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Space and time in the human brain

by

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Che la tua vita non sia una vita sterile.
Sii utile.
Lascia traccia.
Illumina con la fiamma della tua fede e del tuo amore.
San Josemaría Escrivá

Don’t let your life be barren.
Be useful.
Make yourself felt.
Shine forth with the torch of your faith and your love.
St. Josemaría Escrivá

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other university. This dissertation is my own work and contains nothing which is the outcome of work done in collaboration with others, except as specified in the text and Acknowledgements. This dissertation contains fewer than 65,000 words including appendices, bibliography, footnotes, tables and equations and has fewer than 150 figures.

Maria Bianca Amadeo
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Abstract

Space and time perception are inherently part of human life. All human sensory modalities are constantly involved in the complex task of creating a spatial and temporal representation of the external world. However, when representing space, people primarily relies on visual information, and when representing time, the most reliable information is, in fact, audition. This thesis aims to deepen the understanding of how vision and audition shape the development of some aspects of spatial and temporal representations in the human brain. This project uses blindness and deafness as models to disentangle the relative contribution of the missing sensory modality to mechanisms involved in spatial and temporal perception. Literature concerning auditory spatial abilities in blindness, and visual temporal abilities in deafness, show both enhanced and impaired skills in the presence of sensory deprivation. A deeper understanding of processes involved in the development of spatial and temporal representation is important, not only because space and time are inherently part of everyday life, but also as a means to quantify the perceptual consequences of visual or auditory loss. Indeed, improving this understanding, from a clinical perspective, will help develop effective rehabilitation strategies to improve spatial and temporal skills that have been impaired.

This thesis highlights that some spatial and temporal skills require functional recruitment of areas likely involving the visual and auditory cortices, respectively. Spatial orienting auditory attention and complex auditory spatial representation elicit specific activations in parieto-occipital areas, and complex visual temporal representation elicits specific activations in temporal regions. Stating the possibility of domain-specific features in the supramodal organization of sensory cortices, this thesis reveals that sensory experience could formulate a prerequisite for developing at least some of those features. Indeed, while the late lateralized parieto-occipital response associated with spatial orienting auditory attention is even enhanced in people who are blind, lack of vision clearly hampers some complex auditory spatial abilities and the underlying early lateralized activation of occipital cortex. The early lateralized activation of occipital cortex is lost in early blind people and after prolonged blindness in people who became blind later in life. Similarly, lack of audition impairs certain complex visual temporal abilities and the underlying early activation of the temporal cortex.

Moreover, this thesis investigates possible interactions between spatial and temporal representations. Data show that, when spatial or temporal skills are poor, individuals benefit from coherent spatiotemporal information. More specifically, young children and blind people, who are unable to build complex spatial representations, seem to rely on temporal cues to infer spatial coordinates in their environments. In a symmetrical fashion, evidence suggests that deaf people, who show difficulties in building complex temporal representations, use spatial cues to decode temporal features of the world.

Findings from this thesis contribute to a more comprehensive picture of neural mechanisms governing humans' development of spatial and temporal representations, with important implications for clinical outcomes following blindness and deafness. If spatial and temporal judgments interact, we should consider new rehabilitative techniques in which we could simultaneously manipulate spatial and temporal cues to convey richer information.

Table of Contents

List of Figures

List of tables

Chapter 1

Introduction

Since our first day of life, we interact with the environment through our senses. All our sensory modalities are constantly involved in the complex task of creating a spatial and temporal representation of the external world. Our senses constantly provide complementary information, which needs to be merged in order to perceive a coherent environment. Areas once thought dedicated to processing information of a given sensory modality are now known to process inputs from multiple senses (Rosenblum et al., 2017). This multisensory nature of the brain has been recently described as supramodal, meaning that it reflects a cortical architecture for which task, rather than sensory system, is the primary design principle (Struiksma et al., 2009). Nowadays, research agrees that different sensory modalities are more appropriate to process specific environmental proprieties. Specifically, vision is typically considered the most reliable sense for spatial representation (e.g. Alais and Burr, 2004), whereas audition is the most accurate sense to represent temporal information (e.g. Bresciani and Ernst, 2007). However, how exactly the spatial and temporal domains are coded by the brain is still an open issue.

In light of supramodal architecture of the human brain, the main aim of the thesis is to deepen into how the visual and auditory systems shape the development of some aspects of spatial and temporal representations. Chapter 2 and Chapter 3 of the thesis investigate whether the task-specific supramodal architecture of the brain can be partially explained by a domain-specific organization at visual and auditory cortical level. Specifically, in each of the two chapters, either space or time is considered as the putative domain and the role of visual or auditory experience on the possible domain-specific cortical organization is tested. Subsequently, Chapter 4 of the thesis investigates possible interactions between spatial and temporal representations of unisensory visual or auditory inputs. Specific attention is paid to how the representation of one domain can be affected or even inferred by the information coming from the other domain.

To reach its goals, this project involves the study and comparison of different populations, such as typical children and adults, as well as blind and deaf adults. Indeed, blindness and deafness are useful models to disentangle the relative contribution of the missing sensory modality to underlying mechanisms involved in auditory spatial and visual temporal representations. Literature concerning auditory spatial abilities in blindness, and visual temporal abilities in deafness, show both enhanced and impaired skills in the presence of sensory deprivation. Thus, a deeper understanding of processes involved in the development of spatial and temporal representations is important, not only because space and time are inherently part of everyday life, but also as a means to quantify the perceptual consequences of visual or auditory loss. This understanding, from a clinical perspective, can help develop effective rehabilitation strategies to improve spatial and temporal skills that have been impaired.

1.1 The complexity of communication between sensory systems

The communication between sensory modalities during the first years of life can be very complex. Sensory systems are not mature at birth and undergo specific fine-tunings during development. The maturation processes are not only different across sensory modalities (e.g. first touch develops, followed by audition and then vision), but also there is a difference in the developmental rates of different aspects within each sensory system. For example, some auditory abilities develop early in infancy, such as auditory frequency discrimination (Olsho, 1984, Olsho et al., 1988) and temporal discrimination (Trehub et al., 1995), whereas other more complex and experience-dependent skills require more time to reach mature levels, such as facilitation of speech perception in noise (Elliott, 1979, Johnson, 2000) or auditory spatial bisection precision (Gori et al., 2012b). Similarly, some visual properties, like binocular vision, color perception, and some kinds of visual motion perception, mature rapidly within 8 to 12 months of age (for a review, see Atkinson, 2002), but this is not the case for all visual perceptual skills. The development of complex form and motion perception (Gori et al., 2012a, Del Viva et al., 2006, Ellemberg et al., 2004, Kovacs et al., 1999, Sciutti et al., 2014), visual acuity and contrast sensitivity (Brown et al., 1987) are just some examples of abilities that continue to improve until 5 to 14 years of age.

However, a particular environmental property (such as the size of an object or its spatial position) is perceived by more than one sensory system at the very same time, and one of the difficult tasks of our brain is to integrate different sensory signals. In adults, redundant sensory signals are usually integrated in an optimal manner, improving the precision of the independent estimates from individual senses (unisensory estimations, Alais and Burr, 2004, Ernst and Banks, 2002, Landy et al., 2011). This means that in adulthood the accuracy and precision of the encoding of an event, congruent in space and in time, improves when the information from multiple senses is integrated. At a neurophysiological level, it has been shown that multisensory regions in higher-order association cortices

(Felleman and Van Essen, 1991, Massaro, 1999) play an important role in integrating information between modalities, and initializing and controlling the localization and orientation of motor responses. Areas in the temporal lobe, such as superior temporal sulcus (Beauchamp, 2005, Foxe et al., 2002), areas in the parietal lobe, such as the intraparietal sulcus and the superior parietal lobule (Bolognini et al., 2005, Bremmer et al., 2001, Bushara et al., 1999, Molholm et al., 2006), as well as areas in the frontal lobe, such as the prefrontal cortex (Bushara et al., 1999, Laurienti et al., 2003), show specific activation to multisensory stimuli. Even subcortical areas, such as the superior colliculus, the basal ganglia, and the putamen, were shown to contain multisensory neurons (Meredith and Stein, 1983, Stein and Meredith, 1993). Specifically, studies in animals revealed that the midbrain structure superior colliculus is structured in layers: in the superficial layers there are unisensory neurons, in the deeper layers there are neurons that respond to the combination of visual, auditory, and tactile stimuli (Stein et al., 2009). These latters respond to spatiotemporally coincident multisensory stimuli with a multisensory enhancement (Meredith and Stein, 1986). Recently, it has been argued that multisensory processing in adults interests also the earliest stages of stimulus processing in classical “unisensory” areas (e.g. Calvert et al., 1999, Calvert et al., 1997, Giard and Peronnet, 1999, Cappe et al., 2010). These results suggest that multisensory integration operates through both feedback projections to the unisensory cortices from multisensory regions, as well as through direct connections between the unisensory areas themselves (Falchier et al., 2002, Rockland and Ojima, 2003).

In cats and monkeys, multimodal responses of neurons in the superior colliculus are not present at birth but develop late (Stein et al., 1973, Wallace and Stein, 2007, Wallace and Stein, 2001). In this direction, multisensory integration in humans develops gradually over childhood (Gori, 2015). Some basic forms of integration, such as reflexive orienting towards an audio-visual signal (Neil et al., 2006), develop quite early, but some others, such as integration of visual-haptic signals for orientation and size (e.g. Gori et al., 2008), develop over time. Recent works demonstrated that during childhood unisensory dominance prevails over multisensory integration for some perceptual tasks. The brain needs to calibrate the different sensory systems and integrate redundant signals: these processes require time and maturation (Gori et al., 2008, Nardini et al., 2008). According to the cross-sensory calibration theory (Gori, 2015), the reason why young individuals do not integrate sensory information is that during childhood, when the body is subjected to rapid changes which affect the sensory systems in various ways, the most accurate sense for a given perceptual task is used to calibrate the other senses. For example, sensory modalities involved in a spatial perception task must constantly recalibrate during development in order to take into account anatomical and physiological swings, and cross-sensory calibration is more important than optimizing perception through integration. This theory explains the lack of integration at early stages of life, since the use of one sense to calibrate another necessarily precludes integration of redundant information to improve precision (Gori, 2015). Overall, calibration does not always occur in the same direction, but the more accurate sense for a specific environmental property should calibrate the less accurate ones. In this context, recent studies highlight that different sensory modalities are more appropriate to process specific environmental proprieties. In the next sections, I introduce research about the crucial role of vision and audition on the developmental of spatial and temporal proprieties of the environment respectively.

1.2 Spatial representation in a multisensory environment

“Space perception is a process through which humans and other organisms become aware of the relative positions of their own bodies and objects around them. Space perception provides cues, such as depth and distance, which are important for movement and orientation to the environment” (Encyclopedia Britannica). Since birth, infants start to create a spatial representation of the environment and quickly develop some spatial skills, such as the ability to discriminate between above vs. below and left vs. right (Quinn, 1994, Quinn et al., 1996), and to process spatial object dimensions such as height (Baillargeon et al., 1985, Baillargeon and DeVos, 1991), distance location (Newcombe et al., 1999), and angles (Lourenco and Huttenlocher, 2008).

To perceive a multisensory world, humans need to combine the spatial information arriving from all the sensory modalities into a coherent multisensory spatial representation. The visual modality seems to have a crucial role in this important step (Pasqualotto and Proulx, 2012), offering in a single frame an immediate and complete representation of the surrounding layout (Tinti et al., 2006). The brain receives high-resolution spatial information directly from the retina, and vision seems to be necessary for aligning neural representations of space for different sensory modalities (King, 2009, King, 2014, Welch and Warren, 1980). The leading role of vision in inferring space is evident in the interaction with the other senses: when sensorial conflict occurs, audition and touch are strongly biased by simultaneously presented visuo-spatial information (Pick et al., 1969, Flanagan and Beltzner, 2000, Botvinick and Cohen, 1998, Bertelson and Aschersleben, 2003, Anderson and Zahorik, 2011, Zahorik, 2001). When a visual stimulus is presented simultaneously but in conflict with an auditory stimulus for example, this latter is localized toward the location of the visual one. This phenomenon is known as ‘ventriloquist effect’ (Warren et al., 1981, Mateeff et al., 1985) and it results from optimal cue combination, where each cue is weighted according to its statistical reliability (Alais and Burr, 2004). At neurophysiological level, although studies showed that unisensory areas are dedicated to modality-specific spatial perception (e.g. Ahveninen et al., 2006, Tata and Ward, 2005), this piece of research runs parallel to several functional neuroimaging and TMS studies in humans and electrophysiological studies in animals that suggested a contribution of visual occipital areas to spatial processing of sounds (Zimmer et al., 2004, Poirier et al., 2005, Lewald et al., 2004, Fishman and Michael, 1973, Morrell, 1972). This evidence supports a task-specific supramodal organization of the brain (see Cecchetti et al., 2016a, Heimler et al., 2015, Amedi et al., 2017). Other studies concur with the crucial role of visual system in space representation, noting that, in young children, the representation of the auditory space is dominated by visual experience. Gori et al. (2012b) used the Bayesian approach to study the development of audio-visual integration in space. They showed that optimal integration of audio-visual information occurred around the age of 12 for a complex spatial task. Indeed, in that audio-visual spatial task, children younger than 12 years old showed visual dominance rather than optimal bimodal integration. These results are in line with the cross-sensory calibration theory (Gori, 2015, Warren et al., 1981), suggesting that during development the visual system could have a crucial role to calibrate the auditory system for spatial representation (e.g. Gori et al., 2012b, Loomis et al., 1998, Da Silva, 1985). At the same time, converging evidence from animal studies suggests that the development of multisensory interactions between vision and other senses depends on early perceptual experience and neurons in the superior colliculus are involved (Stein et al., 2009). For example, after visual adaptation with prismatic spectacles, auditory spatial maps of juvenile barn owls change (Knudsen, 1998), while visual deprivation in young ferrets is associated with disordered auditory spatial map development (King and Carlile, 1993). In humans, studies have identified similar transitory effects where auditory spatial representation was altered after short periods of adaptation to non-aligned auditory and visual stimuli (Recanzone, 1998, Zwiers et al., 2003).

To sum up, research from different fields agrees vision provides the most accurate and reliable information about the spatial properties of the external world, and thus it dominates spatial perception (Alais and Burr, 2004, Welch and Warren, 1980). But, how exactly vision shapes the development of spatial representation and the underlying mechanisms is still not clear. Moreover, if visual experience is so important, this leaves a question regarding what happens to spatial representation when the visual input is missing. Taken together, results suggest that the absence of vision may interfere with the development of spatial representation. This would be especially true if the visual impairment emerges at birth, when multisensory communication is fundamental for the development of spatial representations (Gori et al., 2014, Vercillo et al., 2016). However, contrasting results indicate that visually impaired people can show either enhanced or impaired spatial skills, leading to the hypothesis that vision could play a different role depending on different spatial aspects. Research about auditory spatial representation following visual deprivation is deeper discussed in Chapter 2. To enrich this topic, in Chapter 2, the thesis investigates neural correlates of auditory spatial skills in early and late blind people. By comparing neural activity between blind and sighted people during specific spatial tasks, we can explore a possible domain-specific supramodal organization of the brain and the role of visual experience on it.

1.3 Temporal representation in a multisensory environment

Time perception refers to the “experience or awareness of the passage of time” (Encyclopedia Britannica). It is essential for many everyday life activities: it occurs while we stare at the hands of the clock slowly moving when we are bored, but also while listening to our favorite song or listen to speech unfolding in time. From the moment of their birth infants are immersed in time, and some temporal skills are fast to develop (Pouthas et al., 1993). Given the importance of having an internal representation of time, newborns learn quickly to distinguish temporal intervals and durations between events (Brackbill and Fitzgerald, 1972), and their brain responds for example to temporal deviations in a repetitive sequence of auditory stimuli similarly to the adult brain (Brannon et al., 2004). Temporal abilities naturally improve and become more sophisticated throughout childhood into adolescence (for a review, see Allman et al., 2012, Droit-Volet, 2013).

As for spatial representation, to perceive a coherent temporal representation and successfully interact with our environment, we need to combine temporal information derived from different sensory modalities. It was 1963 when Paul Fraisse stated that "hearing is the main organ through which we perceive change: it is considered as the ' time sense' " (1963). More recent studies support this idea, showing that the auditory system is the most accurate one to represent temporal information (e.g. Guttman et al., 2005, Bresciani and Ernst, 2007, Burr et al., 2009, Barakat et al., 2015). Behavioral results showed that audition prevails in audio-visual temporal tasks. For instance, a single flash is perceived as two flashes when presented with two concurrent beeps (Shams et al., 2000), and the perceived frequency of flickering lights is influenced by an auditory stimulus presented simultaneously at a different rate (Gebhard and Mowbray, 1959, Shipley, 1964). Similarly, visual rhythm perception can be modified through auditory, but not visual, training (Barakat et al., 2015). Even if the primary sensory cortices can show modality-specific processing for time perception (e.g. Shuler and Bear, 2006, Ghose and Maunsell, 2002), several neuroimaging studies suggest also an important sensory-independent role of the auditory cortex on temporal representation, in favor of a task-specific supramodal organization of the brain (Heimler et al., 2015, Cecchetti et al., 2016b). For instance, activation of the superior temporal gyrus has been observed during temporal processing of visual stimuli with fMRI (Coull et al., 2004, Ferrandez et al., 2003, Lewis and Miall, 2003), and TMS over the auditory cortex has been shown to impact on time estimation of both auditory and visual stimuli (Kanai et al., 2011), as well as tactile events (Bolognini et al., 2010). Moreover, it has been shown that the posterior part of the high-level auditory cortex is involved in processing temporally complex sounds (Kusmierek and Rauschecker, 2014, Obleser et al., 2007), including music (Hyde et al., 2008). Given the superiority of audition over the other sensory systems for time perception, the auditory modality might offer a temporal background for calibrating other sensory information. In support of this hypothesis, when performing a complex audio-visual multisensory temporal task, both young children and adults mostly rely on auditory information to estimate the multisensory temporal position of the stimulus (Gori et al., 2012b). As supported by the cross-sensory calibration theory (Gori, 2015), audition, which seems to be the most reliable sensory modality for temporal judgments, could be used to calibrate the other sensory channels for temporal perception during development. In line with this hypothesis, sensitivity to time during development increases faster for the auditory than the visual modality (Zelanti and Droit-Volet, 2012), and children’s time estimates are more precise for auditory than visual stimuli (Droit-Volet et al., 2007). McGovern et al. (2016) recently demonstrated that benefits derived from training on a spatial task in the visual modality transfer to the auditory modality, and benefits derived from training on a temporal task in the auditory modality transfer to the visual modality. Since the converse patterns of transfer were absent, they suggested a unidirectional transfer of perceptual learning across sensory modality, from the dominant to the non-dominant sensory modality.

As introduced in Section 1.2 about visual modality, the development of multisensory interactions between senses seems to depend on early perceptual experience (e.g. Merabet and Pascual-Leone, 2010, Cardon et al., 2012, Lazard et al., 2014). As a consequence, lack of auditory experience might interfere with the development of a temporal representation of the environment (Gori et al., 2017). Again, if audition provides the most accurate and reliable information about the temporal properties of the external world, dominating temporal perception, one can wonder what happens then to temporal representation when the auditory input is missing. As for spatial representation, previous studies in deaf people show mixed results with regards to temporal processing skills, highlighting both enhancements and deficits in temporal competences brought about by auditory loss. Much research is needed to better understand how audition shapes the development of temporal representation and the underlying mechanisms, as well as the development of temporal representation when the auditory input is missing. Visual temporal representation following auditory deprivation is deeper addressed in Chapter 3. Indeed, in Chapter 3, the thesis investigates neural correlates of complex visual temporal skills in both typical and deaf adults. By comparing neural activity between deaf and hearing people during a temporal task, we can deepen our understanding of domain-specific supramodal organization of the brain and the role of auditory experience on it.

1.4 Objectives of the thesis

In light of the state-of-art, the first step of the thesis involves investigating neural mechanisms of space and time representation in children and adults with or without sensory disabilities. Thanks to the use of the Electroencephalography (EEG) technique, in

Chapter 2 and Chapter 3, we shed light on specific neural circuits that serve certain complex auditory spatial and visual temporal skills. In this, we pay specific attention to the visual and auditory brain's contribution, regardless of the sensory modality conveying the signal. This thesis uses blindness and deafness as models as they offer valuable insights into the role of the missing sensory modality on spatial and temporal perception. Soon after, I introduce literature concerning auditory spatial abilities in blindness and visual temporal abilities in deafness, raising a question as to why some skills are enhanced while some others are impaired in sensory disabilities. In this way, the second and third chapters clarify the impact that sensory deprivation has on certain complex spatial and temporal abilities and underlying neural correlates. In particular, Chapter 2 reveals that, in blind people, the late lateralized parieto-occipital response associated with spatial orienting auditory attention is even enhanced. On the other hand, it shows a strong deficit in building complex auditory spatial representation following blindness, likely due to a weaker and not lateralized activation in areas likely involving the visual cortices. Chapter 3 describes the negative impact of deafness on complex visual temporal representation, likely owing to a lack of activation in areas plausibly involving auditory cortices. Based on the behavioural and neurophysiological results that Chapter 2 and 3 report, a consequent goal of the current thesis is to investigate a possible interaction between spatial and temporal representations.

Almost eighty years ago, Jean Piaget (1962) stated that the temporal metric is strictly related to spatial metric development: “Space is a still of time, while time is space in motion” (Piaget, 1927, p.2). Unfortunately, Piaget did not discuss the role of different sensory modalities on this link. Starting from Piaget's idea, in Chapter 4 this thesis investigates a possible role of temporal information to decode spatial information and vice-versa. Specifically, we test whether, when spatial or temporal skills are poor, such as in blindness, deafness or during development, people could benefit from coherent spatiotemporal information. In Chapter 5, which is the final chapter, we discuss this thesis' primary results with consideration to existing literature, and we introduce a new hypothesis about how vision and audition may collaborate to estimate space and time. We address the goals of this thesis mainly using the bisection paradigm – a complex metric task that consists of evaluating spatial distances or temporal intervals between stimuli, stressing relative comparisons between them. This paradigm introduces the possibility for us to test complex spatial or temporal abilities within the visual (i.e. flashes) or auditory (i.e. beeps) modality, and simultaneously manipulate the spatial and temporal proprieties of the environment.

Since space and time are inherently part of everyday human life, the final goal of the current thesis is to provide a more comprehensive picture of neural mechanisms governing spatial and temporal perception. This has also important implications for clinical outcomes following blindness and deafness. Indeed, knowing why some skills are enhanced or impaired following sensory deprivation would offer a chance to consider new rehabilitation programs that activate compensatory strategies at an early age.

Chapter 2

Spatial representation and blindness

In Chapter 1, I introduced the leading role of vision on developing spatial representation. Starting from this evidence, one can expect that lack of visual input during early development and absence of a visual frame of reference during life could cause severe spatial impairments in visually impaired individuals. Thus far, research has yielded contradictory results about spatial performance following visual loss.

Historically, the blind brain has been primarily investigated from the perspective of the compensatory ability of visual areas to process non-visual information (Sadato et al., 1996, Kupers and Ptito, 2011, Frasnelli et al., 2011, Renier et al., 2014). According to the "sensory compensatory hypothesis", exceptional perceptual abilities characterize the remaining sensory modalities of blind individuals to compensate for visual deprivation (Rice, 1970, Miller, 1992). Over the years, a growing body of literature sustains this hypothesis (e.g. Théoret et al., 2004, Roder and Neville, 2003). For space representation, experimental support comes for example from studies showing that early blind subjects have enhanced skills in localization of peripheral sounds in the horizontal plane (Lessard et al., 1998, Roder et al., 1999, Zwiers et al., 2001), relative distance discrimination (Voss et al., 2004, Kolarik et al., 2013), building cognitive spatial maps underlying simple auditory localization (Tinti et al., 2006, Fortin et al., 2008), or performing immediate hand-pointing localization task (Rossetti et al., 1996). In particular, Lessard et al. (1998) investigated spatial mapping in early blind individuals by considering monaural and binaural listening conditions. In the former, either the right or the left ear was blocked with a soft foam earplug (mean attenuation = 37.5 dB SPL) and covered by a hearing protector muff (mean attenuation, 29 dB SPL); researchers then conducted pilot experiments with broadband noise bursts ranging from 25 to 60 dB SPL to make sure that no sounds were perceivable by subjects. The authors observed that early blind subjects' abilities in localizing a single sound was characterized by equal or better accuracy than sighted subjects. Moreover, contrarily to sighted individuals, early blind were also able to correctly localize sounds monaurally. As for spatial attention, faster reaction times but similar accuracy have been recorded during selective (and divided) attention paradigms in blind when compared to sighed people (Collignon and De Volder, 2009, Collignon et al., 2006).

