditory motion selectivity along the geodesic path between hMT+/V5 and PT regions in the left and right hemispheres (top panel) and the auditory motion selectivity along the posterior-anterior axis.



**Figure 1. Auditory Motion selectivity along the geodesic path between hMT+/V5 and PT.** Top panel represents the geodesic path in the left and right hemispheres. The triangles indicate the peak coordinates from the visually localizer hMT+ auditory motion experiment (Conj. hMT+: EB conj. SC, group conjunction analysis, Comp. hMT+: EB > SC group comparison analyses) from the empirical work in Chapter 3. Bottom panel represents the auditory motion selectivity (beta parameter estimates (arbitrary units), BPE) in early blind (purple) and sighted (gray) individuals. The shade represents  $\pm$  SEM.

In this figure, auditory motion selectivity is represented with the difference between the beta parameter estimates of motion and static. The sighted group showed more static activation compared to the motion in the most posterior regions but along the axis a gradual increase was observed for the auditory motion selectivity. In line with aforementioned studies, in the early blind group, the auditory motion selective recruitment occurs in the posterior to anterior regions and a gradual decrease in the auditory motion selectivity along the axis. Interestingly, at the peak coordinate of PT, the sighted group shows higher activity compared to early blinds.

For auditory motion processing, early blind individuals showed enhanced recruitment of posterior regions (hMT+/V5) and decreased activity in the most anterior region (PT) compared to the sighted individuals. This result supports the notion of interplay between hMT+/V5 and PT in case of early blindness. Furthermore, the presence of auditory information in the anterior portion of hMT+/V5 in the sighted, suggests an involvement of this region in sighted in processing non-visual information. In case of blindness, the involvement of hMT+/V5 is enhanced.

### 4.4. Cross-modal responses in visual cortex of late-blind individuals

What would happen if someone loses sight later in life, after the full development of the visual system? Would we observe similar reorganization principles as in early blinds or would crossmodal plasticity express using different mechanisms since building on occipital regions that have been fully developed for vision? According to the supramodal brain approach, occipital regions should compute its function independently of the visual experience. Therefore, non-visual motion processing in the late blind individuals should activate hMT+/V5.

Previous studies have shown that while spatial sounds recruited right middle occipital gyrus (in the vicinity of hMT+/V5) and cuneus in the early blinds (Collignon et al. 2011), late blinds showed lack of functional specialization for spatial sounds (Collignon et al. 2013) in the occipital cortex. Similarly, hMT+/V5 revealed significantly different activity in early and late blind individuals (Bedny et al. 2010). In early blind individuals, hMT+/V5 is activated for auditory motion. However, activity in late-blind adults for moving sounds is below baseline, like in sighted subjects (see Chapter 1 Fig. 5). Interestingly, in a blind individual who lost his sight after the age of 2-3, the responsiveness of hMT+/V5 was more similar to sighted group rather early blind group (Bedny et al. 2010). Despite more than 50 years of visual deprivation, in this individual, visual motion area hMT+/V5 region were not recruited for auditory motion. These results suggest that functional specialization of occipital regions depend on the visual experience, in contrast with the supramodal brain approach suggestion. Investigating the functional specialization of hMT+/V5 in the late blind individuals could provide further evidence on the format (supramodal or sensory-related) of this region and on the impact of the crossmodal plasticity in its reorganization.

Overall, we hypothesize that the recruitment of the hMT+/V5 and auditory motion direction information in late-blind individuals could be similar to what we observed in the sighted in the present study.

We have seen that early blindness triggers interplay between hMT+/V5 and PT; however, the lack of domain specific functional reorganization in the late blind individuals suggests that the redistribution of the computational workload between hMT+/V5 and PT would not be observed.