Compensatory mechanisms at neural level may provide an explanation for the enhanced spatial perceptual abilities in the remaining senses commonly observed in visually deprived humans (e.g. Gougoux et al., 2005, Collignon et al., 2009, Voss and Zatorre, 2012). The brain is highly plastic and compensatory mechanisms can be adopted to sustain spatial skills. Neurophysiological results indicate subcortical and cortical structures, as well as their constitutive white matter tracts, undergo substantial structural and functional reorganization following visual deprivation (Ptito et al., 2008, Cecchetti et al., 2016b, Reislev et al., 2016). A clear response of visual occipital cortex of blind individuals is elicited by somatosensory and auditory stimuli (e.g. Gougoux et al., 2005, Weeks et al., 2000, Poirier et al., 2005, Renier and De Volder, 2005, Striem-Amit and Amedi, 2014, Voss and Zatorre, 2012, Collignon et al., 2009, Rauschecker, 1995, Collignon et al., 2011). Specifically, nowadays research agrees that the deprived visual cortices maintained to a certain extent their task specializations, although recruited by nonvisual input (for a review, see Dormal and Collignon, 2011, Heimler et al., 2014). Literature refers to this phenomenon as sensory-independent supramodal cortical organization (see Ricciardi et al., 2014), or task-specific sensory-independent organization of the brain (see Heimler et al., 2015). The absence of visual input also drives to an increased functional connectivity between primary auditory cortex and occipital regions (Collignon et al., 2013). Interestingly, reorganization following blindness involves the volume of lateral geniculate nuclei too (Cecchetti et al., 2016b). Although volumetric changes were not observed in the superior colliculus (Cecchetti et al., 2016b), the latter is selectively recruited during auditory tasks in blind individuals (Coullon et al., 2015). Moreover, anatomical changes interest non-visual areas, such as the auditory (e.g. Korte and Rauschecker, 1993, Elbert et al., 2002) and the somatosensory (Sterr et al., 1998, Park et al., 2009) cortices.

If the lack of vision can drive the functional recruitment of the visual areas and enhancements on the remaining senses, it has been also shown that the lack of visual input negatively affects the development of some additional processing. The "perceptual deficiency hypothesis" claims that, for both auditory and tactile skills, the improvement following visual deprivation is not uniform and seems to be dependent on different factors (e.g. age of onset, severity of blindness, kind of task, etc.). Actually, blindness impairs some spatial skills, raising some doubts about the extent of cross-modal plasticity in the case of vision loss. Taking into account the auditory modality, visually impaired individuals show deficit in estimating the absolute distance of auditory cues (Wanet and Veraart, 1985, Kolarik et al., 2013, Kolarik et al., 2017), performing tasks involving spatial imagery (Cattaneo et al., 2008), metric representation of the auditory space (Gori et al., 2014, Finocchietti et al., 2015), auditory distance discrimination or proprioceptive reproduction (Cappagli et al., 2017). Moreover, while similar performance between blind and sighted individuals is observed for the localization of sounds within the frontal domain (within 45° from the midline), poorer skills have been reported in blind people along the mid-sagittal plane when increasing background noise (Zwiers et al., 2001). Specifically, only simple localization of peripheral and not central sounds exceeds that of sighted individuals (Roder et al., 1999, Zwiers et al., 2001, Lessard et al., 1998). These results support those of anatomical studies showing that strong auditory projections are present in the peripheral but not in the central visual field, possibly facilitating colonization (Falchier et al., 2002). Researchers have also reported deficits of blind people in representation and updating of haptic spatial information (Pasqualotto and Proulx, 2012). However, while neural correlates for auditory enhancement in blind individuals have been widely studied, neural correlates for auditory impairments have received less attention over the years. The perspective highlighting impairments in auditory spatial representation following visual deprivation is supported by neurophysiological evidence in animals. In animals, it has been shown that visual feedback plays an important role for auditory spatial learning and for the normal development of acoustic spatial maps in the superior colliculus (King and Carlile, 1993, King et al., 1988, Knudsen and Brainard, 1991, Heffner and Heffner, 1992).

Furthermore, space perception has been extensively studied in early blindness, whereas research about late blindness is to date limited (for a review, see Voss, 2016, Voss, 2013). However, the study of late blindness offers valuable insights. This is because the unique combination of visual calibration in childhood and prolonged blindness in adulthood together shapes the spatial hearing of late blind subjects. According to recent data, auditory spatial skills and cortical responses of late blind (LB) individuals lay between those of early blind and sighted individuals. It would seem that this group neither benefits from the spatial hearing enhancements observed in early blind subjects, nor does it exhibits any specific perceptual deficits. Unlike early blind subjects, there is no evidence of enhanced monaural localization abilities (Voss et al., 2008, Collignon et al., 2011) and late blind adults do not show any spatial impairments for audio motion perception on the horizontal axis (Finocchietti et al., 2015), haptic orientation (Gori et al., 2010), auditory distance discrimination and proprioceptive reproduction (Cappagli et al., 2017). Contrarily to early blind people, late blind subjects also succeed in absolute auditory distance estimation (Wanet and Veraart, 1985), locational judgments after a perspective change in small-scale space (Lehtinen-Railo and Juurmaa, 1994), audio shape recognition and navigation tasks (Gori et al., 2017). However, late blind individuals are better able compared to sighted people to use spectral cues when localizing sound position in peripheral regions, similarly to early blind subjects (Gougoux et al., 2004, Fieger et al., 2006). Turning attention to cross-modal plastic changes following late blindness, the literature shows again different results. On the one hand, auditory or tactile recruitment of occipital regions has been observed in late blind individuals (Voss et al., 2006, Buchel, 1998, Burton, 2003), suggesting that compensatory mechanisms can be adopted to improve spatial skills even when vision is lost later in life. On the other hand, some studies claim that functional or structural reorganization is almost impossible beyond some critical periods (e.g. Cohen et al., 1999, Sadato et al., 2002, Noppeney, 2007). Moreover, some researchers ascribe a central role to blindness onset (e.g. Li et al., 2016, Li et al., 2013), whereas others point out some effects associated with blindness duration (e.g. Wang et al., 2013). To complicate matters in this topic, one of the major issues concerning literature on late blindness is the lack of consistency across different studies in classifying blind individuals as early or late blind subjects. A given individual may be arbitrarily categorized as “early blind” in one paper and as “late blind” in others, making comparisons between findings impossible. For instance, some authors classify individuals with onsets of blindness occurring after the age of 5 as LB subjects (Gougoux et al., 2004), whereas others consider 9 years of age as cut-off (Fieger et al., 2006, Bedny et al., 2012) or even 13 years of age (Voss et al., 2008, Sadato et al., 2002, Cohen et al., 1999).

Taken together, these findings suggest that the mechanisms that subtend the development of spatial representation remain unclear. The available literature highlights that the role of visual modality on spatial representation varies based on spatial properties, producing in some cases improved or impaired skills in blind individuals. The underlying mechanisms require clarification. A clearer definition of the underlying processes involved in spatial competence enhancements and deficits caused by visual loss is important because the development of spatial cognition is strictly related to developing social cognition. The ability to independently navigate and orient ourselves in space facilitates engagement in social interactions, which are indeed problematic in blind children (e.g. Guralnick et al., 1996). In the next sections, I illustrate possible cortical mechanisms underlying some auditory spatial skills in blindness. Specifically, I first focus on auditory-evoked activation of visual parieto-occipital cortex in the context of auditory spatial attention. This is in order to examine whether and to what extent the specific parieto-occipital response to sound is present in blind individuals and thus mediated by visual experience (Section 2.1). Then, I focus on the role of visual experience on the construction of complex auditory spatial representation and neural correlates. This will be addressed by presenting studies involving early (Section 2.2) and late (Section 2.3) blind people. Results demonstrate that visual experience is not a prerequisite for the development of neural correlates associated with auditory spatial orienting attention, but it is necessary for neural processing of other complex auditory spatial information. Findings of Chapter 2 shed light on some aspects of plastic reorganization that take place when vision is absent, but also offer important insights about the functional development and organization of the sighted brain itself.

2.1 Exp. 1: Reflexive orienting of auditory spatial attention in early blindness

Recent findings challenge the assumption that visual cortex is solely processing visual information, as several studies have revealed that non-retinal inputs can trigger neural responses in areas traditionally assumed to be visual in sighted individuals (e.g. Romei et al., 2009, Vetter et al., 2014). Specifically, it has been shown that peripheral, task-irrelevant sounds elicit activity in contralateral visual cortex of sighted people, as revealed by a sustained positive deflection in the event-related potential (ERP) over the occipital scalp contralateral to the sound's location (McDonald et al., 2013). This Auditory-evoked Contralateral Occipital Positivity (ACOP) appears between 200–450 ms after sound onset, and its neural generators have been ascribed to the ventrolateral extrastriate visual cortex (Brodmann's Area BA19, see also results from a EcOG study by Brang et al., 2015). In sighted individuals, these lateralized changes over occipital areas have been studied using cross-modal exogenous attention tasks in which peripheral sounds are followed by a visual target either at the same or opposite location as the sound, and have shown that the neural effects are associated with enhanced visual performance at the sound's location (McDonald et al., 2013, Feng et al., 2014). Based on these results, these lateralized enhancements over visual areas have been interpreted as indexing the reflexive orienting of cross-modal spatial attention to the sound's location. Interestingly, similar lateralized changes over occipital cortex have also been observed in purely auditory tasks – where the observer never sees a visual stimulus (McDonald et al., 2013, Stormer et al., 2016). In this study, we investigated what underlies these spatially lateralized audio-visual cortical interactions (see Amadeo et al., 2019d). One possibility is that this cross-modal spatial mapping between audition and vision emerges with experience, i.e., that exposure to co-localized sounds and visual inputs is necessary. Another possibility is that such mapping is inherent to the organization of the occipital cortex, reflecting a built-in mechanism of spatial attention across modalities which does not depend on audio-visual inputs.

To test these alternative hypotheses, we examined congenitally blind and sighted individuals. We compared the lateralized response over visual areas triggered by peripheral, salient sounds. If the sound-induced lateral effects over occipital cortex emerge independently of visual experience, we would predict they also occur in blind individuals. As the ACOP has been found robustly and mostly independently of task in sighted individuals (McDonald et al., 2013), it seems plausible that these spatially lateralized responses also occur in blind individuals. Thus, one might assume that this component is elicited in blind individuals as well, consistent also with research showing enhanced spatial attention abilities in blind people (Zwiers et al., 2001, Lessard et al., 1998, Roder et al., 2002). If this is the case, the lateralized enhancement represents the neural signature of the reflexive orienting of spatial attention – regardless of input modality. Alternatively, if this cross-modal activation depends on an observer's experiences with spatially overlapping audio-visual inputs, we would predict that it is absent in blind individuals. The literature points to complex cross-modal interactions in blind individuals that may depend on stimulus type and the exact task used. While there is abundant research showing that blind individuals show strong and reliable responses to sounds in visual cortex (Amedi et al., 2007, Bedny et al., 2011, Focker et al., 2012, Kujala et al., 1995, Lane et al., 2015, Roder et al., 2002), it is unknown whether peripheral, task-irrelevant sounds would elicit spatially lateralized responses in visual areas of blind individuals. This is important because it would suggest that spatial information – at least at the level of the hemifield (left vs. right) – is coded in the visual cortex, regardless of input modality and regardless of visual or cross-modal experience.

Methods

Experimental procedure

To test our hypotheses, ERPs were recorded in 12 early blind (EB; mean age ± standard deviation - SD= 37±15 yo; F= 7; see table 2.1 for details) and 12 sighted (S; 31±8 yo; F= 7; t-test comparing age between groups: t(18.2)= 1.18, p= 0.3) subjects during a unimodal auditory task as in previous studies investigating the ACOP (McDonald et al., 2013). Exclusion criteria were history of neurological or cognitive deficits. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Genova, Italy) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained prior to testing.

Participants were blindfolded and sat in a silent room, 180 cm away from the center of an array of 23 speakers spanning ±25° of visual angle (with 0° representing the central speaker, negative values on the left, and positive values on the right; Fig. 2.1). The task consisted of listening to a stream of sounds that were presented in random order and at unpredictable times (i.e. variable inter-stimulus-interval: 2000-2500 ms). The auditory stream included task-irrelevant bursts of pink noise (83 ms duration, 0.5–15 kHz, 60 dB SPL) delivered from the left or right sides (i.e. ±25° eccentricity), and 1000 Hz target tones (83 ms duration, 60 dB SPL) delivered from the center (i.e. 0° eccentricity). Participants were instructed to press a button every time they heard a central target tone, while ignoring the peripheral noise bursts. The experiment consisted of 5 blocks of 128 trials. In each block, the proportions of noise bursts and tones were set to 55% and 45% respectively. We measured reaction times (RT), as the time between target tone and button press. Button press was allowed only after central target tones and it was required to proceed with the task (i.e. no false positives or omissions could be recorded).

During the task, high-density EEG was recorded from 64 scalp electrodes using the Biosemi Active Two EEG System. Before testing, all subjects were directed to maintain a stable head position and to fixate straight ahead. However, head and body orientation were continuously monitored during the experiment by the researchers.

PARTICIPANT	AGE	GENDER	PATHOLOGY	BLINDNESS ONSET	RESIDUAL VISION
S1	52	M	Retinopathy of Prematurity	Birth	Light and shadow
S2	77	F	Retinitis Pigmentosa	Birth	No vision
S3	62	F	Atrophy of the eyeball	Birth	Light and shadow
S4	25	M	Leber amaurosis	Birth	No vision
S5	52	F	Retinitis Pigmentosa	Birth	No vision
S6	58	M	Uveitis	Birth	No vision
S7	59	M	Glaucoma	Birth	Light and shadow
S8	42	F	Glaucoma	Birth	Light and shadow
S9	28	F	Retinopathy of Prematurity	Birth	No vision
S10	27	F	Retinopathy of Prematurity	Birth	No vision
S11	24	F	Glaucoma	Birth	No vision
S12	27	F	Microphthalmia	Birth	No vision

Table 2.1 Clinical details of the blind group (N= 12).
The table shows chronological age, gender, pathology, age of blindness onset, and residual vision at testing for each participant.

Preamplifiers in each electrode were used to reduce noise between the electrode and the amplification/digitization system (BioSemi ActiveTwo, BioSemi B.V. Amsterdam), allowing high electrode impedances. Electrode offsets were kept below 35 mV. The continuous EEG was recorded referenced to a Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode, which replace the ground electrodes used in conventional systems. CMS and DRL form a feedback loop, thus rendering them references. A first-order analog anti-aliasing filter with a half-power cutoff at 3.6 kHz was applied (see www.biosemi.com). Data were sampled at 512 Hz (2048 Hz with a decimation factor of 1/4) with pass-band from DC to 134 Hz. In order to monitor horizontal eye movements, two additional electrodes were placed at the left and right outer canthi for EOG recording and trials showing horizontal ocular movements were discarded by visual inspection. EEG was filtered between 0.1 and 45 Hz and filtered data were referenced to the average of left and right mastoids. For the ERP analyses, we followed closely the procedures employed in a prior study investigating the ACOP component in sighted individuals (McDonald et al., 2013). Thus, the EEG analysis focused on the ERPs triggered by the task-irrelevant noise bursts. For each subject, a minimum of 166 stimuli per position (left and right) after artifact rejection was required.

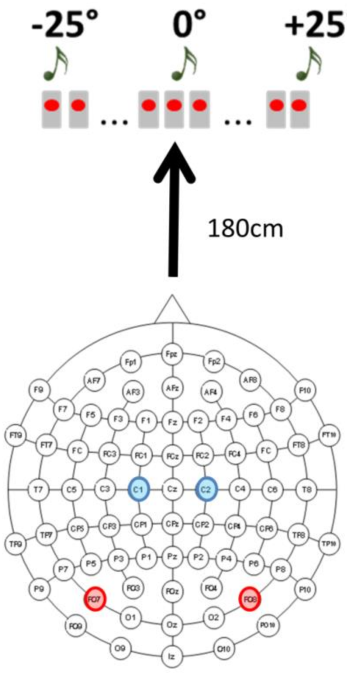

Figure 2.1 Experimental Setup and electrode montage.
Participants were blindfolded and sat in a silent room, 180 cm away from the center of an array of 23 speakers spanning ±25° of visual angle (with 0° representing the central speaker, negative values on the left, and positive values on the right). In the analysis, left (PO7) and right (PO8) parieto-occipital electrodes and left (C1) and right (C2) central electrodes were considered.

On average, there were 349 trials per subject across left and right sound trials. ERPs elicited by the left and right noise bursts were collapsed across sound position (left, right) and hemisphere of recording (left, right) to obtain ERP waveforms recorded on the hemisphere contralateral and on the hemisphere ipsilateral with respect to stimulus location. Lateralized ERP waveforms were calculated as the relative difference between the contralateral and ipsilateral responses. Based on previous literature (McDonald et al., 2013, Picton, 2010), we focused on two posterior electrode sites (PO7/PO8) for the ACOP analysis, and on two central electrode sites (C1/C2) to examine auditory processing. Mean ERP amplitudes at parietal-occipital electrode sides (PO7/PO8) were computed by averaging the voltage in a 250–500 ms time window after the onset of the peripheral sound. For each group, scalp topographies of mean ERP amplitude in the 250-500 ms time window were created separately for the left and right sounds (-25° and +25°), before averaging the two hemifield responses. The window was chosen based on previous literature (McDonald et al., 2013) in order to investigate the ACOP component in blind compare to sighted people.

To examine whether the ACOP was present in each group, the resulting mean amplitudes in the 250–500 ms time window were analyzed in an omnibus ANOVA with Group (S, EB) as a between-subjects factor, and Electrode site (Contralateral, Ipsilateral relative to the sound location) as a within-subjects factor. Planned pairwise comparisons were conducted with two-tailed t-tests to see whether the ACOP was reliably present in each group. As the ACOP is defined by the relative difference between the contralateral and ipsilateral activation, to investigate the difference between groups we also ran a two-tailed t-test on the lateralized mean amplitude difference at parietal-occipital electrode sides in the selected time window. In order to address any latency group differences, we computed the average onset, offset, and duration for contralateral and for ipsilateral electrodes and compared them between sighted and blind individuals. Specifically, for each subject, we independently considered the average ERP of contralateral and ipsilateral electrodes. We computed the mean and the SD of the ERP during the baseline. Then, for each time point within the 250-500 ms time window, we performed a Z-test to compare the ERP at that time with the baseline activity, applying FDR correction to p-values. We retained as onset of the component the first time within the 250-500 ms corresponding to a significant deflection from the baseline ($p< 0.05$ after FDR correction). Similarly, the offset was estimated as the latest time within the time window different from baseline. The duration was given by the difference between the offset and the onset of the deflection. Next, we compared the latency of onset and offset, considering the responses ipsilateral and contralateral relative to the sound location separately. Similarly, we also compared across groups the duration of the ipsilateral and contralateral waveforms. Furthermore, since the blind right and left visual cortices have shown different roles (e.g. with relation to language and memory processing in the left visual cortex), we checked for hemispheric effects in the blind group by analyzing ERP elicited at parietal-occipital electrode sides (PO7/PO8) by the left (-25°) and right sounds (+25°) separately. Thus, we performed paired t-tests to compare the ERP mean amplitude in the ACOP time window between PO7 and PO8 when they were ipsilateral relative to the stimulus position in space, and between PO7 and PO8 when they were contralateral relative to the stimulus position in space. We similarly compared the ACOP (contralateral-ipsilateral) elicited when the stimulus was delivered from the left, with the ACOP (contralateral-ipsilateral) elicited when the stimulus was delivered from the right. For the blind group, we also investigated whether the ACOP amplitude was influenced by blindness duration through correlational analyses (since they were early blind subjects blindness duration coincided with chronological age). Moreover, a two-tailed t-test with group (S, EB) as a between-subjects variable was conducted to compare RT between sighted and blind people. To exclude the presence of confounding effects due to eye-movement, we also performed t-tests to test whether the mean response of the eye deviation measured by EOG significantly differs from zero within each group, and whether it differs across groups. The irrelevance of eye-movement is evident in plots showing the amplitude of ocular movements calculated as the difference between the left and the right EOG for blind and sighted subjects.

Results

The EEG analysis focused on the ERPs triggered by the task-irrelevant noise bursts in order to investigate the ACOP component in early blind and sighted participants. ERPs elicited by noise bursts at central (C1/C2) and parieto-occipital (PO7/PO8) electrodes of early blind and sighted subjects are reported in Figure 2.2 and Figure 2.3 respectively.

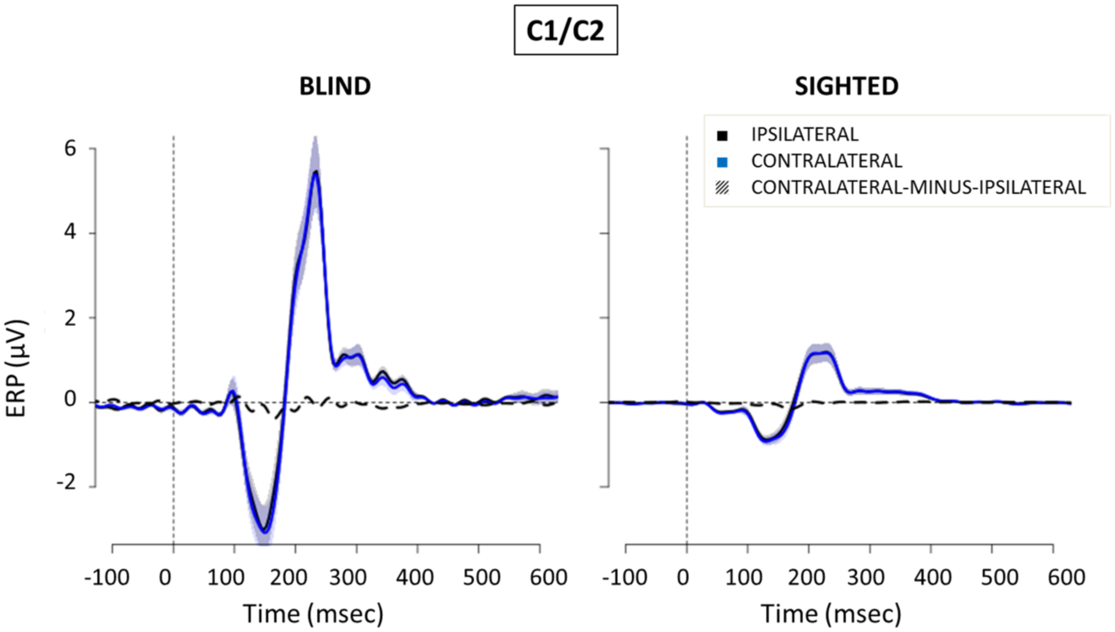

Figure 2.2 ERPs (mean±SEM) elicited by peripheral noise bursts at central (C1/C2) electrodes in blind (left) and sighted (right) subjects.
In blue, ERPs collapsed over central scalp sites contralateral to the side of the stimulus presentation. In black, ERPs collapsed central scalp sites ipsilateral to the side of the stimulus presentation. Dashed line, contralateral minus ipsilateral difference amplitude. On the x-axis, 0 is sound onset.

Several typical auditory ERP components were observed in the initial 200 ms following cue onset in central area (Fig. 2.2), including the N1 (110–140 ms) and a slightly later P2 (210–250 ms) over bilateral scalp regions. These negative ERP components reflect modality-specific sensory processing within the auditory cortex (Picton, 2010) and, as expected (e.g. Roder et al., 2007), are enhanced in blind compared to sighted individuals. With regards to the posterior scalp regions (see Fig. 2.3), the earlier components are still more pronounced in blind than in sighted individuals, in line with previous literature reporting a posterior shift in the scalp topography of the auditory ERP responses following blindness (Roder et al., 1999, Kujala et al., 1992, Rosler et al., 1993). For both groups, in the initial 200 ms following sound onset no differences emerged between the ERP waveforms recorded over the posterior sites contralateral and ipsilateral to the auditory cue. However, for both sighted and blind participants a stronger activation in contralateral compared to ipsilateral scalp sites appeared between 250 and 500 ms, as evident from the timing and amplitude of difference waveform created by subtracting the ERP recorded ipsilaterally from those recorded contralaterally (Fig. 2.3, dashed line).

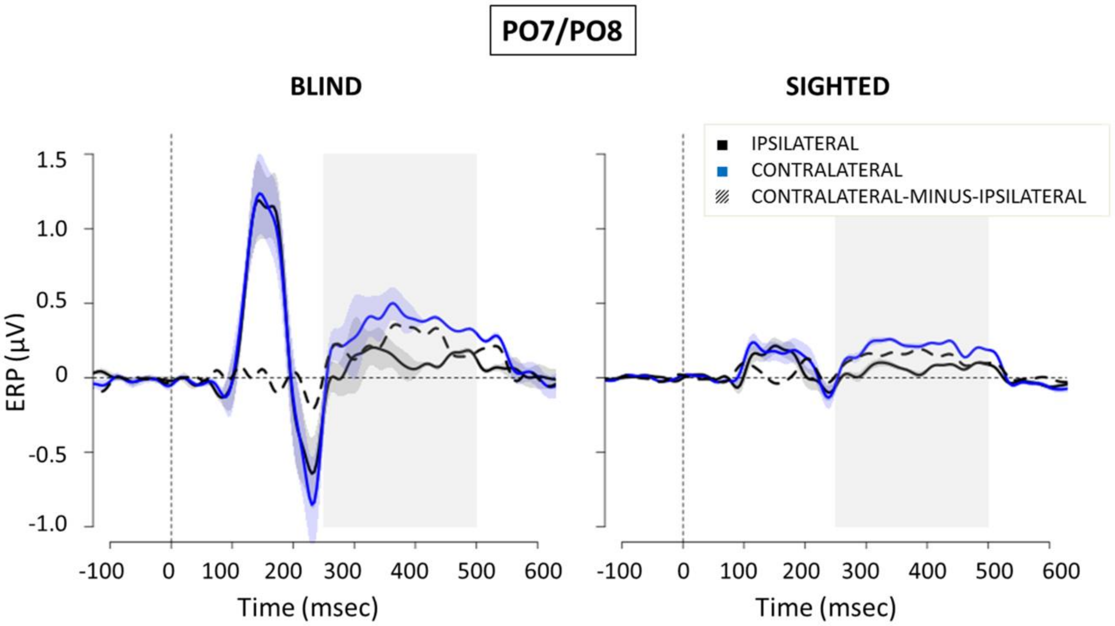

Figure 2.3 ERPs (mean±SEM) elicited by peripheral noise bursts at parieto-occipital (PO7/PO8) electrodes in blind (left) and sighted (right) subjects.
In blue, ERPs collapsed over parieto-occipital scalp sites contralateral to the side of the stimulus presentation. In black, ERPs collapsed over parieto-occipital scalp sites ipsilateral to the side of the stimulus presentation. Dashed line, contralateral minus ipsilateral difference amplitude. The gray area indicates the time window of the ACOP (250-500 ms). On the x-axis, 0 is sound onset.

In Figure 2.4, we show the scalp maps of the mean ERP amplitude in 250-500 ms time window for blind (Fig.2.4 top) and sighted (Fig. 2.4 bottom) subjects, when noise bursts were presented from either the left (-25°; Fig. 4 left) or right (+25°; Fig. 2.4 right). The topographies of the mean ERP amplitude in the ACOP time window are shown before averaging the two hemifield responses.

Statistical analysis to investigate whether the ACOP was present in each group revealed a significant interaction (F(1,22)= 11.25, p= 0.002, Generalized Eta Squared - GES= 0.01) between Group (S, EB) and Electrode site (Contralateral, Ipsilateral relative to the sound location). Pairwise comparisons revealed a greater positivity over the contralateral relative to the ipsilateral posterior-occipital scalp in both sighted (t(11)= 19.85, p< 0.001, d= 3.02) and blind (t(11)= 8.54, p< 0.001, d= 0.82) groups. Thus, similar to sighted individuals, blind participants showed the presence of an ACOP, as noise bursts elicited a significant positive activation over contralateral relative to ipsilateral scalp sites with respect to the stimulus position in space. A planned pairwise comparison of the contralateral-minus-ipsilateral waveform in the same time window and sites revealed a larger amplitude difference in blind compared to the sighted (t(12.4)= 3.35, p= 0.005, d= 1.37; see Fig. 2.5), suggesting that the ACOP was more pronounced in visually impaired people. Although the GES of the omnibus ANOVA indicates a mild effect size, the Cohen's d for t-tests reveal a larger effect size. We checked whether the ACOP was stronger over one hemisphere, but did not observe differences between left and right electrode sites. In particular, the right and left hemisphere processed the noise bursts similarly from the left (i.e. -25°) and the right (i.e. +25°) side (t-test to compare PO7 with PO8 when they were ipsilateral relative to the stimulus position in space: t(11)= 1, p= 0.3; t-test to compare PO7 with PO8 when they were contralateral relative to the stimulus position in space: t(11)= 0.02, p= 0.98). Moreover, the ACOP elicited when the stimulus was delivered from the left was similar to the ACOP elicited when the stimulus was delivered from the right (t(11)= 0.05, p= 0.6).

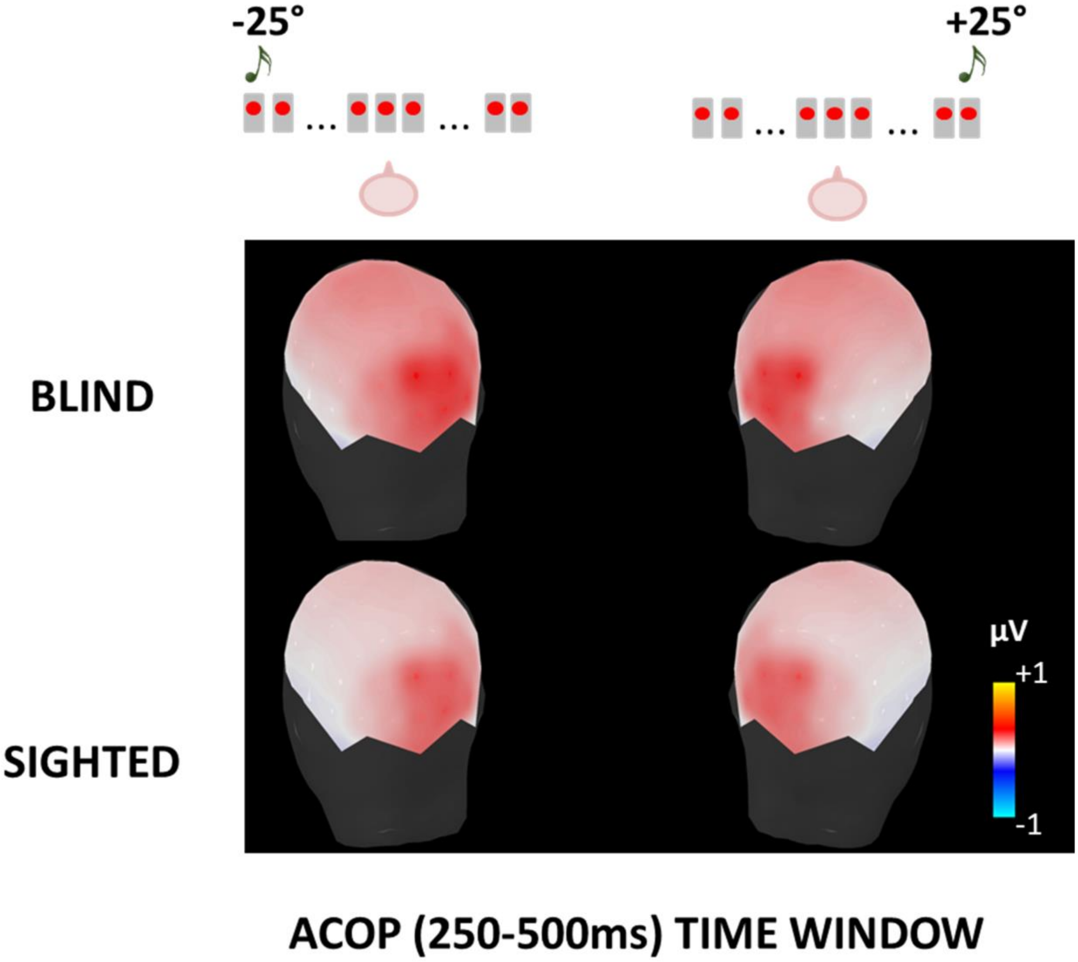

Figure 2.4 Scalp maps of the mean ERP amplitude in the selected time window (250-500 ms) after peripheral noise bursts, obtained before averaging the two hemifield responses.
The stimulus was presented in space from either - 25° (i.e. left side of the subject; see left panel) or +25° (i.e. left side of the subject; see right panel). First row represents blind subjects, second row represents sighted subjects.

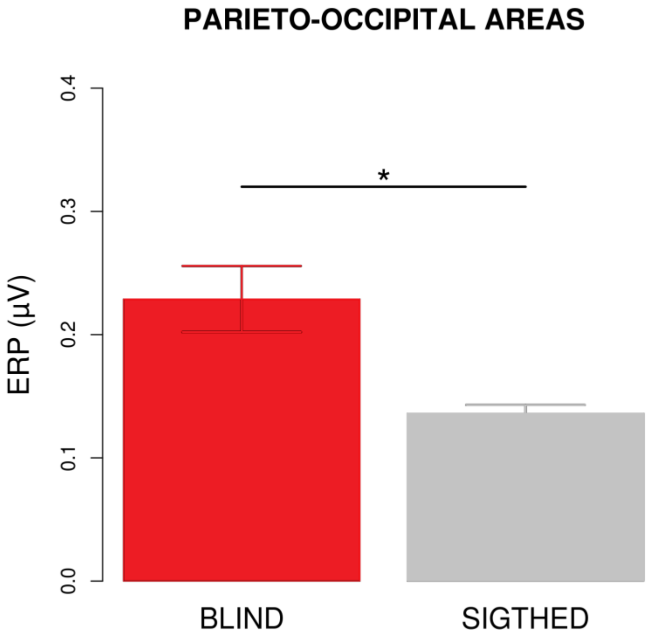

Figure 2.5 Lateralized (contralateral-minus-ipsilateral) ERP amplitude (mean±SEM) for blind (left) and sighted (right) group in the time window between 250-500 ms after peripheral noise bursts.
The star indicates a significant difference between the groups ($p<0.05$).

We did not find significant latency differences between groups, neither for the onset nor for the offset of the contralateral (onset: t(22)= 0.79, p= 0.4; offset: t(22)= -1.32, p= 0.2) and ipsilateral (onset: t(22)= 0.65, p= 0.5; offset: t(22)= -0.16, p= 0.9) waveforms within the ACOP time window. Also the duration of the ipsilateral and contralateral component within the selected time window did not differ across groups (for contralateral t(22)= -1.17, p= 0.3; for ipsilateral: t(22)= -0.67, p= 0.5). We can exclude that the effects originated from spurious eye-movement towards the apparent location of the stimulus (see Fig. 2.6). Indeed, the average response of the eye deviation measured by EOG is very low and did not significantly differ from zero neither for sighted (t(11)= 1.63, p= 0.1) nor for blind (t(11)= 1.04, p= 0.3) participants. Moreover, the average ocular deflection recorded by EOG is similar between blind and sighted (t(12.4)= 1.41, p= 0.2). Finally, no differences were observed for RTs comparing blind (mean RT= 344.6±92.8 ms) and sighted (mean RT= 348.2±53.1 ms) groups (t(17.5)= -0.12, p= 0.9). As regards the impact of blindness duration on the ACOP amplitude, there was no significant association between the two variables (r= -0.04, p= 0.9).

In Supplementary Materials of Amadeo et al. (2019d), we show the ERPs elicited by central targets at central (C1/C2; Supplementary Figure 1) and parieto-occipital (PO7/PO8; Supplementary Figure 2) electrodes for blind and sighted subjects. As expected for the processing of central sounds (e.g. Roder et al., 2007, Roder et al., 1999), there are no evident differences between the two groups at central scalp sites. However, the amplitude of the N1 elicited by central tones is higher than the amplitude of the same component elicited by unpredictable task-irrelevant noise bursts. This is also in lines with other research (Roder et al., 1999), showing that the N1 amplitude progressively decreases in response to sounds increasingly distant from the attended speaker.

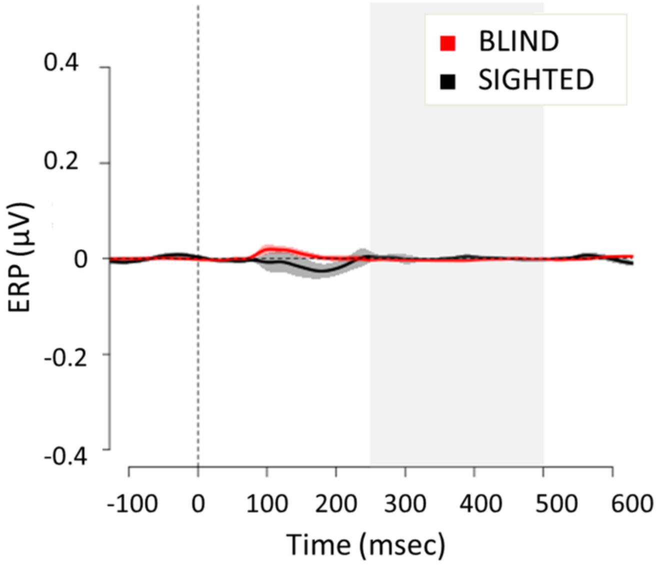

Figure 2.6 Mean (±SEM) amplitude of ocular movements calculated as the difference between the left and the right EOG for blind (red) and sighted (black) subjects.
On the left, average of trials in which the stimulus was delivered from -25° (i.e. from left); on the right, average of trials in which the stimulus was delivered from +25° (i.e. from right). On the x-axis, t = 0 is sound onset. The shaded area delimits the selected time window (250-500 ms).

Discussion of results

The present study examined whether the lateralized enhancement of visual cortex by peripheral sounds (i.e. the ACOP) previously observed in sighted individuals was also present in the congenitally blind. We revealed that the ACOP is evident, and even more pronounced, in blind people compared to the same response in sighted individuals. This finding suggests that the lateralized changes in visual activity are a supramodal signature of spatial orienting attention independently of audio-visual experiences.

The stronger visual response to auditory stimuli in blind is in agreement with other studies showing that compensatory mechanisms are triggered by visual deprivation, driving brain structures normally involved in the processing of visual information to be activated by other kind of sensory signals (see introduction of this Chapter). Specifically, the recruitment of ventral extrastriate occipital areas has been reported in congenitally blind people during auditory localization tasks (e.g. Weeks et al., 2000, Gougoux et al., 2005, Collignon et al., 2007), supporting the implication of these visual regions in spatial hearing following blindness. Thus, the higher activation in blind compared to sighted individuals may be explained by mechanisms of cross-modal plasticity that strengthen some multisensory neural connections which are present in sighted individuals as well. Previous research also showed a superior ability of blind people to localize sounds particularly when those occur in the periphery (Roder et al., 1999, Fieger et al., 2006, Lessard et al., 1998). Although previous studies investigated group differences in voluntary auditory attention, challenging a direct comparison with the current study in which participants were asked to ignore the peripheral sounds, we may suggest that any differences in sound processing between blind and sighted individuals are most strongly pronounced at peripheral visual field locations, both for voluntary and involuntary attention.

The results of this study provide other two important points of discussion which will be better addressed in the general discussion in Chapter 5. The first implication involves the cross-sensory interactions between vision and audition at cortical sites: the late auditory-induced supramodal activation of contralateral visual cortex does not require visual input to develop but is instead enhanced due to sensory impairment. Hence, multisensory interactions between the visual and auditory cortices do not necessarily depend on a lifelong multisensory experience. The second implication sheds light on the structural and functional organization of the visual cortex in blind people: this is the first time that a response selective to the spatial position of a sound is reported over visual cortex of blind individuals. Indeed, although the involvement of occipital cortical areas in purely auditory tasks is commonly reported in blind individuals (Burton, 2003, Amedi et al., 2007, Lane et al., 2015, Roder et al., 2002, Focker et al., 2012, Kujala et al., 1995), previous studies in blindness failed to show neural activity in visual cortex selective to the spatial position of sounds. One study (Thaler et al., 2011) reported a contralateral activation of the calcarine cortex in one blind echolocator but in response to sounds that contained both clicks and the returning echoes, with respect to control sounds that did not contain the echoes. The fact that the sound-induced activations over visual areas are spatially lateralized even in blind individuals suggests that the visual cortex is inherently organized retinotopically – at least at the level of the hemifield.

2.2 Exp. 2: Complex spatial representation in early blindness

Many works highlighted enhanced auditory processing in blind individuals, suggesting that they compensate for lack of vision with greater sensitivity of the other senses. However, this is not always true and the lack of visual experience affects the development of some auditory spatial skills. Few years ago, researchers demonstrated severely impaired auditory precision in early blind individuals performing an auditory spatial bisection task (Gori et al., 2014, Vercillo et al., 2016). Their thresholds for bisecting three consecutive, spatially separated sounds were seriously compromised, ranging from three times typical thresholds to total randomness. Contrary to works studying pitch and timbre discrimination (Gougoux et al., 2004, Doucet et al., 2005), or single sounds localization in space (Roder et al., 1999, Lessard et al., 1998), the bisection task requires relative comparisons of distances in space, taxing sophisticated and well-calibrated spatial auditory map of Euclidean relationships.

Sighted individuals, who succeed at the spatial bisection task, show a specific ERP response in occipital areas, likely involving the visual cortex (as estimated by source analysis), between 50-90 ms after the second of the three sounds of the task (Campus et al., 2017). The second sound can be considered the starting point for building a spatial metric. Interestingly, a similar activation is missing after the same acoustic stimuli during the temporal bisection task, which involves the evaluation of temporal intervals between three sounds. The early occipital response observed in sighted people results strong and contralateral to the spatial position of the second sound. Actually, the response of sighted individuals during auditory spatial bisection mimics many characteristics of the visual-evoked C1 ERP component (Di Russo et al., 2002). Indeed, i) it is in the same time window as visual C1, i.e. 50-90 ms, which represents also a key time window in the earliest stages of multisensory integration (Campus et al., 2017); ii) it appears in the same scalp areas, i.e. in occipital electrodes with generators likely involving visual cortices; iii) it is contralateral to the sound position in space, as would be expected for a visual stimulus. These findings suggest that the acoustic recruitment of the visual brain may be fundamental for auditory spatial bisection in sighted individuals, supporting a possible domain-specific supramodal organization of the visual brain. Starting from this, if visual regions have an important role for the auditory spatial bisection task in sighted people, one may expect that the deficit observed in blind individuals for this task (Gori et al., 2014) is related to a different processing of auditory spatial representations in these cortical regions. While neural correlates for auditory enhancement in blind individuals have been extensively explored, the neural correlates behind their auditory impairment during the spatial bisection task are still unknown. Here, we tested this hypothesis by studying the neural correlates associated with auditory spatial bisection skills in early blind individuals (see Campus et al., 2019). To this end, ERPs and psychophysical responses were recorded in sighted and early blind individuals during an auditory spatial bisection task.

Methods

Experimental procedure

A group of 16 early blind subjects (EB; mean age ± standard error of means - SEM= 42±15 yo; F=11) and a group of 16 sighted subjects (S; 42±16 yo; F=11) were recruited to participate in this study. Clinical details of blind participants are summarized in Table 2.2. All subjects reported normal hearing and no history of neurological, cognitive or other sensory-motor deficits except for total blindness. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Participants provided written informed consent prior to testing.

PARTICIPANT	AGE AT TEST	GENDER	PATHOLOGY	AGE COMPLETE BLINDNESS
S1	38	M	Retinopathy of Prematurity	Birth
S2	25	F	Retinopathy of Prematurity	Birth
S3	49	M	Retinopathy of Prematurity	Birth
S4	20	F	Congenital Glaucoma	Birth
S5	72	F	Depth damage of vision in both eyes	Birth
S6	52	F	Atrophy of the eyeball	Birth
S7	38	F	Retinopathy of Prematurity	Birth
S8	26	F	Retinitis pigmentosa	Birth
S9	55	M	Uveitis	Birth
S10	28	F	Retinopathy of Prematurity	Birth
S11	22	F	Congenital Glaucoma	Birth
S12	60	F	Atrophy of the eyeball	Birth
S13	56	M	Congenital glaucoma	Birth
S14	38	F	Congenital cataracts and malformation of the lens	Birth
S15	55	M	Retrolental fibroplasia	Birth
S16	48	F	Retinitis pigmentosa	Birth

Table 2.2 Clinical details of early blind participants (N= 16).
The table shows age at test, gender, pathology, and age since subjects became completely blind.

Participants sat in a silent room, 180 cm away from the center of an array of 23 speakers spanning ±25° of visual angle (with 0° representing the central speaker, negative values on the left, and positive values on the right; Fig. 2.7A). For each trial, three short sounds (namely S1, S2, S3; 500 Hz, 75 ms duration, 60 dB Sound Pressure Level (SPL)) were delivered at three different spatial positions and timings (Fig. 2.8). The first (S1) and third sound (S3) were always delivered at -25° (i.e. left) and +25° (i.e. right) degrees respectively, with temporal separation fixed at 1.5 seconds. The second sound (S2) could occur randomly and independently from either -4.50° or 4.50° in space (Fig. 2.8A), and at either -250 ms or +250 ms in time from the middle of the temporal sound sequence (Fig. 2.8B). These values correspond to approximately 75% of correct answers for spatial and temporal bisection thresholds in sighted people; they have been evaluated in a preliminary session on 5 sighted subjects. To avoid stereotypical responses, S2 was also presented at 0° and at 0 ms during catch trials. Inter-trial interval was 1250±250 ms.

Subjects performed a spatial bisection task, and a temporal bisection task as control, in two distinct randomized blocks. In one block, they judged whether the distance between S1-S2 was smaller or larger than the distance between S2-S3 in the spatial domain, referred as “narrow” and “wide” respectively (i.e. spatial bisection). In the other block, they were asked whether the interval between S1-S2 was smaller or larger than the interval between S2-S3 in the temporal domain, referred as “short” and “long” respectively (i.e. temporal bisection). Stimuli were identical in blocks, with S2 varying randomly and independently both its spatial position (±4.5°) and its temporal delay (±250 ms). Hence, the only difference between blocks fell on the question, which required subjects the construction of either a spatial or a temporal representation. Blocks consisted of 120 trials for each condition (small first interval, large first interval), and there were 15 catch trials. In the spatial bisection task, narrow/wide first interval corresponds to S2 delivered from the left (-4.5°) or right (+4.5°) side of the subject respectively. Temporal separation between sounds was large enough to allow a complete decay of the ERP response. To avoid possible spurious neural responses, subjects were asked to answer using a pushbutton immediately after S3. We measured execution times (i.e. the time between S3 and button press), and subject performance (i.e. the percentage of correct responses). Subjects were warned to maintain a stable head position while fixating straight ahead. Their position, as well as their head orientation and EOG signal, were continuously monitored during the test by the experimenters. In fact, during the experiment, EEG and EOG were acquired using Biosemi Active Two EEG System following the same procedure applied in the study described in Section 2.1 (see Methods). EEG was filtered between 0.1 and 100 Hz. Stereotypical (e.g. eye blinks) and non-stereotypical (e.g. movement, muscle bursts) transient high-amplitude artifacts were removed using an automated artifact rejection method named Artifact Subspace Reconstruction (ASR), which is available as a plug-in for EEGLAB software (Delorme and Makeig, 2004, Mullen et al., 2013).

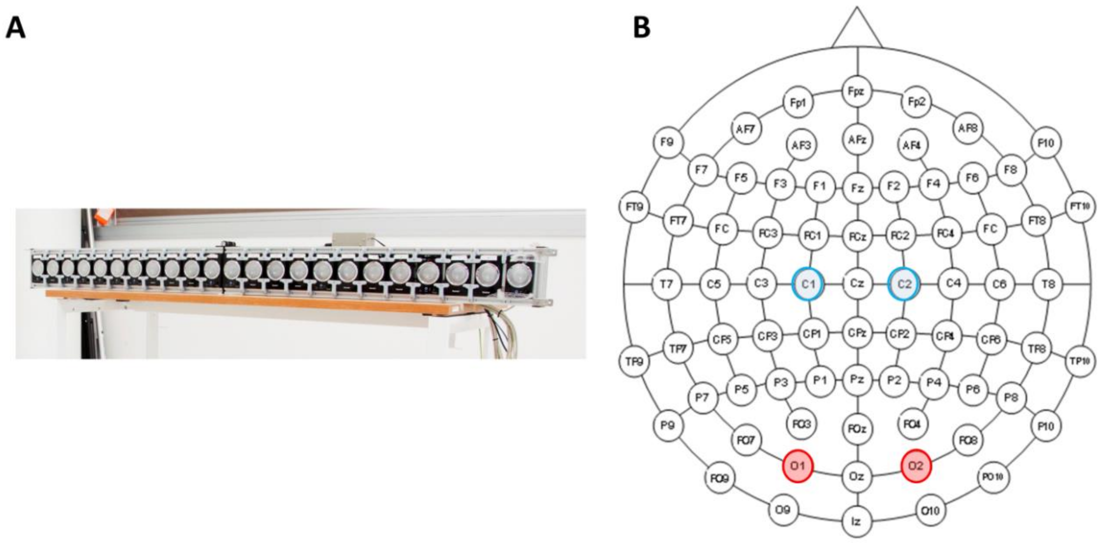

Figure 2.7 Setup (A) and EEG montage (B) for auditory spatial and temporal bisection.
(A) Subjects listened to a sequence of three stimuli (S1, S2, S3) delivered from the lower visual hemifield and judged whether the distance/interval between S1-S2 was smaller or larger than the distance/interval between S2-S3, either in space (i.e. spatial bisection) or time (i.e. temporal bisection) domain. (B) Electrode montage for EEG recording and electrodes considered in EEG data analysis. In blue, left (C1) and right (C2) central electrodes; in red, left (O1) and right (O2) occipital electrodes.