#### 4.4. Putative mechanisms of cross-modal responses

What are the mechanisms that could drive such extension of the crossmodal recruitment of hMT+/V5 for auditory motion in the blind? At the neural level, rewiring subcortical or cortico-cortical circuitries have been suggested to support crossmodal plasticity (Bavelier & Neville 2002). In the mole rat, a subterranean rodent with extremely reduced peripheral visual system, occipital areas showed retained organization, despite thalamo-cortical visual pathway is colonized by auditory input mediated by projections from the subcortical structures to the dorsal lateral geniculate nucleus (Bronchti et al. 2002). In addition, cortico-cortical connections seem to play an important role in mediating crossmodal recruitment of occipital areas. In sighted, recent findings have proposed that multisensory integration starts already in the primary sensory cortices (Kayser & Logothetis 2007; Noesselt et al. 2007; Lewis & Noppeney 2010; Molholm et al. 2002; Lee & Noppeney 2014; Rohe & Noppeney 2016) via (1) thalamo-cortical connections (Lakatos et al. 2007), (2) direct (anatomical) connections between sensory areas (Falchier et al. 2002; Rockland & Ojima 2003), or (3) top-down influences from multimodal association areas such as parietal or superior temporal sulcus (Macaluso & Driver 2005; Schroeder & Foxe 2002; Driver & Noesselt 2008). While both subcortical and cortico-cortical mechanisms potentially contribute to the functional reorganization in the early blind individuals, voxel-based-morphometry (VBM) have shown, in these individuals, atrophy in both grey and white matter structures (Noppeney et al. 2005; Shu et al. 2009; Wang et al. 2014). Moreover, diffusion tensor imaging (DTI) studies also demonstrated atrophy in the white matter pathway that convey visual input from the lateral geniculate nucleus (LGN) of the thalamus to the occipital cortex (Leporé et al. 2010; Wang et al. 2013). In the blind individuals, the evidences of atrophy in the circuits between occipital cortex and the subthalamic cortices emphasize the role of cortico-cortical mechanisms for the presence of non-visual sensory input in the occipital cortex. The existence of cortico-cortical connections for the purpose of multisensory integration, could explain our findings of motion direction information in hMT+/V5 both in sighted and blind individuals.

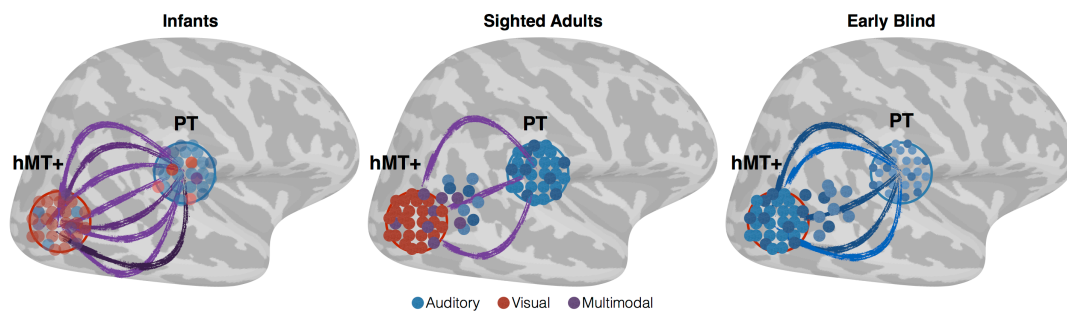
Under normal development, excessive synaptic pruning occurs by the age of 8 months. Almost 40% of the synaptic density vanishes and stabilizes approximately by the age of 11 (Huttenlocher 1990; Huttenlocher & de Courten 1987). Visually deprived cats show maintenance of normally pruned cortico-cortical and thalami-cortical projections to the visual cortex (Berman 1991; Karlen et al. 2006; Kingsbury et al. 2002). Moreover, sighted cats and monkeys show existence of transient long-range projections from the auditory cortex to the visual cortex (Innocenti & Price 2005; Falchier et al. 2002; Rockland & Ojima