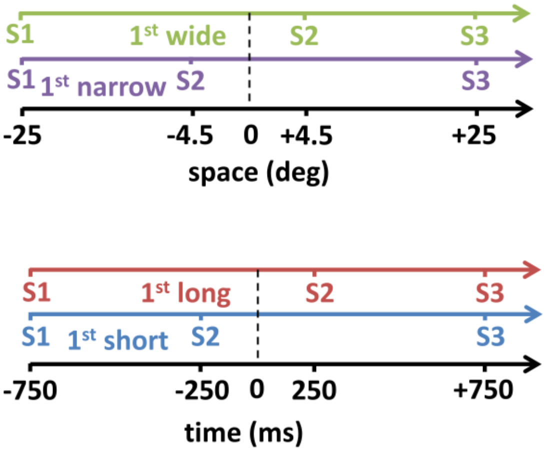

Figure 2.8 Experimental protocol for spatial and temporal bisection tasks.
For each trial, S1 and S3 were delivered from -25° and +25° in space respectively, with 0° representing the central speaker, negative values on the left and positive values on the right **(a)**. S2 could occur randomly and independently from ±4.5° in space **(a)** and at ±250 ms in time **(b)** with respect to the physical spatial and temporal midpoints (dashed vertical line: 0° and 0 ms). To avoid stereotypical subject responses, S2 was also presented at 0° and at 0 ms during catch trials.

ASR uses a sliding window technique whereby each window of EEG data is decomposed via principal component analysis and is compared statistically with data from a clean baseline EEG recording. Within each sliding window, the ASR algorithm identifies principal subspaces which significantly deviate from the baseline and then reconstructs these subspaces using a mixing matrix computed from the baseline EEG recording. In this study, we used a sliding window of 500 ms and a threshold of 3 standard deviations to identify corrupted subspaces. Moreover, channels were removed if their correlation with other channels was inferior to 0.85, or if their line noise relative to signal was more than 4 standard deviations from the channel population mean. Time windows were removed when, after the application of the previously described criteria, the fraction of contaminated channels exceeded the threshold of 0.25. Other parameters were kept as default. EEG data were further cleaned using Independent Component Analysis (Delorme and Makeig, 2004). Specifically, two EEGLAB toolboxes were used, namely SASICA (Chaumon et al., 2015) and IC_MARC (Frolich et al., 2015), keeping all parameters as their default. For component rejection, criteria reported in the corresponding validation papers were followed, mainly based on abnormal topographies and/or spectra. In addition, data were referenced to the average of left and right mastoids.

Sensor level analysis

The ERP analyses followed closely the procedures employed in a prior study investigating complex auditory spatial representation in sighted participants (Campus et al., 2017), based on the hypothesis that early blindness could drive to different early cortical responses during the spatial bisection task, in particular after S2. Thus, as in previous work, the present study focused on neural responses to S1 and S2, for the spatial and temporal bisection tasks. In fact, S2 represents the starting point for the development of a metric, whereas S1 can be considered as a control. Neural responses to the S3 were not taken into account since the last sound could involve more complex mechanisms related to the metric definition, and it could be compromised by behavioral answers.

EEG data were averaged in synchrony with S1 or S2 onsets to compute ERPs, considering a period of 200 ms before S1 onset as a baseline for both sounds. For each condition of the two bisection tasks, a minimum of 40 trials after artifact rejection was required. The total number of trials was around 855 for each condition, approximately 55 per subject; catch trials were not considered. Both correct and incorrect trials were analyzed for two reasons. Firstly, to increase statistical power. Secondly, to investigate the relationship between cortical activation and given response, which reflects the perceived extension of the first interval independently of its real physical extension. Based on our hypothesis (Campus et al., 2017), we focused on electrodes linked to visual and auditory processing (O1 and O2 in occipital areas, C1 and C2 in central areas; Fig. 2.7B) and on a time window between 50 and 90 ms after each sound. Mean ERP amplitude was computed by averaging the voltage in the selected time window. Scalp topographies of mean ERP amplitude in the 50-90 ms time window were realized for each condition (small first interval, large first interval) of space and time bisection tasks.

For statistical comparisons, ANOVA was run considering as factors Sound (S1, S2), Task (Space, Time), Hemisphere (Left, Right), First distance/interval extension (Narrow/Short, Wide/Long), and Group (EB, S). Paired two-tailed t-tests were conducted as post-hoc comparisons with probabilities treated as significant when lower than 0.05 after Bonferroni correction, applied to each subset of post-hoc comparisons separately. The association between individual performance and ERP was addressed with linear regression of individual mean ERP amplitude in the selected time window against the percentage of trials in which each subject perceived the first distance/interval as wider/longer.

Source level analysis

To investigate the cortical generators of the ERP components influenced by the experimental factors, a distributed sources analysis was performed with the Brainstorm software (Tadel et al., 2011), following the same procedure described in previous study involving sighted individuals (Campus et al., 2017). We used standard 1 mm resolution brain of the Montreal Neurological Institute (non-linear average of 152 subjects, processed with FreeSurfer 5.3 ICBM152; Fonov et al., 2009), we performed forward modeling using three-layer (head, outer and inner skull) symmetric boundary element model (BEM) generated with OpenMEEG (Gramfort et al., 2011), and we estimated source intensities using sLORETA approach (Pascual-Marqui, 2002). Since individual MRIs were not available, the Brainstorm output using a constrained approach could be unrealistically precise (in terms of visualization). Therefore, to avoid misleading over-interpretation, dipole orientations were let free to assume whichever (unconstrained) orientation instead of fixed them to the cortex surface. We averaged source activation for each subject of the two groups and condition within the selected time windows. Subsequently, we estimated the norm of the vectorial sum of the three orientations at each vertex. In the end, pairwise comparisons were investigated with paired t-test, correcting results for multiple comparisons of source grid points with FDR method (Benjamini and Hochberg, 1995), using p= 0.0001 as a threshold. To verify the specificity of the activation after S2 in the spatial bisection task, we compared sighted with early blind group considering the tasks (space and time) and the sounds (S1 and S2) separately.

Results

First of all, we confirmed the previous psychophysical studies (Gori et al., 2014, Vercillo et al., 2016) showing a deficit in early blind individuals in performing a spatial bisection task. Compared with sighted (S), early blind (EB) participants showed (mean±SEM) lower probability of correct response (EB= 65.6±1.9, S= 88.5±2.2, t(15)= -11.32, p< 0.001) and similar execution times (t(15)= 1.38, p= 0.19). The deficit was not present in the temporal bisection task, for which the probability of correct response (t(15)= -0.29, p= 0.77) and execution times (t(15)= 0.02, p= 0.99) were not significantly different between the two groups.

More importantly, a first omnibus ANOVA on the mean ERP amplitude in the 50-90 ms time window showed a strong interaction between Sound (S1, S2), Task (Space, Time), Hemisphere (Left, Right), First distance/interval extension (Narrow/Short, Wide/Long) and Group (EB, S; F(1,30)= 33.11, p< 0.001, GES= 0.51). We subsequently performed hypothesis-driven follow-up ANOVAs and post hoc comparisons. First, we hypothesized that S2 could specifically modulate the interaction between other factors. Therefore, we performed two separate ANOVAs (one for each sound), with Task, Hemisphere and First distance/interval extension as within subject factors, and Group as between subject factor. As expected, we found a significant interaction between Task, Hemisphere, First distance/interval extension and Group for S2 (F(1,30)= 35.04, p< 0.001, GES= 0.43). On the contrary, for S1 we found only an expected main effect of the Hemisphere, given that S1 way always played from the left (-25°; F(1,30)= 4.75, p= 0.03, GES= 0.19). Thus, we focused analyses on S2, separately evaluating the two Tasks (Space, Time). Therefore we performed two separate ANOVAs (one for Space, the other for Time), with Hemisphere and First distance/interval extension as within subject factors, and Group as between subject factor. For the spatial domain, we found a significant interaction between Hemisphere, First distance/interval extension and Group (F(1,30)= 37.21, p< 0.001, GES= 0.43), while for the temporal domain we did not find any significant interaction (F(1,30)= 0.18, p= 0.67, GES= 0.001). Post-hoc analyses involved only S2 in the spatial domain, revealing a stronger lateralized early activation in sighted compared to early blind subjects.

Figure 2.9 illustrates the scalp maps elicited by S2 delivered from -4.5° (left panel) and +4.5° (right panel) in the 50-90 ms time window during the spatial bisection task, for sighted (Fig. 2.9A) and early blind participants (Fig. 2.9B). Positivity is evident in occipital areas for both groups. However, we can observe that in visually deprived individuals the occipital positivity resulted attenuated in sites contralateral with respect to the S2 position in space and increased in ipsilateral ones. Specifically, when the first distance was narrow (S2 delivered from left, -4.5°), the contralateral electrode O2 showed a strongly higher response in sighted individuals (t(30)= 6.21, p< 0.001), while the ipsilateral electrode O1 showed a moderately higher response in early blind individuals (t(30)= 3.82, p< 0.001). Symmetrically, when the first distance was wide (S2 from right, +4.5°) the contralateral electrode O1 showed a strongly higher response in sighted subjects (t(30)= 6.96, p< 0.001), while the ipsilateral electrode O2 showed a moderately higher response in early blind subjects (t(30)= 3.70, p< 0.001). As expected (Campus et al., 2017), only the spatial but not the temporal bisection task elicited the specific early occipital response. Moreover, any specific early occipital response to S1 appeared neither for sighted nor for early blind subjects (see Fig. 2.10A), independently of the task domain. Interestingly, for both sighted and early blind subjects we found a later response (P140), selective again for S2 during the spatial bisection task but without any lateralization effects (See Fig. 2.10B). P140 was more pronounced in sighted subjects, probably reflecting a stronger activation of an extended dorsal stream.

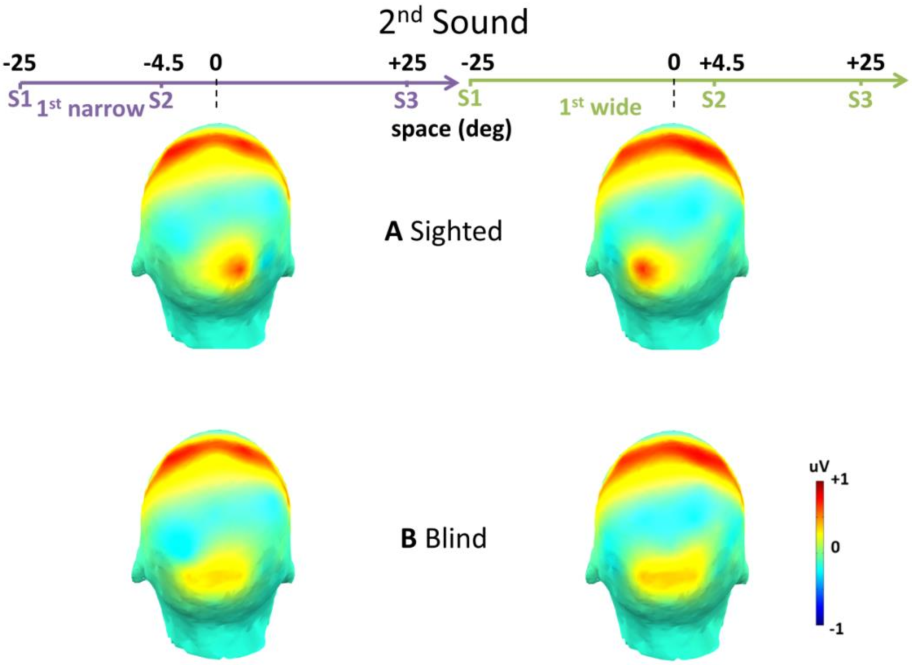

Figure 2.9 Scalp maps of the mean ERP amplitude in the selected time window (50-90 ms) after the second sound of the spatial bisection task, for sighted (A) and early blind (B) groups. Left and right panels of the figure report the conditions in which S2 was presented from either left (i.e. -4.5°, narrow first distance) or right (i.e. +4.5°, wide first distance), respectively, independently of timing (±250 ms). The positivity involving parieto-occipital areas showed a specific contralaterality only in sighted subjects (**A**). In blind participants (**B**), the parieto-occipital response was strongly attenuated and not contralateral to S2 spatial position.

The time window considered in the analyses was the first one presenting a task-related modulation, while a later activation seems to occur, more pronounced and lateralized in sighted individuals, and lower and not lateralized in early blind participants.

To verify that the early evoked response is associated with the perceived position of S2 rather than with its physical location, for each physical extension of the first distance/interval (narrow/short, wide/long) we correlated individual ERP responses recorded in O1 and O2 with the individual percentage of trials in which the first distance/interval was perceived as wider/longer (Fig. 2.11). As shown in Figure 2.11A, for sighted subjects the ERP amplitude in O1 and O2 was significantly associated with subject performance in the space but not the temporal bisection task. Specifically, the percentage of trials in which participants reported the first distance as narrow (i.e. S2 perceived as delivered from the left) and wide (i.e. S2 perceived as delivered from the right) correlates with the ERP amplitude in the occipital contralateral electrodes, O1 and O2 respectively (for O1 and wide first distance $r= 0.9$, $p< 0.001$, for O2 and narrow first distance $r= -0.89$, $p< 0.001$). Instead, early blind subjects did not show any similar correlation, during neither the spatial nor the temporal bisection task.

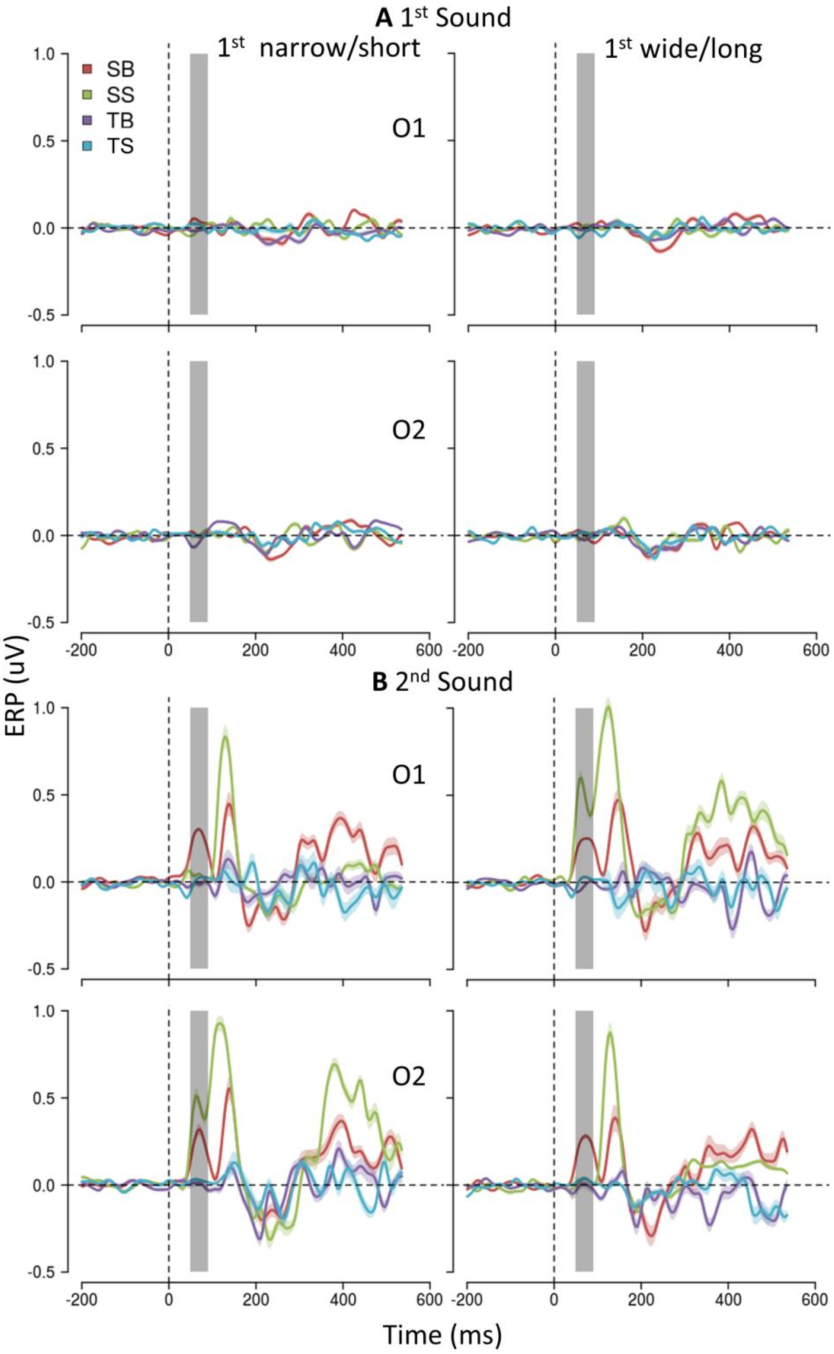

Figure 2.10 Modulation of the occipital ERP response due to S2 physical position during spatial and temporal bisection tasks.

ERPs (mean±SEM) in O1 (first row) and in O2 (second row) after S1 **(A)** and S2 **(B)** are reported separately for each group and task (Space bisection in Blind: SB, Space bisection in Sighted: SS, Time bisection in Blind: TB, Time bisection in Sighted: TS).On the left, trials in which S2 was delivered from the left hemispace (spatial bisection), or with shorter temporal separation from S1 (temporal bisection), giving rise to a narrow first distance/short first interval. On the right, trials in which S2 was delivered from the right hemispace (spatial bisection), or with longer temporal separation from S1 (temporal bisection), given rise to a wide first distance/long first interval. On the x-axis, t= 0 is sound onset. Shaded areas delimit 50–90 ms time window.

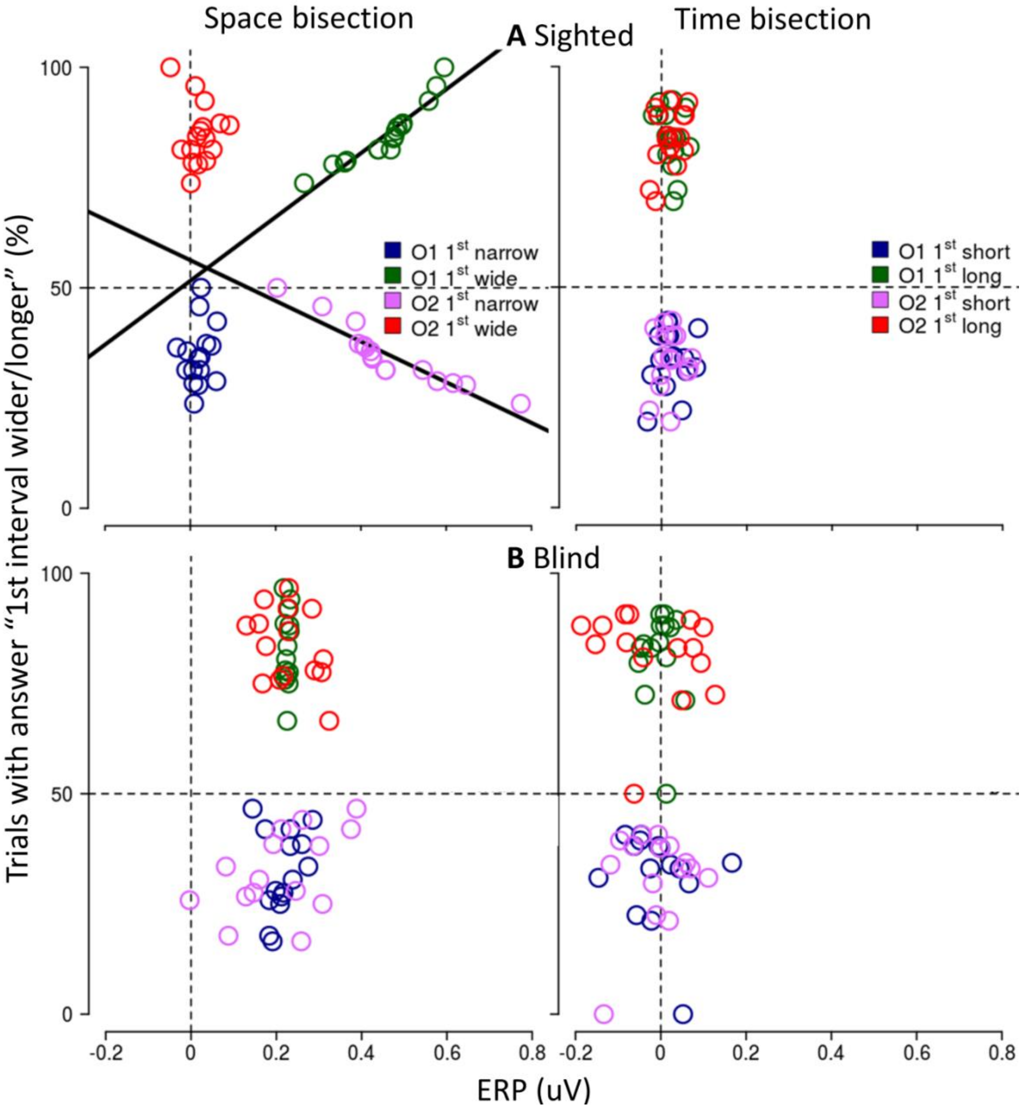

Figure 2.11 Correlation between the perceived localization of S2 and mean ERP amplitude in the selected time window after S2, evaluated for sighted (A) and blind (B) group separately. We separately consider the conditions in which the first distance/interval was physically narrow/short and wide/long (respectively, narrow/wide for spatial bisection, see left panel; short/long for temporal bisection, see right panel). For each condition and each subject, individual mean ERP amplitude in O1 (blue and green) and O2 (red and pink) is plotted against the percentage of trial in which the subject perceived the first distance/interval as wider/longer, i.e. wider in the spatial bisection task and longer in the temporal bisection task. In spatial bisection, perceiving narrower and wider first distance corresponded to perceiving S2 delivered from left and right side respectively. Black regression lines represent significant correlations. Sighted subjects (**A**) show a specific correlation between perceived localization of S2 during the spatial bisection task and ERP response in contralateral occipital electrodes.

According to our data, the effect did not originate from eye-movements towards the apparent sound position. Indeed, the average ocular deflection recorded by electrooculography (EOG) is equal and not different from zero when grouping according to the position of S1 or S2, for both physical (for the lowest p-value, S: t(15)= 0.62, p= 0.54, EB: t(15)= 0.82, p= 0.42) and perceived distance/intervals (for the lowest p-value, S: t(15)= 0.72, p= 0.48, EB: t(15)= 1.11, p= 0.29).

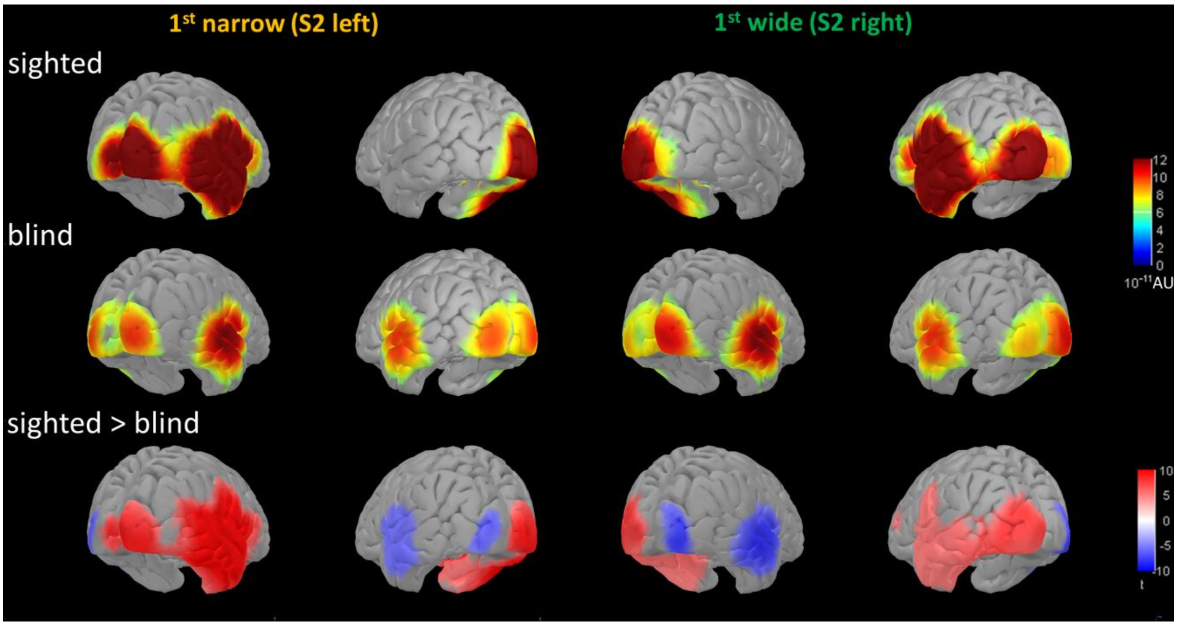

Figure 2.12 Average source activity within the 50–90 ms time window after S2 is compared between sighted and blind subjects.
Left and right panels of the figure respectively report the conditions in which the first distance was narrow (i.e. S2 from left) or wide (i.e. S2 from right). The first two lines represent average normalized source activation for sighted (first row) and blind subjects (second row), in arbitrary (normalized) units (AU). Last line reports the results of paired two tailed t-tests; the scale is in terms of t-statistic. Significant values of t-statistic are displayed: reddish and bluish colors indicate stronger activations in sighted and blind subjects respectively, while the intensity indicates the magnitude of t (i.e. the streght/significance of the difference). Only t-values corresponding to p< 0.0001 after FDR correction are displayed. An early activation of visual regions contralateral to sound spatial position is elicited by S2 during spatial bisection in sighted subjects, while it is more attenuated and ipsilateral in blind individuals.

To test that the response of interest was actually involving generators in visual cortex, we compared the two groups at source level. Only after S2 in the spatial bisection task do we observe significant differences, which are shown in Figure 2.12. Left and right parts of the figure report the conditions in which the first distance was narrow (S2 from the left) or wide (S2 from the right) respectively. The first two rows display average normalized source activation of sighted subjects (first row) and early blind subjects (second row). The last row shows the result of the t-test comparing groups, displaying signed values of t-statistic: reddish and bluish colors mean stronger activations in sighted and early blind subjects respectively, while the intensity of the color indicates the significance (strength) of the difference. To minimize the risk of false positives, exclusively t-values corresponding to $p< 0.0001$ post FDR correction are considered significant and represented. Thus, comparing groups in the 50-90 time window during spatial bisection, sighted subjects showed a stronger occipital and temporal activation contralateral to the spatial position of the sound, while early blind subjects exhibited a reduced activation in contralateral cortical areas and an increased activation in ipsilateral cortical areas. These differences between groups were absent after S1 in spatial bisection task, when both groups showed only a similar activation of temporal cortex contralateral to the sound. Similarly, no differences emerged between the two groups considering either S1 or S2 in the temporal bisection task. For more details see Supplementary Materials in Campus et al. (2019).

Discussion of results

This experiment investigated the neural correlates of the deficit in complex spatial representation previously observed in blind people with psychophysical methods (Gori et al., 2014). In sighted people, the construction of spatial representation necessary for spatial bisection task elicits early activation of contralateral occipital areas, likely involving visual cortices (Campus et al., 2017). In this work, we showed that the response of occipital cortices during auditory spatial bisection is different for early blind individuals. Compared to sighted people, they exhibit a reduced activation in contralateral cortical areas, and an increased activation in ipsilateral cortical areas.

The fact that in early blind individuals the laterality is absent seems to indicate that early visual experience mediates the development of the contralateral early occipital response observed in sighted people. Thus, visual modality may have a key role in developing an early occipital response specific for complex auditory spatial representation. Results are in agreement with previous behavioral studies (Gori et al., 2014, Vercillo et al., 2016), and reveal that the neural correlates of the spatial bisection deficit reported in blind individuals might correspond to the reduction of the early occipital contralateral activation. In sighted subjects, the early acoustic recruitment of the visual brain may be necessary to build a spatial representation of the environment with the high resolution and flexibility that only the visual brain is capable of implementing. Lack of vision seems to impact on this process and underlying neural circuits, bringing to impairment in understanding Euclidean relationships, such as those involved in solving a spatial bisection task. Blind individuals may rely on later visual processing stages to drive spatial information. The link between the early cortical activation and spatial bisection abilities is further confirmed by the fact that in sighted but not in blind people we observed a strong correlation between behavioral performance at the spatial task and the amplitude of the early ERP response in contralateral occipital areas.

We think that our results do not reflect a specific deficit at central auditory location or effects due to enhanced peripheral auditory processing in blind individuals (Roder et al., 1999). It has been previously showed (Gori et al., 2014) that blind people can locate single sounds acoustically identical to the second sound similarly to sighted people, even for angles as small as those used in this study (±4.5°). These previous results suggest that blind people could overall direct selective attention to the spatial positions of the sounds but are not able to specifically relate and compare the different spatial. Thus, our effect does not originate simply from different auditory attentional skills to left or right positions of sounds, or from different auditory attentional skills between sighted and blind individuals. In fact, we found a contralateral activation in temporal electrodes and auditory cortices as expected for the processing of auditory stimuli (Naatanen and Picton, 1987, Campus et al., 2017) in both groups, but a contralaterality in occipital cortex was observed specifically in sighted individuals. Similarly, attention to space can be expected to weakly affect early ERPs, such as the observed occipital response and the N1 (Roder et al., 1999, Lange et al., 2006). Moreover, our data do not reflect a mere indirect auditory activation mediated by the acoustic thalamus specific for sighted individuals (Komura et al., 2005): during the temporal bisection task we did not find any strong early occipital responses in both sighted and blind participants. Moreover, behavioral performance indicates that there was no deficit in memory per se in the group of early blind individuals: there was no difference in performance and execution times between sighted and early blind participants for the temporal bisection task.

To conclude, our data suggest a key role of visual experience in complex spatial representation within the auditory modality, suggesting that domain-specific supramodal organization of the visual brain can be in some cases dependent on sensory experience. Based on the results of this study, we can speculate that cortical activation underlying the C1 ERP component plays a fundamental role in the construction of complex representation in the spatial domain, independently of the involved sensory modality, but this mechanism depends on visual experience. By showing that the impairment in building complex spatial representation following blindness is likely due to a weaker and not lateralized activation of the occipital cortices, Chapter 2 also increases knowledge about underlying neural processes involved in spatial deficits caused by visual loss.

2.3 Exp. 3: Complex spatial representation in late blindness

Early visual deprivation infers with some complex auditory spatial skills and neural correlate (Section 2.2). We are left with a question as to what happens when blindness occurs later in life. Since late blind individuals experienced both visual exposure and deprivation, investigating their skills and underlying neural activations gives important information about the relationship between vision and auditory spatial perception in humans. In the light of the background illustrated in the introduction of this Chapter, conclusions about spatial abilities and cross-modal plasticity in late blind population are hard to derive. In this study, we explored auditory spatial skills and neural correlates in a group of late blind participants in order to shed light on this research topic, and better disentangle the role of visual experience and deprivation on some spatial skills (see Amadeo et al., 2019a). Specifically, we tested their abilities to compute a spatial bisection task, for which we previously showed a behavioral impairment in early blind subjects, likely due to an attenuated lateralized early occipital response. Indeed, we demonstrated that the construction of complex spatial representation required by the spatial bisection task elicits in sighted but not early blind people an early response of the occipital cortex, which mimics many aspects of the visual-evoked C1 (Campus et al., 2017). Thus, in this work ERPs and psychophysical responses were recorded during spatial bisection tasks in sighted and late blind individuals, replicating the experiment performed with early blind people and described in Section 2.2. Since we showed that vision is fundamental for the spatial bisection task and late blind individuals have been able to see during the first years of life, we expected late blind participants with short blindness duration to be similar to sighted subjects. Hence, we expected them to show the contralateral occipital activation between 50 and 90 ms after the second sound of the spatial bisection and a good performance. On the other hand, the brain is highly plastic and we hypothesized that prolonged sensory deprivation could gradually affect neural circuits related to the construction of a complex spatial representation, driving to a weaker lateralized occipital activation and a consequent decrease in performance. This experiment allowed us to investigate the extent to which late blindness affects the cortical activation of visual areas supposed to modulate complex spatial representation, adding an interesting new perspective about the role of blindness duration.

Methods

Experimental procedure

For this study we recruited 12 late-onset blind (LB) subjects aged between 26 and 68 (mean age±SD: 50±16 yo; F= 3) and 12 age-matched (t(21.5)= -0.33, p= 0.7) sighted (S) subjects (49±14 yo; F= 7). The onset of blindness ranged from 6 to 51 years (24.75±15.82

yo), whereas duration of blindness ranged from 5 to 54 years (25.5±15.29 years). Clinical details of LB participants are summarized in Table 2.3. All subjects reported normal hearing and no history of neurological, cognitive or other sensory-motor deficits except for total blindness. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Participants provided written informed consent prior to testing.

PARTICIPANT	AGE	GENDER	PATHOLOGY	BLINDNESS ONSET	BLINDNESS DURATION
S1	26	M	Leber amaurosis	13	13
S2	26	F	Glaucoma	6	20
S3	29	M	Corneal opacity	17	12
S4	45	M	Glaucoma	6	39
S5	49	M	Retinis Pigmentosa	40	9
S6	51	F	Leber amaurosis	46	5
S7	54	M	Chiasmatic glioma	14	40
S8	58	M	Glaucoma	20	38
S9	65	M	Retinis Pigmentosa	38	27
S10	65	F	Retinis Pigmentosa	32	33
S11	67	M	Retinal detachment	51	16
S12	68	M	Glaucoma	14	54

Table 2.3 Clinical details of the late blind sample (N= 12).
The table shows the chronological age at testing, gender, pathology, the age of blindness onset, and years of blindness duration (i.e. number of years spent without vision) for each participant.

Stimuli and procedure were identical to the experiment described in Section 2.2. Participants sat in a silent room, 180 cm away from the center of an array of 23 speakers spanning ±25° of visual angle (Fig. 2.7A) and had to evaluate whether the spatial distance (i.e. spatial bisection) or temporal interval (i.e. temporal bisection) between the first (S1) and the second (S2) sound was smaller or larger than the one between the second (S2) and the third (S3) sound (Fig. 2.8). EEG data were recorded (Fig. 2.7B) and pre-processed as in the experiment reported in Section 2.2. Similarly, EEG was filtered between 0.1 and 100 Hz, and artifacts were removed using ASR (Delorme and Makeig, 2004, Mullen et al., 2013) and Independent Component Analysis (Delorme and Makeig, 2004). In addition, data were referenced to the average of left and right mastoids. Even the ERP analyses followed closely the procedures previously employed in studies investigating complex auditory spatial representation in sighted (Campus et al., 2017) and early blind (Campus et al., 2019) participants, based on the hypothesis that blindness duration could affect the underlying neural circuits. Thus, as in previous work, the present paper focuses on neural responses to the first (S1) and the second sound (S2), for the spatial and temporal bisection tasks separately. EEG data were averaged in synchrony with S1 or S2 onsets to compute ERPs, considering a period of 200 ms before S1 onset as a baseline for both sounds. For each condition of the two bisection tasks, a minimum of 50 trials after artifact rejection was required. The total number of trials was around 710 for each condition, approximately 59 per subject. Again, we analyzed responses in electrodes linked to visual and auditory processing (O1 and O2 in occipital areas, C1 and C2 in central areas; Fig. 2.1B) and on a time window between 50 and 90 ms after each sound. Mean ERP amplitude was computed by averaging the voltage in the selected time window. Here, ERP waveforms were collapsed across conditions (small first interval, large first interval) and hemisphere of recording (left, right) to obtain ERPs recorded on the contralateral hemisphere and on the ipsilateral hemisphere with respect to stimulus characteristics in space or time. Lateralized ERP responses were calculated as the relative difference between the contralateral and ipsilateral responses. Scalp topographies of mean ERP amplitude in the 50-90 ms time window were realized for each condition (small first interval, large first interval) of spatial and temporal bisection tasks.

Hypothesis-driven analyses

First of all, statistical analyses were conducted to investigate differences in the behavioral performance for the spatial and temporal bisection tasks between sighted and LB groups. Comparisons between percentage of correct responses were performed with two-way ANOVA, considering Group (S, LB) as a between-subjects factor, and Task (Space, Time) as a within-subjects factor. Post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction.

Subsequently, we focused on the spatial bisection task for the LB group. After verifying that data fulfilled criteria necessary for regression analyses, to avoid problems related to overfitting, a hierarchical forward stepwise regression analysis was conducted to test our main hypothesis. Indeed, we hypothesized that prolonged sensory deprivation could gradually affect neural circuits related to the construction of complex spatial representation. Behavioral performance in spatial bisection (i.e. the percentage of correct responses) was the predicted variable. Based on literature (e.g. Li et al., 2016, Li et al., 2013), a first model (Model 1) considered age of blindness onset as a predictor of behavioral performance. Then, a second model (Model 2) entered years of blindness duration (BD) as a second predictor. Finally, in a third model (Model 3) we added also the EEG data. The construction of complex spatial representation was previously found to be reflected by a specific ERP component which mostly involves a time window between 50 and 90 ms after the second sound (S2) of the spatial bisection task, as well as contralateral occipital electrodes (Campus et al., 2017). Hence, as predictor of neural activity in Model 3 we used the lateralized occipital ERP response in the 50-90 ms time window after S2 of the spatial bisection task. ANOVA was used to evaluate each single model and the difference of explained variance between models.

Since the size of our clinical sample was limited to 12 subjects, for Model 3 we also run a bootstrapping-type multiple regression analysis to verify its validity. Thus, we applied ordinary nonparametric bootstrap using the *boot* function of the boot package (Canty and Ripley, 2012) in R (R Core Team, 2017), keeping all parameters to their default, to investigate whether the performance of LB participants in the spatial task could be predicted from the lateralized occipital ERP response in the 50-90 ms time window, BD and blindness onset. The bootstrapped confidence interval (95%) was based on 1000 replications. This analysis gave us the possibility to verify the stability of the results despite the size of the sample. Moreover, to investigate the collinearity between BD and the lateralized ERP amplitude in occipital sites in the selected time window we also run a post-hoc linear regression analysis between these two variables.

In order to exclude a role of chronological age on results, the association between years of blindness and biological age was investigated in the group of LB participants with linear regression analysis, as well as the association in the S group between biological age and lateralized ERP response to S2, and between biological age and performance in the spatial bisection task.

Data-driven analyses

To provide more support for the time-period choice and the topographic effects associated with S2 in the EEG analysis of the LB group, we also reanalyzed data applying common average reference and performed other data-driven analyses based on average-referenced EEG data. We used Microstate EEGLab toolbox version 1.0 (Poulsen et al., 2018) to perform an analysis based on a timepoint-by-timepoint approach. We performed two separate microstate segmentations, considering spatial and temporal bisection separately to identify possibly different processes elicited by the two different tasks. The Topographic Atomize and Agglomerate Hierarchical Clustering (TAAHC) method was adopted. In TAAHC, the user does not have to pre-set the number of clusters. It starts out with all EEG samples having their own cluster and then one cluster is removed at a time. Each iteration of the algorithm consists of finding the "worst" cluster, removes (atomises) it and then reassigns each of its members to the cluster it is most similar to. This process is then continued until there are only two clusters remaining (or a pre-set minimum number of clusters; we kept it to the default of two). The "worst" cluster is defined as the cluster that has the lowest sum of correlations between its members and prototype. We selected and aggregated data across subjects by concatenating the grand average ERPs. We segmented grand average ERPs into microstates and applied a temporal smoothing to the solution by setting a minimum duration of 10 ms for microstate segments to last. To decide the amount of clusters, we checked goodness fit of microstate segmentations by considering global explained variance (GEV) and cross-validation criterion (CV); then we made a qualitative decision based on these measures and the quality of the topographical maps of the microstates. All other parameters were kept at their default.

Moreover, focusing on the neural activity elicited by S2 of the spatial task we used the RAGU Matlab Toolbox (Koenig et al., 2011) to conduct a topographic analysis of covariance (TANCOVA), considering the extension of the first distance of the spatial bisection task as factor with two levels (Narrow first distance, Wide first distance) and blindness duration as covariate. The TANCOVA allowed us to further investigate the association between BD and EEG activity, by combining covariance analysis and resampling methods to overcome the issue of multiple testing across EEG channels. Instead of the lateralized ERP response (i.e. contralateral - ipsilateral channels), in the TANCOVA we considered ERP response of each channel to perform a lower level analysis. Considering as factor the extension of the first interval allowed us to account for the lateralization effect, as the level “narrow” corresponded to stimuli provided from the left, and the level “wide” corresponded to stimuli provided from the right of the subject. In this way, the TANCOVA provides a complementary investigation of how BD affects the lateralization of the ERP responses at different latencies and scalp topographies.

Results

Results of hypothesis-driven analyses

The two-way ANOVA performed to investigate differences in the behavioral performance demonstrated a significant interaction (F(1,22)= 5.09, p= 0.03, GES= 0.1) between Group (S, LB) and Task (Space, Time). As shown in Figure 2.13, although a significant difference between the two tasks (t(11)= 6.38, p< 0.001), all sighted participants succeeded in both the spatial bisection (percentage of correct responses mean±SD: 88.5±2.2%; execution times mean±SD: 0.94±0.13 sec) and temporal bisection tasks (percentage of correct responses: 83.7±2.7%; execution times: 0.95±0.12 sec), confirming previous results (Campus et al., 2017). Turning attention to the LB group, post-hoc t-tests revealed that their performance in temporal bisection (percentage of correct responses: 79±15%; execution times: 0.55±0.19 sec) did not differ neither from temporal performance of sighted participants (t(11.7)= 1.07, p= 0.6), nor from their own performance in the spatial bisection (percentage of correct responses: 64±19%; execution times: 0.74±0.37 sec; t(11)= -1.71, p= 0.2). However, in the LB group percentage of correct responses for spatial bisection was significantly lower compared to that of S group (t(11.28)= -4.46, p= 0.002), ranging from chance level (49%) to excellent (95%) across LB subjects.

Here, we focused on LB participants and specifically on their occipital neural activation 50-90 ms after S2 of the spatial task to test the hypothesis that blindness duration (BD) could affect the neural circuits underlying complex auditory spatial representation (Campus et al., 2017). Stated that data fulfilled criteria necessary for regression analyses (i.e. the residuals were normally distributed and homoscedastic, the errors were independent and the relationships linear), we performed a hierarchical regression analysis with performance in the spatial bisection task as predictive variable.

Based on literature, Model 1 considered age of blindness onset as first predictor and revealed that behavioral performance is not predictable from this clinical variable (for the model: r^2= 0.02, F(1,10)= 0.2, p= 0.7; for age of onset: coefficient estimate= 0.2±0.4, p= 0.7). ANOVA showed a significant improvement of the fit from Model 1 to the Model 2 in which BD was added as a second predictor (F(1,9)= 84.9, p< 0.001). According to Model 2 (r^2= 0.8, F(2,9)= 18.4, p< 0.001), behavioral performance is better predicated by years of BD rather than age of onset (for age of onset: coefficient estimate= -0.4±0.2, p= 0.06, for BD: coefficient estimate= -1.2±0.2, p< 0.001). Moreover, the improvement reached by adding the neural data in Model 3 (F(1,8)= 12.2, p= 0.007) revealed an impact on the performance of the lateralized ERP amplitude in occipital areas. In Model 3 (r^2= 0.9, F(3,8)= 33.3, p< 0.001), both age of onset and the lateralized ERP amplitude are significant predictors (for age of onset: coefficient estimate= -0.5±0.1, p= 0.008, for lateralized ERP amplitude: coefficient estimate= 16.7±4.6, p= 0.007), while BD not anymore (coefficient estimate= -0.4±0.2, p= 0.1).

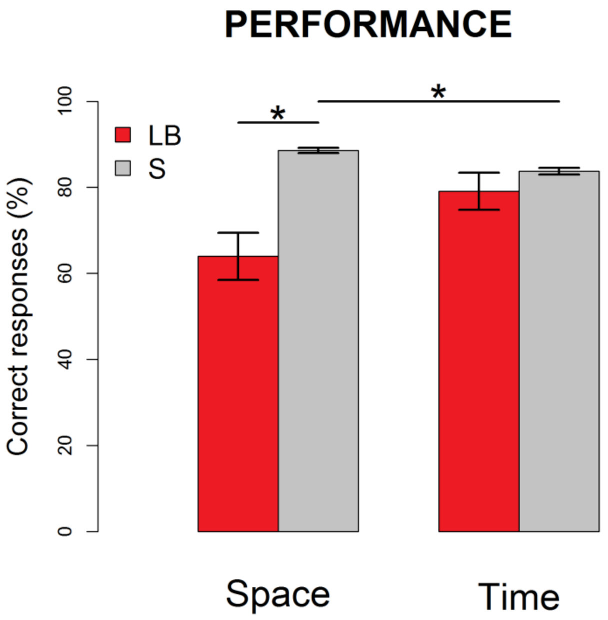

Figure 2.13 Performance (mean±SEM) for spatial (left) and temporal (right) bisection tasks in late blind (red) and sighted (grey) subjects.

All sighted participants were able to perform the tasks, with a significant higher performance in spatial bisection. Late blind participants show significantly lower percentage of correct responses compared to sighted participants in spatial but not temporal bisection. * p< 0.001 after Bonferroni correction.

Since BD is a significant predictor in Model 2 but not in Model 3, in which neural activation was simply entered as predictor, BD and the lateralized ERP amplitude likely explain the same portion of variance. To test the collinearity between these two variables, we also run a post-hoc linear regression analysis (see Fig. 2.14). There exists a strong significant association between BD and lateralized ERP amplitude in the selected time window (for the model: r^2= 0.8, F(1,10)= 36.5, p< 0.001, for BD: coefficient estimate= -0.05±0.008, p< 0.001), supporting the idea that the early lateralized occipital activation mediates the effect of years of blindness on performance. Thus, a biological variable (i.e. the neural response) seems to be a mediator of the effect of a clinical variable (i.e. blindness duration) on a behavioral variable (i.e. spatial bisection performance).

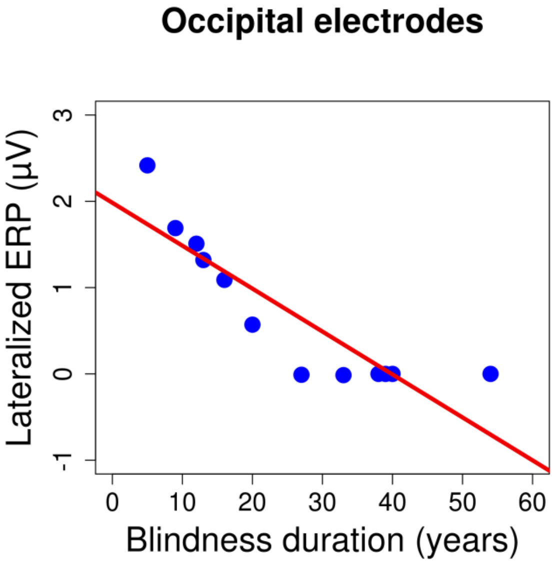

Figure 2.14 Results of the linear regression analysis between BD and neural response in the late blind group.
Years of blindness duration (BD) negatively correlate with lateralized (i.e. contralateral – ipsilateral to S2 position) ERP amplitude in 50-90 ms time window after S2 for the spatial bisection task.

For Model 3, we also re-analyzed data with a bootstrapping-type multiple regression analysis to further verify its validity in our small sample (N=12). This analysis confirmed previous ones, showing that lateralized ERP amplitude (95% CIr = [8.3, 35.9]) and, even though less significant, blindness onset (95% CIr = [-0.8, -0.06]) were able to predict the behavioral performance. Even in this case, BD did not result in a significant predictor (95% CIr = [-1.4, 0.2]), likely due to its collinearity with lateralized ERP amplitude. Thus, our analyses suggest that the early activation in contralateral occipital sites could be considered as a neural correlate of auditory spatial bisection skills, and it is strongly influenced by years of blindness duration.

To isolate the effect of BD on neural correlates associated with the construction of complex spatial representation, we also conducted some analyses considering the chronological age of participants. First of all, BD is not associated with biological age in the LB group (for the model: r^2= 0.2, F(1,10)= 3.05, p= 0.1, for age: coefficient estimate= 0.47±0.27, p= 0.1). Second, in the group of sighted subjects, we revealed neither a significant association between age and performance in the spatial bisection task (for the model: r^2= 0.0004, F(1,10)= 0.004, p= 0.9, for age: coefficient estimate= -0.003±0.05, p= 0.9), nor a significant association between age and the lateralized occipital ERP amplitude in 50-90 ms time window after S2 of the spatial bisection task (for the model: r^2= 0.004, F(1,10)= 0.04, p= 0.84, for age: coefficient estimate= -14.7±71, p= 0.84).

Since according to statistical analyses BD linearly affects neural circuits associated with complex spatial representation, for illustrative purposes, the median of BD (23.5 years) has been arbitrarily used to split the sample in order to represent graphically the different neural activation between those who had been blind for a shorter period of time (i.e. short BD) and those who had been blind for many years (i.e. long BD).