2003). It is possible that sensory loss triggers the activation of preexisting connections or stabilization of normally transient or functionally silent connections (Das & Gilbert 1995; Innocenti et al. 1988; Innocenti & Clarke 1984) and, therefore, these connections may mediate, at least in part, the information flow between visual and auditory cortices (Bavelier & Neville 2002; Collignon et al. 2009; Hannagan et al. 2015; Pascual-Leone et al. 2005). Maintaining exuberant synapses and intermodal connections during early phases of development could facilitate cortico-cortical connections between visual and other sensory areas due to the “what fires together, wires together” Hebbian plasticity (Hebb 1949; Rauschecker 1995), and could be an underlying mechanism for enhanced recruitment of occipital cortex for non-visual processing in early blind individuals. Supporting evidences from dynamic causal modeling of fMRI datasets suggest that early blindness triggers stronger cortico-cortical connections between auditory and occipital areas, together with the enhanced recruitment of occipital areas by auditory modality (Collignon et al., 2013; Klinge et al., 2010). These results suggest that the maintained and enhanced cortico-cortical connectivity may lead the auditory information to evoke responses in the visual cortex.

*What can drive the maintenance of functional specialization of hMT+/V5 while reducing the computational role of PT?* For instance, we have seen that a portion of hMT+/V5 is specialized for auditory motion processing in blind individuals and, to a lesser extent, in sighted one. Increased role of hMT+/V5 accompanied by the decreased involvement of PT for spatial hearing in early blind individuals. Large-scale connectivity patterns are suggested to be the determining factor of functional specialization of occipital areas. More specifically, pre-existing large-scale cortical circuits might be crucial for a region to perform specific tasks (Johnson 2011; Hannagan et al. 2015). According to the biased connectivity framework, enhanced non-visual responses for moving stimuli observed in early blinds may build on pre-existing connections between auditory, tactile and visual motion processing areas (Hannagan et al. 2015; Konkle et al. 2009). Several lines of evidence, including the present work in Chapter 3, suggests that the right extrastriate occipital regions are part of a network of fronto-parietal areas typically involved in spatial attention and awareness (Collignon et al. 2011; Dormal et al. 2016). We therefore make the hypothesis that the regions that are performing specific function maintain their functional organization/specialization but extend their responsiveness toward non-visual inputs due to a potentially intrinsic connectivity biases between regions participating in similar functions across the senses (Pascual-Leone & Hamilton 2001; Mahon & Caramazza 2011; Johnson 2011; Hannagan et al. 2015). Furthermore, a possible communication between the

computationally analog areas via large-scale connectivity could explain this interplay between visual and auditory motion responsive areas in the case of early visual deprivation.

According to our empirical results and previous work in the field, we propose a framework to explain possible auditory motion mechanisms in the brain of infants, sighted, and blind individuals (Figure 2).



**Figure 2. Illustration of putative auditory motion mechanism.** Dots represent motion information in the cortex. Information related to visual motion (red), auditory motion (blue), and multimodal motion (purple). Connections (purple and blue) represent cortico-cortical circuits carrying visual and auditory information between motion responsive areas.

At birth, hMT+/5 and PT might have a rather crude functional specialization for visual and auditory motion, respectively. The two systems are intended to collaborate, for instance, for the purpose of multisensory integration and therefore may have intrinsic connectivity between them (Figure 2A). During development, the more anterior part of hMT+/V5 would show a pattern of motion selectivity in both vision and audition, assumed to arise due to the above-mentioned pattern of connectivity linking the two motion-sensitive systems. Moreover, such large-scale connectivity patterns between auditory and visual regions that are involved in motion processing could be a determining factor for the expression of crossmodal plasticity (Hannagan et al. 2015; Dormal & Collignon 2011). In case of early visual deprivation, building on this biased connectivity, hMT+/V5 is massively extending its response to auditory input while maintaining a preferential tuning to moving stimuli. This extension of auditory motion computation in the visually deprived hMT+/V5 appears to lead to a decrease in the computational load in PT. Both anatomical and functional connections between visual and auditory areas could therefore play a crucial role in re-distributing the computational “workload” analog units.

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