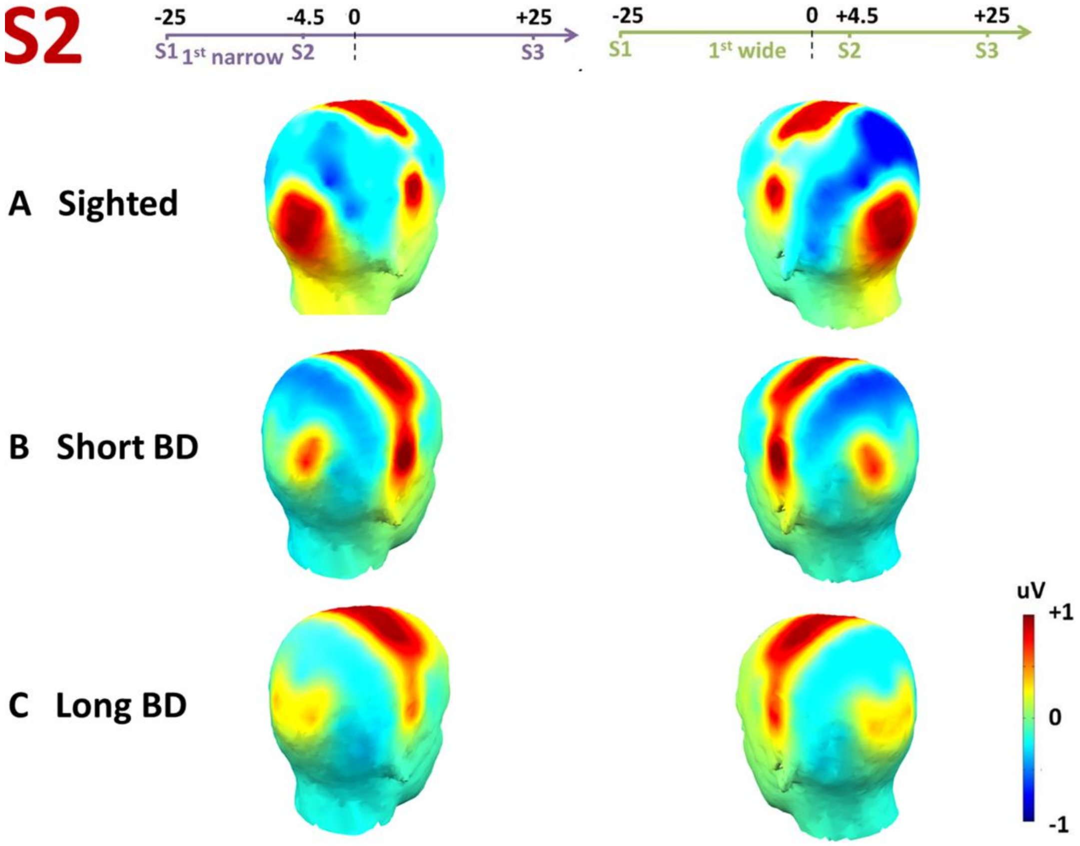

Figure 2.15 Scalp maps of the mean ERP amplitude in the selected time window (50-90 ms) after S2 of the spatial bisection task.

S2 was presented in space from either - 4.5° (i.e. narrow first interval; see left panel) or +4.5° (i.e. wide first interval; see right panel) independently of timing (±250 ms). Only for the sighted group **(A)** and for individuals with shorter BD **(B)** a strong positivity emerges after S2 in occipital areas contralateral with respect to the physical position of the sound. In individuals with longer BD **(C)** the occipital activation results attenuated and not lateralized with respect to the S2 position in space.

Figure 2.15 shows the scalp maps of the mean ERP amplitude in 50-90 ms time window when S2 was presented from either + 4.5° or -4.5° in space independently of timing (±250 ms) during the spatial bisection task. Specifically, scalp maps are realized separately for the group of sighted subjects (Fig. 2.15A), individuals with a short BD (Fig. 2.15B) and with a long BD (Fig. 2.15C). A positivity involving central and contralateral temporal areas is always evident, likely linked to auditory cortical processing and thus in line with previous literature (Naatanen and Picton, 1987, Campus et al., 2017). However, the physical position of S2 elicits a specific occipital ERP response in sighted people and in the individuals with the shorter BD which is not so evident in subjects with the longer BD. As suggested by statistical analyses, subjects who have been blind for a short period show a strong contralateral occipital response to S2, similarly to sighted individuals. However, occipital ERP response proves to be dramatically attenuated and not contralateral to the stimulus position in participants with a long BD. As regards S1 of the spatial bisection task, as expected (Campus et al., 2017) there is simply an unspecific central response and a contralateral temporal activation in all participants.

Similarly, ERPs elicited by S2 at occipital and central electrodes during the spatial bisection task are reported in Figure 2.16 for subjects with short and long BD. As regards the occipital ERP response to S2 (Fig. 2.16A), only subjects with short BD show waveforms very similar to those of sighted individuals described in Campus et al. (2017). Indeed, only individuals with short blindness duration exhibit a prominent positivity between 50-90 ms specifically in contralateral electrodes. In contrast, the 50-90 ms occipital ERP component of the other subjects is strongly reduced and also appears in ipsilateral electrodes. Moreover, as in the studied described in Section 2.2 later activation seems to occur, more pronounced and contralateral in individuals with the short BD, whereas it is lower and not lateralized in respect to the stimulus position in the individuals who have been blind for a longer period of time. As in Campus et al. (2019), a P140 selective for S2 but not lateralized appears in both groups, although it is more pronounced in the one with short BD. Typical auditory ERP response is observed for both groups in central areas (Fig. 2.16B).

Turning our attention to temporal bisection performed as control experiment, Figure 2.17 represents the scalp maps of the ERP amplitude in the selected time window (50-90 ms) after S2, realized separately for the sighted group (Fig. 2.17A), individuals with a short BD (Fig. 2.17B) and those with a long BD (Fig. 2.17C). Although BD has a linear effect on results, the median of BD (23.5 years) has been again arbitrarily used to split the sample for a graphical reason. ERP scalp topography is shown for S2, when it was presented at either +250 ms or -250 ms independently of space (±4.5°). Only a positivity involving central and temporal areas occurs, related to auditory processing (Campus et al., 2017, Naatanen and Picton, 1987). Interestingly, stimuli in spatial and temporal bisection tasks were identical, just the question is different. Thus, S2 location varied in the spatial domain (+ 4.5°/-4.5°) even when subjects were judging temporal intervals, but this aspect was not able to elicit an occipital response during temporal bisection task. Scalp maps of the ERP amplitude in the selected time window (50-90 ms) after S1 of the temporal bisection task are reported in Fig. S1 of Supplemental materials of Amadeo et al. (2019a).

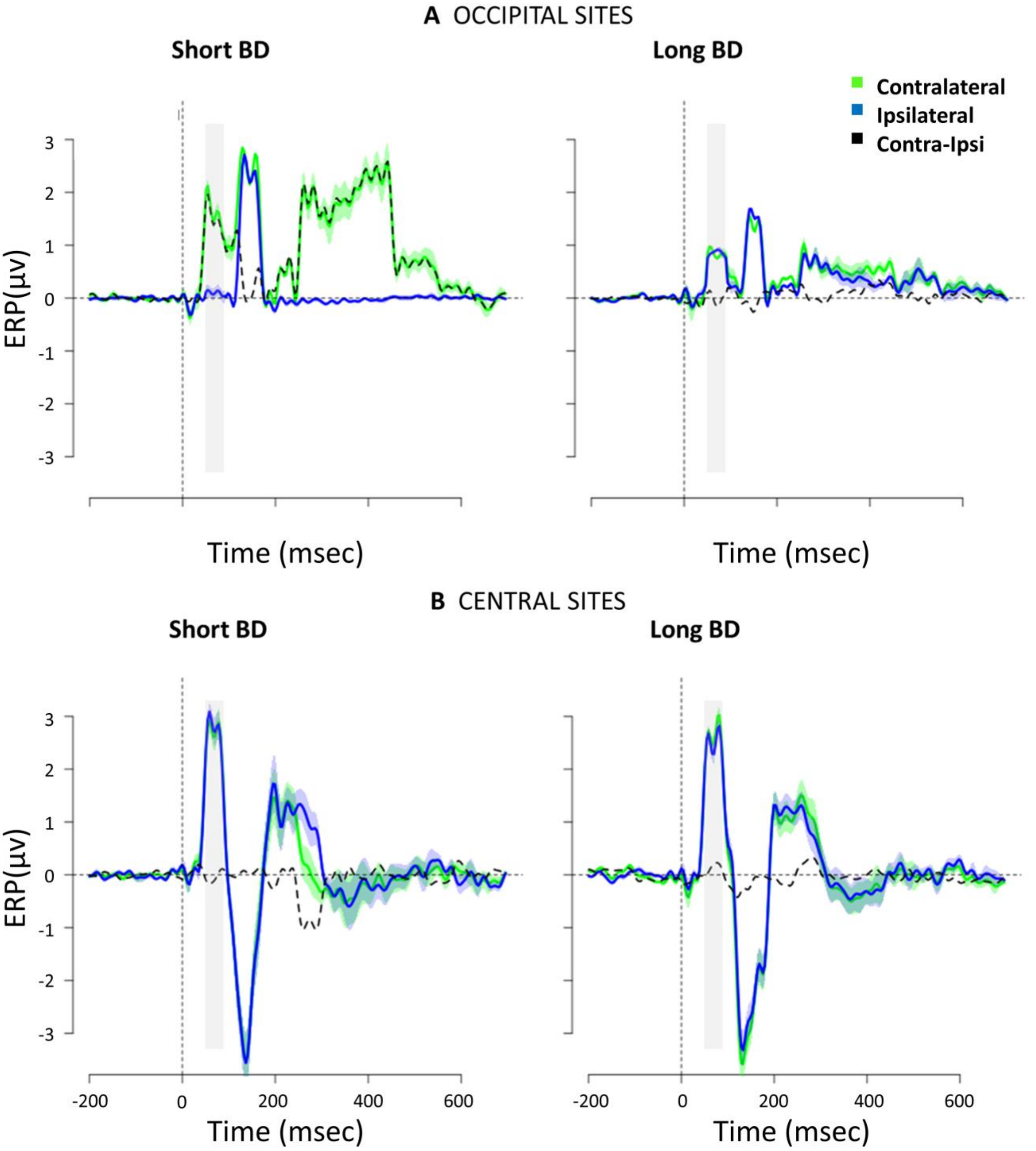

Figure 2.16 ERPs (mean±SEM) elicited by S2 during spatial bisection task in occipital (A) and central (B) areas, realized separately for subjects with short (left) and long (right) BD.
In blue, ERPs collapsed over occipital/central scalp sites contralateral to the side of S2 presentation. In green: ERPs collapsed over occipital/central scalp sites ipsilateral to the side of S2 presentation. In black, contralateral minus ipsilateral difference amplitude. On the x-axis, t = 0 is sound onset. The shaded area delimits the selected time window (50–90 ms).

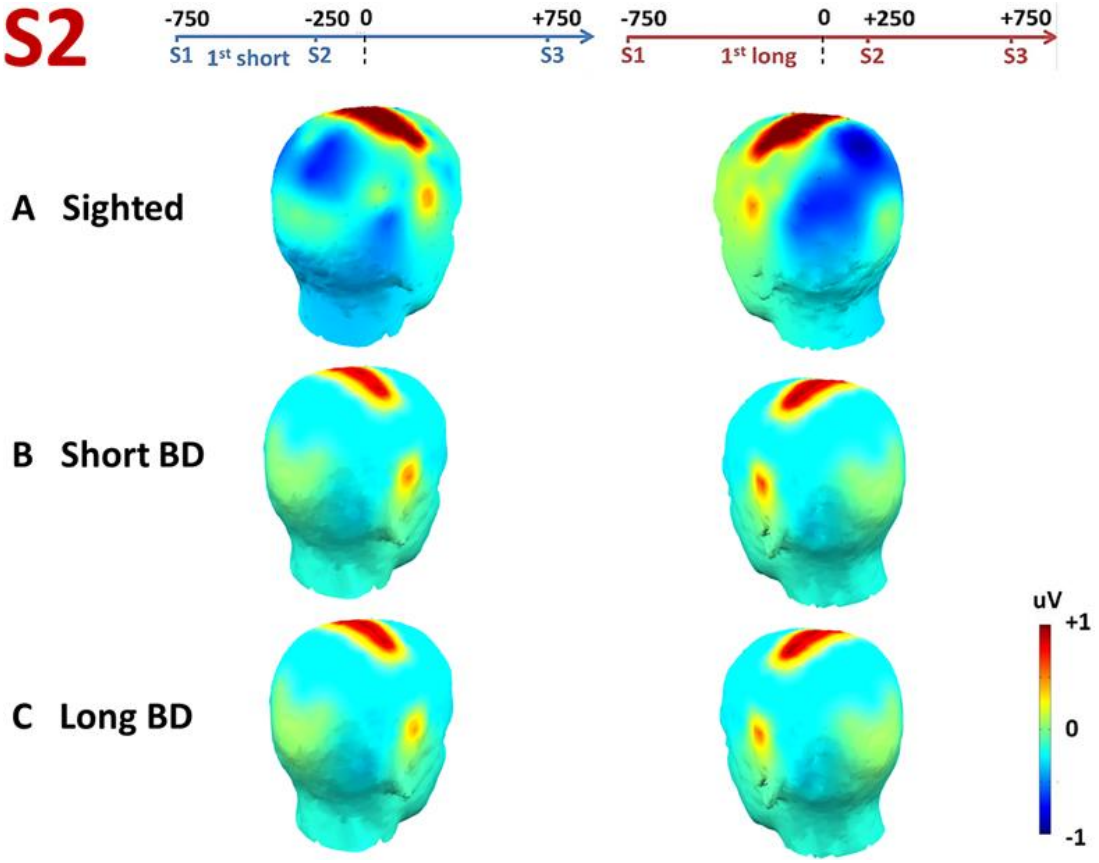

Figure 2.17 Scalp maps of the mean ERP amplitude in the selected time window (50-90 ms) after S2 of the temporal bisection task.
S2 was presented at either -250 ms (i.e. short first interval; see left panel) or +250 ms (i.e. long first interval; see right panel) in timing, independently of space (±25°). A central and temporal activation is observed for all participants: the sighted group **(A)**, individuals with shorter BD **(B)**, and individuals with longer BD **(C)**.

Results of data-driven analyses

The EEG microstate analysis confirmed the homogeneity of ERP response during the selected time window by identifying a microstate around 50-90 ms after S2 for both the spatial (see MS4 in Fig. 2.18A) and the temporal (see MS3 in Fig. 2.18B) bisection tasks. Specifically, four clusters were obtained for the spatial bisection task, which isolate an early response (i.e. MS4 in Fig. 2.18A), a response around 100-200 ms (i.e. MS1 in Fig. 2.18A) likely reflecting a N1b component (Naatanen and Picton, 1987), a cluster around 250 ms (i.e. MS2 in Fig 2.18A) possibly related to a P2 component, and a cluster between 250 and 400 ms (i.e. MS3 Fig 2.18A) likely reflecting late cognitive processes.

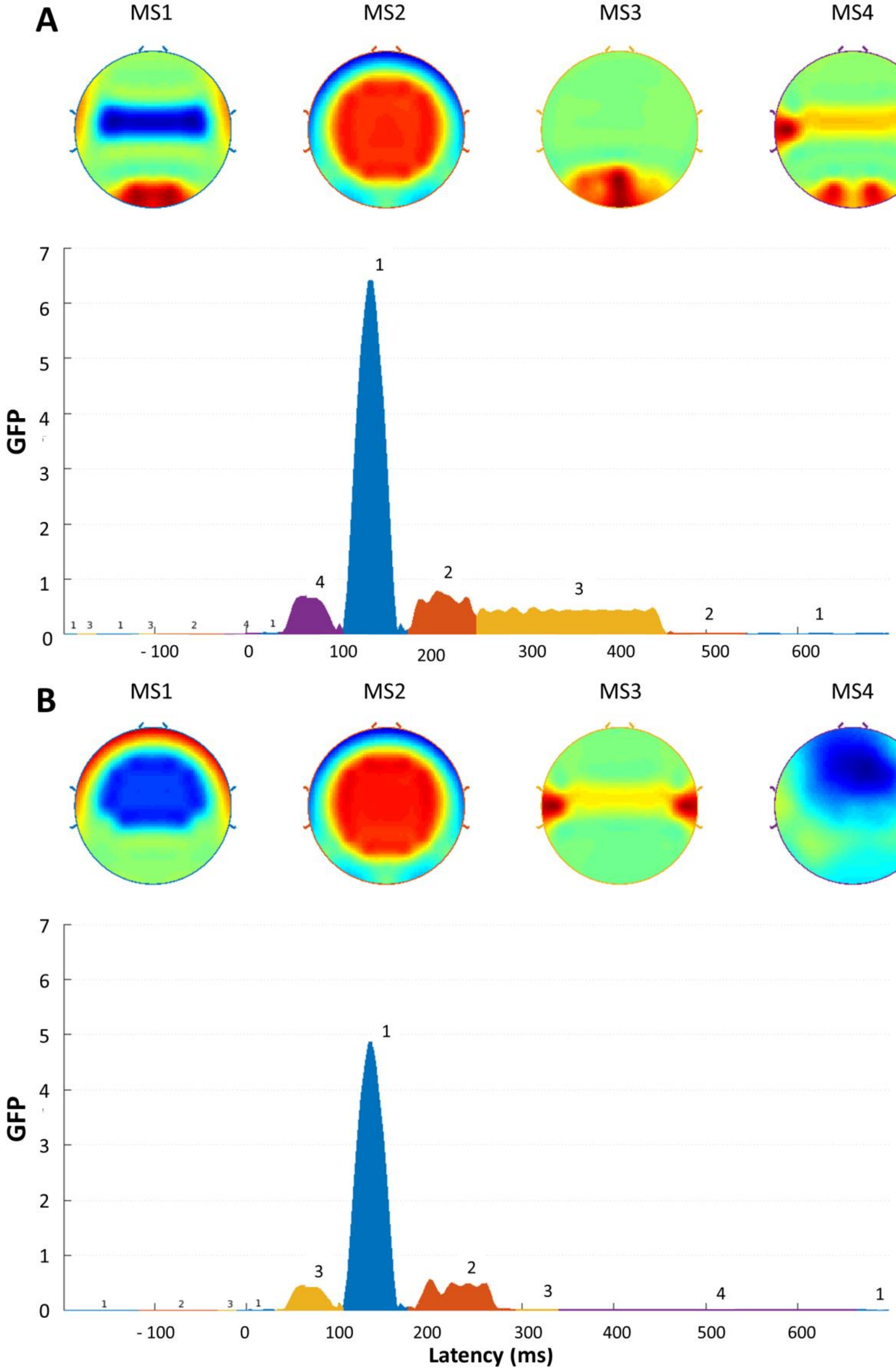

Figure 2.18 Results of the microstates segmentation for the ERP elicited by S2 in the spatial (A) and temporal (B) bisection tasks.

For both spatial and the temporal tasks a microstate is identified approximately encompassing the time window considered in this study (50-90 ms after the stimulus; see MS4 in A and MS3 in B).

Moreover, in support of the specific influence of BD on occipital cortical activity during this specific time window, we performed a TANCOVA considering the ERP response to S2 of the spatial bisection task. TANCOVA revealed a significant interaction (p< 0.05 during the whole 50-90 ms interval) between BD and the extension of the first interval during the spatial bisection task (i.e. the distance between S1 and S2; narrow/wide first distance corresponds to S2 delivered -4.5° or +4.5° respectively). The interaction firstly involves a time window approximately between 50 and 90 ms (Fig. 2.19 left panel) and occipital together with temporal electrodes (Fig. 2.19 right panels).

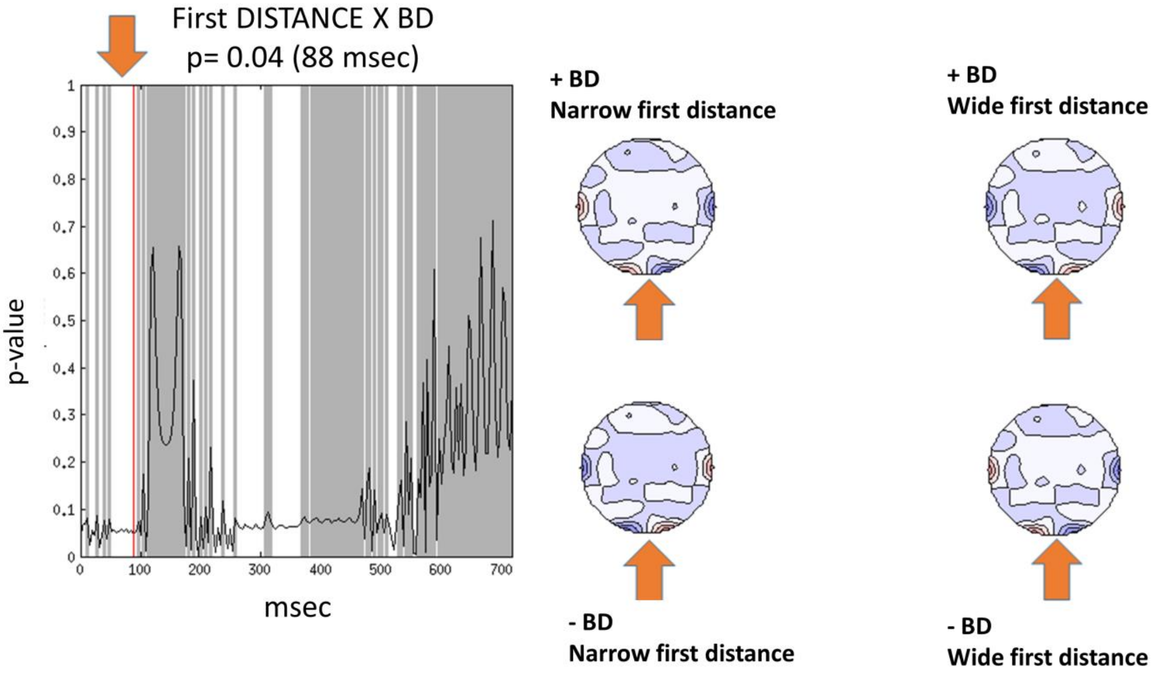

Figure 2.19 Results of TANCOVA.
A specific interaction emerged between Blindness Duration (BD) and the extension of the first distance (i.e. the distance between S1 and S2). Narrow/wide first distance corresponds to S1 delivered from the left (-4.5°) or right (+4.5°) side of the subject respectively. Left panel: white areas correspond to times where the interaction is significant (p< 0.05); the interaction firstly involves a time window approximately between 50 and 90 ms (see the orange arrow). Right panel: the interaction not only involves temporal electrodes (which are expected due to the auditory task), but also occipital electrodes (see orange arrows).

Discussion of results

In this study, we investigated how auditory spatial representation is shaped by vision studying neural circuits and performance during spatial bisection task in late blind individuals. According to our results, years of visual deprivation gradually influence neural correlates associated with the performance in the auditory spatial bisection task.

Subsequent to a period of visual experience, subjects who have been blind for a shorter period of time exhibit the contralateral occipital response to the second sound similarly to sighted individuals (Campus et al., 2017), and are able to perform the spatial bisection task. However, years without vision drive to a weaker and widespread occipital response to the second sound of the spatial bisection task, and to a lower spatial performance. The neural activation and performance of people who have been blind for a longer period of time closely resemble those of early blind individuals described in Section 2.2. Specifically, the hierarchical regression analysis highlights such a strong association between duration of blindness, ERP responses and percentage of correct responses. The early occipital ERP response in the hemisphere contralateral to the second stimulus position mediates the effect of the amount of time spent without vision on the performance in the spatial task. Thus, the reduced laterality of the occipital activation associated with many years of blindness seems to be the explanation for the behavioral deficit reported with behavioral methods. We can exclude that our findings concerning BD derive from biological age. Indeed, blindness duration and biological age do no correlate in the late blind group, and in sighted people chronological age is associated with neither the occipital neural activation nor performance in the spatial bisection task.

Since the construction of complex spatial representation is compromised in early blindness (Gori et al., 2014, Campus et al., 2019), the similarity between neural circuits and competences of late blind individuals with short blindness duration and sighted people suggests that an early visual experience is necessary and sufficient to fully develop neural areas involved in complex representations of space. Yet, one of the main insights of the present work concerns the significant impact of years of blindness on auditory spatial perception. The decrease of the contralateral occipital activation with progressive blindness duration suggests that strategies and neural circuits underlying the construction of complex spatial representation are strongly affected by the absence of vision through long-term neural plasticity. Neural changes associated with blindness duration could be related to a general atrophy of the visual cortical system, resulting in less connectivity between the auditory and visual systems. Several other studies have revealed an effect of blindness duration on neural networks underlying spatial processing in the late blind population (e.g. Tao et al., 2015, Wang et al., 2013, Collignon et al., 2013), highlighting both compensation mechanisms and neuroplasticity limits which affect the structural and functional reorganization of the brain even when visual deprivation occurs later in life (for a review, see Voss, 2013, Dormal et al., 2012).

Other research points to the importance of blindness onset in determining late blind subjects' abilities and neural activations (Li et al., 2016, Li et al., 2013). Although we only find a weaker effect of blindness onset on behavioral responses during the spatial bisection task, our results do not necessarily disagree with previous studies. The onset of blindness may be very compromising when it occurs early in life, but in our sample the earliest onset corresponds to 6 years of age. Early visual inputs set the cerebral architecture underlying spatial functions (Cohen et al., 1997), and the sensitive window for the development of the visual cortex ranges from several months to 10 years after birth for different occipital areas (Lewis and Maurer, 2009, Wattam-Bell et al., 2010). Similarly, the time interval of multisensory integration mechanisms is thought to involve the first 8 years of life (Gori et al., 2008, Gori, 2015). We argue that the age of blindness onset might be specifically impairing when vision loss takes place within the sensitive period, which is not the case in our sample.

To conclude, blindness duration modulates neural circuits and strategies underlying the construction of complex spatial representation in late blind people. The results represent a new step toward understanding the role of vision on spatial perception, as well as how the brain and complex skills react to sensory deprivation.

Chapter 3

Temporal representation and deafness

In Chapter 1, I emphasized not only that vision is the most reliable sense to represent spatial information, but also that audition is the most accurate sense to represent temporal information. Based on this background, deafness represents a natural condition useful to investigate the impact of the auditory system on how we perceive temporal features.

As for blindness, over the years, two opposing views about perceptual skills following auditory deprivation have developed. On the one hand the “sensory compensatory hypothesis” claims that when auditory deprivation occurs, the remaining sensory modalities are potentiated, thus eliciting improved or at least similar behaviors to those of the typical population (e.g. Théoret et al., 2004, Roder and Neville, 2003, Bavelier and Hirshorn, 2010). On the other hand, the “perceptual deficiency hypothesis” asserts that as a consequence of auditory deprivation occurring early in life, other perceptual systems are irreparably impaired, thus preventing efficient interactions with the external environment (Quittner et al., 2007, Voss et al., 2010). Focusing on the abilities to process temporal information in conditions of auditory deprivation, behavioral results are conflicting, and seem to vary based on the type of task and stimuli. When asked to estimate and reproduce duration of visual stimuli, for instance, deaf participants are often found to perform similar or better than controls in the range of milliseconds (Bross and Sauerwein, 1980, Poizner and Tallal, 1987), but not in the range of seconds (Kowalska and Szelag, 2006). However, Bolognini et al. (2012) observed low abilities to reproduce tactile durations in the range of milliseconds. In addition, tactile perceptual thresholds in a simultaneity judgment task are significantly higher in deaf compared to hearing individuals regardless of the spatial location of the stimuli (Heming and Brown, 2005), but opposite results were obtained for a visual temporal order judgment task (Nava et al., 2008). Other previous studies argued that fine-grained temporal precision required for duration discrimination or simultaneity judgments may not develop properly as a consequence of auditory deprivation (Blair, 1957, Withrow, 1968). As supported by the cross-calibration theory (see Chapter 1), they suggested that at least some facets of temporal processing abilities may typically be calibrated through audition, and the lack of auditory input at critical stages during development could hamper this calibration process, resulting in suboptimal abilities (Conway et al., 2009, Poizner and Tallal, 1987). In line with this, while some studies observed no threshold difference between deaf and hearing adults for vibratory frequency discrimination (Levanen and Hamdorf, 2001) and vibratory frequency detection (Moallem et al., 2010), others reported higher frequency detection thresholds following deafness (Frenzel et al., 2012).

Also for deafness, there is evidence suggesting that behavioral advantages are sustained by cross-modal recruitment in deprived auditory cortices. Research in both animals and humans highlight that a deficit in audition, can induce compensatory neural mechanisms leading to increased abilities in spared sensory modalities, such as vision or touch (Strelnikov et al., 2013, Allman et al., 2009, Barone et al., 2013, Lomber et al., 2010). At the neurophysiological level, large-scale reorganization occurs after sensory loss (e.g. Bola et al., 2017, Auer et al., 2007, Finney et al., 2003, Benetti et al., 2017). The auditory cortex starts to be recruited by tactile and visual stimuli (e.g. Finney et al., 2001, Kok et al., 2014, Campbell and Sharma, 2016, Bottari et al., 2014, Karns et al., 2012), and changes within the early visual pathway in absence of auditory input have also been reported following auditory deprivation (e.g. Bottari et al., 2011, Hauthal et al., 2014a). For instance, a recruitment of the auditory cortex is reported for peripheral visual processing (Lomber et al., 2010, Scott et al., 2014) and during motion detection (Buckley et al., 2010, Codina et al., 2011, Stevens and Neville, 2006). Specifically, enhanced motion detection skills in early deaf adults are associated with specific changes in cortical thickness (Shiell et al., 2016), in white matter structure (Shiell and Zatorre, 2017) and in the right planum temporale, an area in the superior temporal cortex involved in visual motion processing in early deaf adults (Fine et al., 2005, Finney et al., 2003, Sadato et al., 2005, Shiell et al., 2015). In a recent work, Bola et al. (2017) observed also that visual rhythm processing in deaf individuals involves the posterior and lateral part of the high-level auditory cortex, typically recruited during processing temporally complex sounds (Obleser et al., 2007, Kusmierek and Rauschecker, 2014, Rauschecker and Scott, 2009, Hyde et al., 2008). These findings are in agreement with a task-specific sensory-independent supramodal organization of the human auditory cortex. In deaf humans the high-level auditory cortex switches its input modality from sound to vision but preserves its task-specific activation pattern independent of input modality, responding to visual rhythm perception. In support of a strict association between cross-modal plasticity and behavioral skills, temporary deactivation of deprived auditory cortices in deaf cats impaired their behavioral performance on visual tasks (Meredith et al., 2011, Lomber et al., 2010), and TMS pulses to auditory regions temporary disrupted tactile temporal performance in deaf adults (Bolognini et al., 2012).

While neural correlates of enhanced abilities following deafness have been widely investigated, there are few studies addressing the plastic changes mediating impaired behaviors. Bolognini et al. (2012) suggested that cross-modal recruitment of the deprived auditory cortex taking place at early stages of sensory processing during a tactile temporal task has a negative impact on the behavior of early deaf adults. Indeed, their behavioral results showed impaired tactile duration discrimination abilities in deaf adults versus hearing controls. However, by delivering TMS to the high-level auditory cortices, such as the superior temporal gyrus (STG), author demonstrated that the later the STG was involved in the temporal task after stimulus presentation, the better participants were able to discriminate between durations. This means that the behavioral impairment reported in the deaf group depended on an earlier recruitment of the STG in deaf participants compared to hearing controls. These results are specific for a temporal task. Indeed, in the same study they also tested tactile location discriminations and found no difference in behavior between deaf and hearing groups, even though there was a similar temporal dynamic for the involvement of the STG during the spatial task in the deaf population. Some other studies reported only little change of the auditory neural structures in deaf animals (e.g. Clemo et al., 2016), and very few new connections between visual and auditory cortices as a result of deafness (e.g. Chabot et al., 2015, Butler et al., 2016).

To sum up, as evident already from findings about spatial representation (see Chapter 2), the principles at the base of cortical reorganization in our brain in case of sensory loss are still not clear. Research suggests that the two hypotheses (i.e. perceptual deficiency vs. compensatory) are not mutually exclusive, and behavioral and brain modifications in deafness drive to some adaptive (i.e. compensatory) as well as maladaptive (i.e. deficiency) outcomes. Moreover, from the above mentioned studies it is evident that the functional role of the auditory system to temporal representation needs further investigation to be understood. In this Chapter, I try to elucidate neural cortical mechanisms underlying the development of complex temporal representation by focusing on the visual sense of time. Specifically, I first take into account hearing people, to study the neural correlates of the ability to build complex visual temporal representation when all senses are available (Section 3.1). Subsequently, I turn attention to what happens in the auditory deprived brain (Section 3.2). I investigate the extent to which the development of the neural network observed in hearing people is dependent on auditory experience. Results show that complex temporal visual representation recruits areas likely involving the auditory brain, and this mechanism seems to rely on auditory experience. Thus, findings from Chapter 3 help in understanding the involvement of the auditory system in complex temporal representation within visual modality, while adding important insights about neural correlates associated with behavioral impairment following deafness. As for blindness, a better comprehension of the enhancements and deficits due to sensory deprivation is necessary to think of rehabilitation strategies and training programs to boost sensory recovery.

3.1 Exp. 1: Complex temporal representation in hearing people

Early activation of visual cortical areas by auditory processing has been reported in sighted individuals supporting the idea that vision and audition interact within low-level cortical sites and at early latencies (Ghazanfar and Schroeder, 2006, Besle et al., 2009, Giard and Peronnet, 1999). Specifically complex spatial representation of sounds elicits an early response in areas likely involving the visual cortex (Campus et al., 2017). On the other hand, an impact of visual inputs into auditory cortex has been observed in non-human primates (e.g. Schroeder and Foxe, 2002), ferrets (e.g. Bizley et al., 2007), rats (e.g. Wallace et al., 2004), and also in humans. As seen in the introduction of this Chapter, a specific recruitment of the auditory cortex by other senses is commonly reported in deaf individuals (e.g. Bottari et al., 2014, Finney et al., 2001, Auer et al., 2007). Although less common, it has been observed in hearing people too (e.g. Calvert et al., 1999, Romei et al., 2007, Besle et al., 2008). Different fMRI studies reported the activation of the superior temporal gyrus during temporal processing of visual stimuli (Coull et al., 2004, Ferrandez et al., 2003, Lewis and Miall, 2003). Similarly Kanai et al. (2011) revealed that TMS over the auditory cortex impacts on time estimation of both auditory and visual stimuli. Since many behavioral studies agree that the auditory system is the most accurate sense to represent temporal information (see Chapter 1), one may expect that the recruitment of the auditory brain is necessary for building a high resolution and flexible temporal representation regardless of the sensory modality delivering the input. This would suggest a domain-specific supramodal organization of the auditory areas, with time being the putative domain. To test this hypothesis, we investigated complex temporal skills within visual modality, aiming to see whether areas likely involving the auditory brain could support the neural processing underlying complex temporal representation. Recent research showed, in an audio-visual multisensory temporal bisection task, both young children and adults use only the auditory information to estimate the multisensory temporal position of the stimulus (Gori et al., 2012b). Interestingly, deaf children with restored hearing do not show this auditory dominance (Gori et al., 2017). In light of the crucial role of audition on temporal bisection task, we decided to perform this paradigm. It is a challenging task that specifically involves the construction of complex temporal representation and could require an early auditory activation independently of the sensory modality of the stimulus. Thus, we recorded ERPs and psychophysical responses in a group of hearing participants while performing a visual temporal bisection task, and a visual spatial bisection task as control experiment.

Methods

Experimental procedure

We assessed temporal and spatial visual bisection abilities in 17 hearing subjects (mean age±SD: 25±5 yo) with no history of visual or neurological problems. The sample size was decided prior to data collection based on a previously published study testing spatial bisection abilities and neural correlates in healthy adults (Campus et al., 2017). A power analysis (two-tailed t-test, Cohen's d= 1.35 estimated by a pilot study with 5 subjects, α= 0.05) indicated a minimum of 15 participants to reach a power of 0.85. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki.

Setup and experimental procedures were identical to the experiments described in Section 2.2 and 2.3 involving early and late blind participants, with the difference that here we used visual instead of auditory stimuli. Thus, participants sat in a silent room, 180 cm away from the center of an array of 23 light-emitting devices spanning ±25° of visual angle (with 0° representing the central light-emitting device, negative values on the left, and positive values on the right; see Fig. 2.7A, as the same device allows delivering auditory or visual stimuli). For each trial, three short flashes (namely S1, S2, S3; red color, 2.3° diameter, 75 ms duration and 20 cd/m^2 luminance) were delivered at three different spatial positions and timings (Fig. 2.8). Subjects performed a temporal and a spatial bisection task in two distinct randomized blocks: they judged whether S2 was temporally (i.e. temporal bisection task) or spatially (i.e. spatial bisection task) farther from S1 or S3. Stimuli were identical between blocks. The first (S1) and third flash (S3) were always delivered at -25° and +25° degrees respectively, with temporal separation fixed at 1.5 seconds. The second flash (S2) could occur randomly and independently from either -4.50° or +4.50° in space (Fig. 2.8A), and at either -250 ms or +250 ms in time from the middle of the temporal flash sequence (Fig. 2.8B). As in the experiments previously described, S2 was also presented at 0° and at 0 ms during catch trials (number of catch trials = 15). Thus, each block consisted of 60 trials x four conditions: 1) S2 from -4.50° at -250 ms, 2) S2 from -4.50° at +250 ms, 3) S2 from +4.50° at -250 ms, and 4) S2 from +4.50° at +250 ms. The inter-trial interval was 1250±250 ms and subjects were asked to answer using a pushbutton immediately after S3. We measured execution times, and subject performance. During the tasks EEG was collected from 64 scalp electrodes using the Biosemi ActiveTwo EEG System, see Section 2.1 for further details about EEG recording. EEG data were then filtered between 0.1 and 100 Hz, and cleaned using ASR (Delorme and Makeig, 2004, Mullen et al., 2013) and Independent Component Analysis (Delorme and Makeig, 2004), removing for each subject up to 5 independent components (see Methods in 2.2). In addition, data were referenced to the average of all channels.

Behavioral and Sensor Level Analysis

Performance and execution times in the temporal and spatial bisection tasks were compared using two-tailed t-tests, with probabilities treated as significant when lower than 0.01. Here, we were specifically interested in testing the hypothesis that during temporal bisection the second flash could produce a contralateral activation in temporal areas, mimicking what is observed in auditory tasks. Therefore, we focused analyses on the neural responses to S1 and S2, for the spatial and temporal bisection tasks separately. Indeed, S2 can be considered the starting point for the development of a temporal metric, whereas S1 can be considered as a control. Neural responses to S3 were not taken into account since the last flash could involve more complex mechanisms related to the metric definition, and it could be compromised by behavioral answers. As in the experiments testing auditory spatial and temporal skills (see Section 2.2 and 2.3), EEG data were averaged in synchrony with S1 or S2 onsets to compute ERPs, considering a period of 200 ms before S1 onset as a baseline for both flashes. Catch trials were not considered in statistical analyses. After artifacts rejection, the total number of trials was around 940 for each condition, approximately 55 per subject. Conditions were subsequently merged based on S2 spatial position ensuring approximately 110 trials per subject for each cell of the experimental design.

To select the time window of interest we analyzed data using a timepoint-by-timepoint approach with Microstate EEGLab toolbox (Poulsen et al., 2018). Based on our hypothesis and supported by the microstate analysis, we took into account electrodes linked to visual (O1 and O2) and auditory processing (T7, T8, and Cz). Mean ERP amplitude was computed by averaging the voltage in the selected time window, merging conditions based on S2 spatial position (i.e. 120 trials with S2 delivered from -4.5° and 120 trials with S2 delivered from +4.5°). For both the bisection tasks, ERP waveforms were collapsed across conditions and the hemisphere of recording (left, right) to obtain ERPs recorded on the contralateral hemisphere and on the ipsilateral hemisphere with respect to stimulus characteristics in space. Lateralized ERP responses were calculated as the relative difference between the contralateral and ipsilateral responses. Scalp topographies of mean ERP amplitude in the 50-90 ms time window were realized for spatial and temporal bisection tasks, considering the two spatial positions of S2 (±4.5°) separately.

To investigate the different neural responses after S1 and S2 for the temporal and spatial tasks, we performed two-tailed t-tests comparing the mean lateralized ERP amplitudes in the selected time window. Probabilities were treated as significant when lower than 0.05 after Bonferroni correction. The association between the ERP response in contralateral temporal sites and performance at the temporal bisection task was addressed using linear regression. For each subject and trial we computed the mean lateralized ERP amplitude in the 50-90 ms time window. Then, we averaged across trials and, for each subject, we correlated this average against the percentage of correct responses (thus considering one point for each subject).

Source Level Analysis

In order to reconstruct the cortical generators of the ERP components, we employed a distributed sources analysis using the Brainstorm software (Tadel et al., 2011). We followed exactly the same procedure described in Section 2.2 (see Methods). To get a more complete and understandable representation of sources, we did not consider the lateralized ERP, but the standard ERP responses. Source activation was averaged for each subject and condition within the selected time window and the norm of the vectorial sum of the three orientations at each vertex was calculated. Paired t-tests were used to investigate pairwise comparisons, the FDR method (Benjamini and Hochberg, 1995), considering p= 0.0001 as a threshold, was applied to results to deal with multiple comparisons. To probe the specificity of the activation after S2 during the temporal bisection task, we compared the neural response after S2 between the temporal and the spatial bisection tasks, considering S2 positions in space (±4.5°) separately.

Results

Behavioral analyses revealed a slight but significant decrease in performance (t(16)= 9.03, p< 0.001; see Fig. 3.1) and an increase in execution time (t(16)= -5.56, p< 0.001) for the temporal compared with the spatial bisection task. Here, we focus on ERPs in response to S1 and to S2.

Results of the microstate segmentation for the ERP elicited by S2 of the temporal and spatial bisection tasks identify the earliest significant microstate at around 50-90 ms after S2 was presented (Fig. 3.2). It involves mainly occipital areas during the spatial bisection task but also temporal and fronto-central areas during the temporal bisection task.

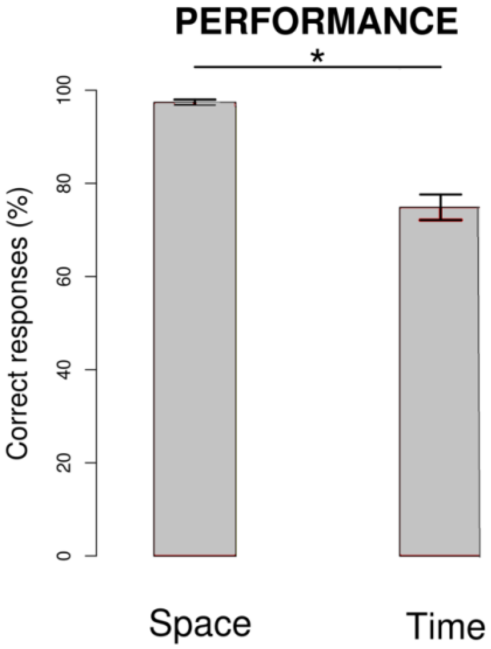

Figure 3.1 Performance (mean±SEM) for spatial (left) and temporal (right) bisection tasks in typical participants.
Although all participants performed above chance level for both task, performance slightly decreased in temporal bisection. * p< 0.001 after Bonferroni correction.

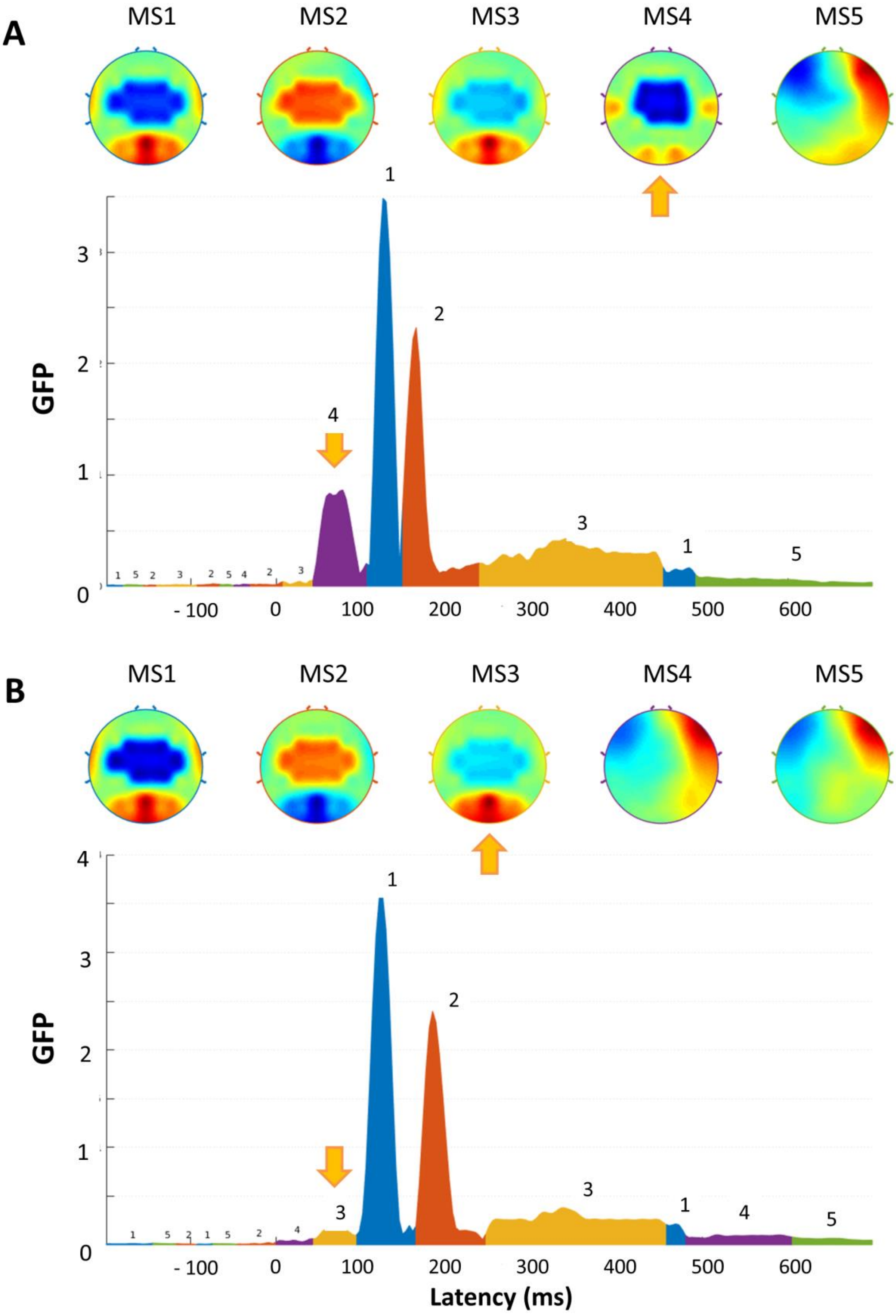

Figure 3.2 Results of the microstate segmentation for the ERP elicited by S2 of the temporal (A) and spatial (B) bisection task.

For both tasks, the earliest significant microstate is identified at around 50-90 ms after S2 (see orange arrows). It involves mainly occipital areas during the spatial bisection task but also temporal and central areas during the temporal bisection task.

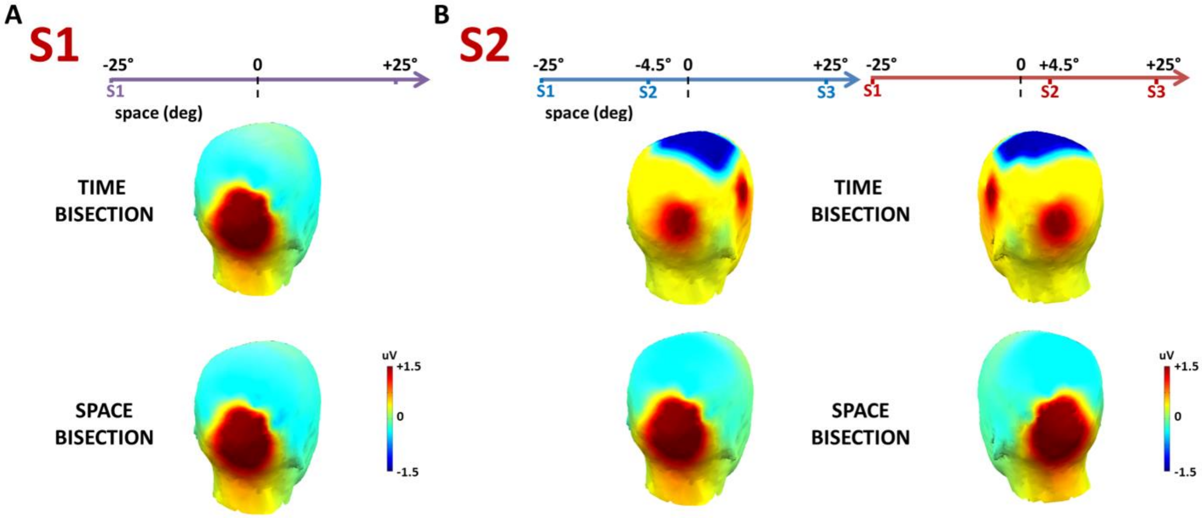

Figure 3.3 Scalp maps of the mean ERP amplitude in the selected time window (50-90 ms) after S1 (A) and S2 (B) of the temporal (top) and spatial (bottom) bisection tasks. S1 **(A)** was always delivered from -25°; S2 **(B)** was presented from either -4.5° (B left) or +4.5° (B right) in space. A contralateral occipital activation is always present independently of the stimulus and the experimental question. A fronto-central and contralateral temporal activation is observed only after S2 of the temporal bisection task.

We report the scalp topographies of the mean ERP amplitude in the 50-90 ms time window after S1 during the temporal (Fig. 3.3A top) and the spatial (Fig. 3.3A bottom) bisection tasks. Independently of the experimental question (i.e. spatial or temporal bisection), only a positivity involving the occipital area contralateral to the visual stimulus position in space (i.e. -25°) occurs. This response likely reflects visual cortical processing in line with previous literature (Di Russo et al., 2002, Foxe et al., 2008). Figure 3.3B shows the scalp maps of the mean ERP amplitude in the selected time window after S2 when S2 was presented from either -4.5° (Fig. 3.3B left) or +4.5° (Fig. 3.3B right) in space independently of timing (±250 ms) during the temporal (Fig. 3.3B top) and the spatial (Fig. 3.3B bottom) bisection tasks. For both tasks, a positivity involving occipital sites contralateral to S2 spatial position is still evident. However, during the temporal bisection task, S2 also elicits strong negativity in fronto-central areas and a prominent positivity in contralateral temporal regions which are absent during the spatial bisection. By comparing between the two tasks the lateralized (i.e. contralateral minus ipsilateral difference amplitude) ERP response to S2 in temporal regions, we demonstrate that the amplification in contralateral temporal areas in the selected time window is specific for the temporal domain ($t(16)= -25.41$, $p< 0.0001$). Instead, there was no difference in the occipital response to S2 between the spatial and the temporal bisection tasks ($t(16)= -1.29$, $p= 0.2$, $d= 0.05$, CId=[-0.9, 1]). Moreover, although the temporal separation between the first two flashes was large enough to allow a complete decay of the ERP response, the temporal component in the 50–90 ms time window is specific for S2 and not for S1 of the temporal bisection task (t(16)= -24.13, p< 0.0001, d= 8.65, CId= [5.43, 11.84]). This result confirms the specific role of the S2 as the starting point for building a metric in the temporal bisection task.

ERP waveforms recorded over the temporal and occipital scalp contralateral and ipsilateral to S2 are reported in Fig. 3.4, separately for the temporal and spatial bisection tasks. As expected, for both tasks typical visual ERP components are observed in the initial 200 ms following cue onset, including the C1 (50–90 ms), the P1 (110–130 ms) and slightly late N1 (150-200 ms) over the contralateral occipital scalp (Fig. 3.4 right). The latency of the C1 and N1 visual-evoked components is slightly earlier for the temporal compared with the spatial bisection task. For the temporal task, only, we observe a positive early component over temporal scalp regions in the hemisphere contralateral to the cued location (Fig. 3.4 left). The difference between the contralateral and ipsilateral activation started 50 ms after cue onset and peaked at around 70 ms post-cue. During the temporal task, we also observed a later positivity in temporal area (P140), selective again for S2 and thus confirming the plausible involvement of these areas in complex temporal representation.

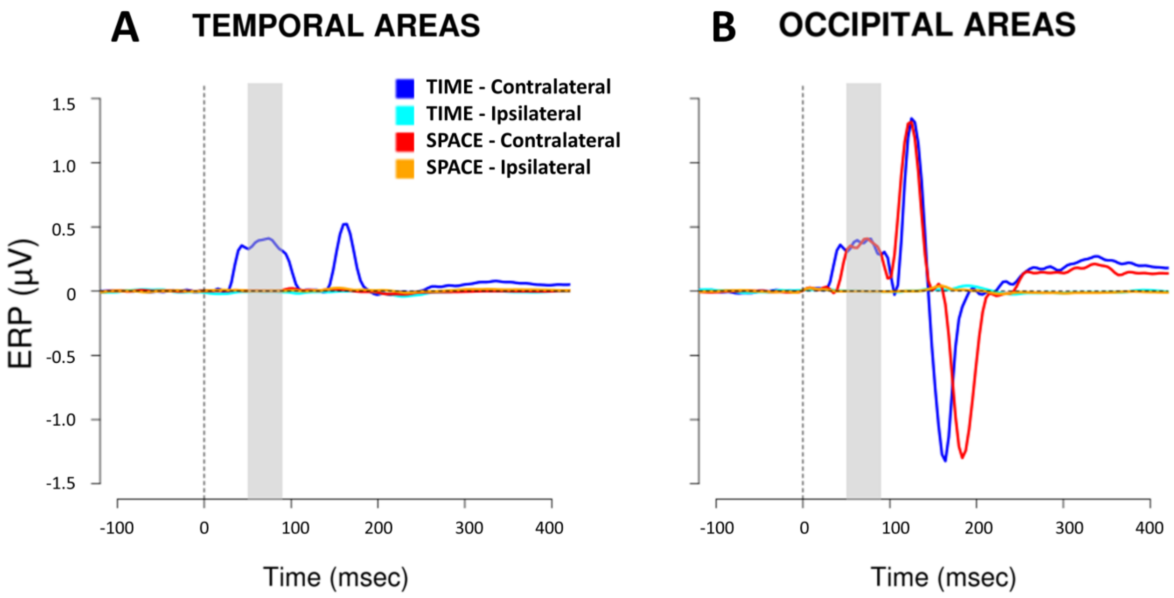

Figure 3.4 ERPs elicited by S2 during the temporal and spatial bisection tasks in temporal (A) and occipital (B) areas.

ERPs collapsed over temporal (i.e.T7/T8)/occipital (i.e. O1/O2) scalp sites contralateral to the spatial side of S2 presentation are in blue and red during temporal and spatial bisection respectively. ERPs collapsed over temporal/occipital scalp sites ipsilateral to the spatial side of S2 presentation are in cyan and orange during temporal and spatial bisection respectively. On the x-axis, t = 0 is stimulus onset. The shaded area delimits the selected time window (50–90 ms).

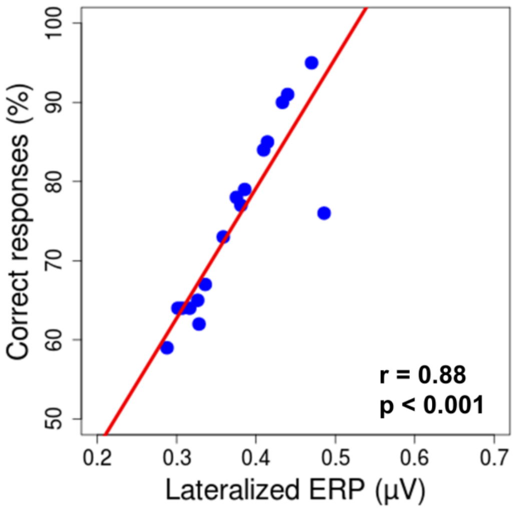

Figure 3.5 Results of the linear regression analysis between performance and early ERP response in temporal scalp regions (i.e. T7/T8) during temporal bisection.
Each point represents one subject. Percentage of correct response in the temporal bisection task positively correlates with lateralized (i.e. contralateral – ipsilateral to S2 position) ERP amplitude in 50-90 ms time window after S2 for the temporal bisection task. Corresponding Pearson correlation coefficient (r) and significant level (p-value) are reported.

The positive and negative early ERP components reported, respectively, in fronto-central and temporal sites during the temporal bisection task resemble modality-specific sensory processing within the auditory cortex (Picton, 2010). Note that the stimuli in the two tasks were identical, with the same spatial and temporal characteristics and the only difference falling in the experimental question. Through correlational analysis, we probed a specific association between performance in the temporal domain and neural response to S2 over temporal regions in the 50-90 ms time window. Specifically, an increase in the contralateral activation in temporal sites corresponds to a higher percentage of corrected responses (r= 0.88, p<0.0001; see Fig. 3.5).

We can exclude the fact that the effect originated from spurious eye-movement towards the apparent location of the stimulus. Indeed, the average response of the eye deviation measured by EOG is very low (i.e. for temporal bisection: -0.011±0.004 µV; for spatial bisection: -0.013±0.005 µV), and did not significantly differ between the two tasks (t(16)= -1.54, p= 0.1, d= 0.15, CId= [-0.8, 1.1]).

Furthermore, to provide more evidence that the early positivity over the temporal scalp is actually involving generators in auditory temporal areas, we performed source level analyses (Fig. 3.6). Considering S2, both bisection tasks elicited a cortical response in the occipital region contralateral to the physical position of the stimulus, while only the temporal bisection also produced a strong and specific contralateral temporal activation. Therefore, compared with the spatial bisection, temporal bisection, after S2, elicits a stronger early activation in the hemisphere contralateral to the physical flash, not only in occipital areas related to visual perception but also in temporal areas likely related to auditory perception.

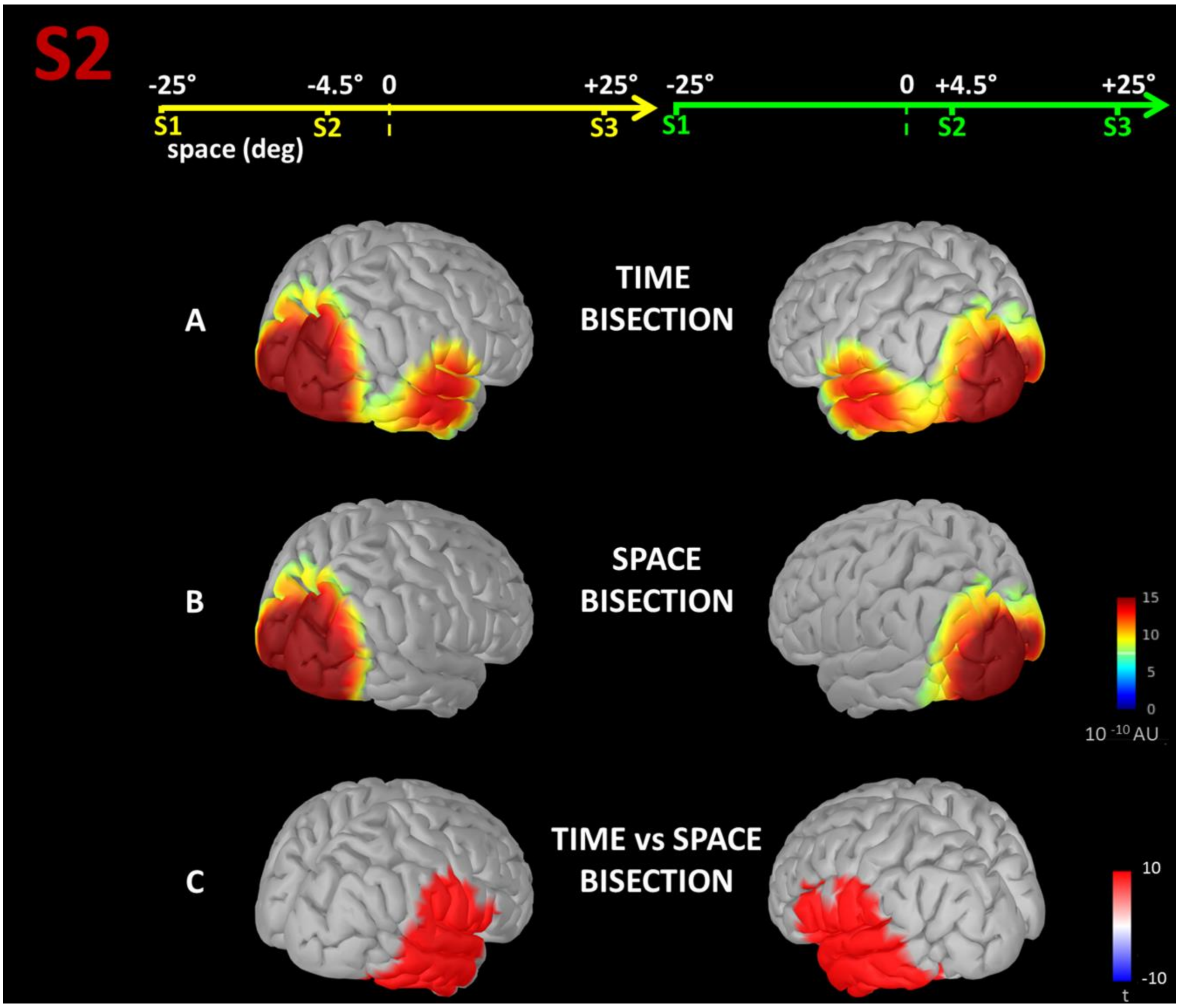

Figure 3.6 Average source activities within the 50-90 ms time window after S2 are compared between the temporal and the spatial bisection tasks.
Left and right panels report the conditions in which S2 was delivered from the left (i.e. -4.5°) or the right (i.e. 4.5°), respectively. Average normalized source activation for the temporal (A) and the spatial (B) bisection is reported in arbitrary (normalized) units (AU). Last line (C) reports the results of paired two-tailed t-tests; the scale is in terms of t-statistics. Significant values of t-statistics are displayed: reddish and bluish colors indicate stronger activations in temporal and spatial bisections, respectively, while the intensity indicates the magnitude of t (i.e. the strength/significance of the difference). Only t-values corresponding to $p< 0.0001$ after FDR correction are displayed.

Discussion of results

With this study, we provide support for a pivotal role of areas likely involving the auditory brain in complex visual temporal representation. We demonstrated that visual flashes during temporal, but not spatial, bisection elicit an early ERP response compatible with an activation of the auditory cortex.

Indeed, when subjects were asked to temporally bisect three consecutive flashes, an early strong response appears in fronto-central and temporal scalp areas. This response mimics some aspects of the N1 ERP component usually elicited by auditory stimuli, which appears negative over the front-central scalp and inverted at mastoids (Naatanen and Picton, 1987). In particular, our ERP component involves a time window (i.e. 50-90 ms) similar to that characterizing the first subcomponent of the auditory-evoked N1 (i.e. N1a peaking at 70 ms), and presents also a similar spatial selectivity in auditory sites (i.e. contralateral to the spatial position of the stimulus). In fact, the auditory-evoked N1a exhibits greater amplitude in auditory cortex contralateral to the ear receiving the stimulation (Naatanen and Picton, 1987, Reite et al., 1981, Pantev et al., 1986).

The specific latency and topography that we report could be explained by the use of clean spatially lateralized brief flashes as stimuli (70 ms, 2.3° diameter). Moreover, the reduced signal in the ipsilateral scalp sites in our data may be due to the joint application of both the ASR and the ICA techniques for artifact rejection during EEG pre-processing analyses (Nathan and Contreras-Vidal, 2015, Bulea et al., 2014). A similar spatial pattern also characterized our visual-evoked C1 component peaking simultaneously (50-90 ms) in contralateral occipital areas (in agreement with Di Russo et al., 2002). However, it is very unlikely that the response in temporal scalp sites reflects a far field effect derived from the occipital response because, if this was the case, the temporal activation should be present also during the spatial bisection task. Although visual stimuli are identical, there is no response at all involving temporal scalp areas during the spatial bisection task, which requires the evaluation of spatial distances instead of time intervals between the three flashes. Even more interesting, the early visual-evoked activation during the temporal bisection is associated with the performance: the higher the response in temporal scalp regions, the higher the accuracy at the temporal bisection task. This result stresses the specific association between complex visual temporal skills and the recruitment of areas likely involving the auditory brain.

Unfortunately, even with the best possible EEG source localization technique, it is hard to provide the exact location of the cortical areas which generate our early component in fronto-central and temporal scalp areas. Generators of auditory-evoked N1 specifically involve primary and association auditory cortices in the superior temporal gyrus, in Heschl's gyrus and planum temporale (Godey et al., 2001, Zouridakis et al., 1998, Celesia, 1976, Giard et al., 1994). On the other hand, we can state that our component originates generically in a wide temporal area which covers the auditory cortex too, but we cannot exclude that it could derive from nearby polymodal areas in superior temporal gyrus.

Consequently, we cannot sustain a direct association between the two ERP components. Nonetheless, in light of the similarities between the visual-evoked component observed here and the auditory-evoked N1 component, it seems that the neural signal originates at the level of early sensory cortex and similar mechanisms of early analysis elicited by auditory stimulation could be recruited when subjects have to build visual temporal representations of events. In this regard, we also observed that the focus on time in the temporal bisection task drives to a slightly earlier onset of the occipital component (C1) compared to the same component elicited during the spatial bisection task. Since temporal representation mostly relies on audition (Burr et al., 2009), this seems in line with Giard and Perronet (1999), who showed that the activation of the visual cortex in response to audio-visual stimuli occurred earlier than to visual stimuli alone.

Although previous data show that the auditory-evoked N1 is affected by spatial attention (Naatanen and Picton, 1987), we do not think this factor can explain the results. Indeed, mere attention to space cannot explain why the early visual-evoked auditory ERP component we observed is specific for the temporal bisection task yet it is absent after the same visual inputs during the spatial bisection task. Plus, a pure attentional effect could not explain why the early response appears only after the second (i.e. at ±4.5°) and not the first flash of the temporal sequence (i.e. at -25°). We think that the cortical activation we observed is specifically associated with the building of complex temporal representation. However, we cannot exclude the likelihood that one process involved in the construction of complex visual representation metric could be the temporal expectation, as the fronto-central and temporal scalp response increases from the first to the second flash. In this context, other brain areas previously linked to explicit time estimation could explain the frontal topography of our early component, such as the insula, the premotor cortex, and the ventro-lateral prefrontal cortex (Bueti et al., 2008b, Bueti et al., 2008a, Coull and Nobre, 2008, Pouthas et al., 2005).

To conclude, the present study suggests that the recruitment of the auditory brain may be necessary to build complex temporal representation within the visual modality, supporting a domain-specific supramodal organization of the brain. Although future studies should investigate other unisensory and multisensory contexts, a speculation is that the brain uses auditory representations to deal with complex temporal representation across multiple sensory modalities. Moreover, this temporal encoding may rely on neural mechanisms similar to those underlying the auditory-evoked N1 component.

3.2 Exp. 2: Complex temporal representation in deafness

Hearing adults succeed at the visual temporal bisection task, which involves judging the relative presentation timings of three flashes. Specifically, in the previous Section 3.1, we demonstrated that hearing people show a ERP response in areas likely involving the auditory cortices, between 50-90 ms after the second flash of the temporal bisection task. Interestingly, a similar activation is missing after the same visual stimuli during the spatial bisection task, which involves the evaluation of spatial distances between three flashes. The early response described in hearing people results strong and contralateral to the spatial position of the second flash, mimicking some characteristics of the N1 ERP component usually peaking after the onset of auditory stimuli (Naatanen and Picton, 1987). Indeed, i) it is in the same time window as the auditory subcomponent N1a, i.e. 50–90 ms; ii) it shows a compatible topography, i.e negative in fronto-central sites and positive in temporal sites, with generators likely in auditory cortices; and iii) it is contralateral to the flash position in space, as would be expected for an auditory stimulus. These findings suggest that the early recruitment of the auditory brain may be fundamental for complex visual temporal representation in hearing individuals. Starting from this, we may hypothesize that lack of audition affects these neural circuits, impairing temporal bisection performance in deaf people, in which the auditory system is impaired. In support of this hypothesis, we previously showed that early processing associated with the construction of spatial maps during auditory bisection is mediated by visual experience (see Chapter 2). While neural correlates for visual enhancement in deaf individuals have been extensively explored, neural correlates behind their visual impairments have been neglected. If the auditory experience has an important role for the visual temporal bisection task in hearing people (see Section 3.1), we may expect that deaf individuals show a deficit in this task, explained by a different neural processing of visual temporal representations. Here, we tested this hypothesis by studying performance and neural correlates associated with visual temporal bisection skills in deaf individuals. To this end, ERPs and psychophysical responses were recorded in deaf individuals during a visual temporal bisection task and compared with those of hearing individuals.

Methods

Experimental procedure

We compared temporal visual bisection skills of hearing subjects involved in the experiment presented in Section 3.1 (H; N=17; mean age±SD: 25±5 yo) with those of a group of 12 early deaf (D; mean Tage±SD: 40±14 yo), with no history of visual or neurological problems. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki.

Setup and experimental procedures were identical to the experiments described in Section 3.1, and a spatial bisection task was similarly performed as control experiment. Participants were asked to evaluate temporal intervals (i.e. temporal bisection task) or spatial distances (i.e. spatial bisection task) between three flashes (namely S1, S2, and S3), while EEG was continuously recorded. EEG data were pre-processed, filtered between 0.1 and 100 Hz, cleaned using ASR (Delorme and Makeig, 2004, Mullen et al., 2013) and Independent Component Analysis (Delorme and Makeig, 2004), and referenced to the average of all channels (see also Methods in Section 2.2 for more details).

Behavioral and Sensor Level Analysis

Performance (i.e. percentages of correct responses) in the temporal and spatial bisection tasks were compared with two-way ANOVA, considering Group (H, D) as a between-subjects factor, and Task (Space, Time,) as a within-subjects factor. Post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction.

The ERP analyses followed closely the procedures employed in the prior study investigating visual temporal abilities in hearing participants (Section 3.1), based on the hypothesis that deafness could drive to different early cortical responses during the temporal bisection task, in particular after S2. Thus, we focused on neural responses to S1 and S2, for the spatial and temporal bisection tasks. Similarly to the previous experiment, EEG data were averaged in synchrony with S1 or S2 onsets to compute ERPs, considering a period of 200 ms before S1 onset as a baseline for both flashes. After cleaning procedures, the total number of trials was around 1570 for each condition, approximately 54 per subject. Conditions were subsequently merged based on S2 spatial position ensuring approximately 108 trials per subject for each cell of the experimental design.

Based on our aim and hypothesis, we focused on electrodes linked to auditory (T7, T8, and Cz) and visual (O1 and O2) processing, and on a time window between 50 and 90 ms after each flash. Mean ERP amplitude was computed for each group by averaging the voltage in the selected time window, merging conditions based on S2 spatial position (i.e. 120 trials with S2 delivered from -4.5° and 120 trials with S2 delivered from +4.5°). For both the bisection tasks, ERP waveforms were collapsed across conditions and the hemisphere of recording (left, right) to obtain ERPs recorded on the contralateral hemisphere and on the ipsilateral hemisphere with respect to stimulus characteristics in space. Lateralized ERP responses were calculated as the relative difference between the contralateral and ipsilateral responses. Scalp topographies of mean ERP amplitude in the 50-90 ms time window were realized for spatial and temporal bisection tasks, considering the two spatial positions of S2 (±4.5°) separately.

To investigate the differences between groups, the mean lateralized ERP amplitudes in the selected time window were analyzed in an omnibus ANOVA considering as factors Flash (S1, S2), Task (Space, Time), and Group (H, D). Two different ANOVA were performed, one considering the auditory (T7 and T8) and one considering the visual (O1 and O2) neural responses. ANOVA and two-tailed t-tests were conducted as post-hoc comparisons with probabilities treated as significant when lower than 0.05 after Bonferroni correction, applied to each subset of post-hoc comparisons separately. As in the previous study we showed that in hearing individuals there exists a strong correlation between ERP response in contralateral temporal sites and performance at the temporal bisection task, we addressed the same association in deaf individuals using linear regression of mean lateralized ERP amplitude in the 50-90 ms time window against the percentage of correct responses.

Source Level Analysis

As in previous studies (see Methods in Section 2.2), we performed a distributed sources analysis using the Brainstorm software (Tadel et al., 2011) to investigate differences between hearing and deaf groups in the cortical generators of the ERP component taken into account. To get a more complete and understandable representation of sources, we did not consider the lateralized ERP, but the standard ERP responses.

We averaged source activation for each subject of the two groups and condition, within the selected time windows. Then, pairwise comparisons were investigated with paired t-test, correcting results for multiple comparisons of source grid points with FDR method (Benjamini and Hochberg, 1995), using p= 0.0001 as a threshold. Based on our hypothesis, we were specifically interested in cortical generators evoked by S2 during the temporal bisection task, and we compared the neural response to S2 between hearing and deaf individuals, considering the two tasks (spatial and temporal) and S2 positions in space (±4.5°) separately.

Results

First of all, we demonstrated a behavioral deficit of deaf participants in performing the temporal bisection task (Figure 3.7). The two-way ANOVA performed to investigate differences in the behavioral performance revealed a significant interaction (F(1,27)= 13.4, p= 0.001, GES= 0.1) between Group (H, D) and Task (Space, Time). Post-hoc t-tests revealed that the performance of deaf individuals in temporal bisection (percentage of correct responses, mean±SEM: 59±3%) was significantly lower compared to both temporal performance of hearing participants (t(23.6)= 3.61, p=0.003), and their own performance in the spatial bisection (percentage of correct responses: 96±2%; t(11)=11.7, p<0.001). Instead, no deficit was present in the spatial bisection task, for which the probability of correct response was not different between the two groups (t(12.9)=0.44, p=1).

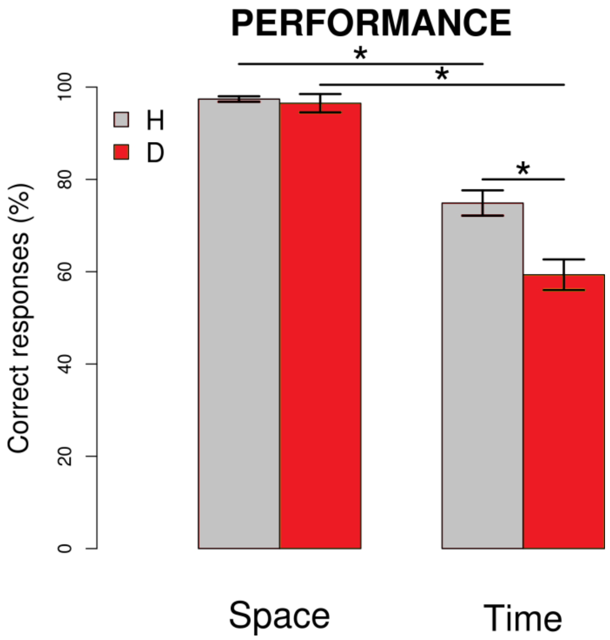

Figure 3.7 Performance (mean±SEM) for spatial (left) and temporal (right) bisection tasks in deaf (red) and hearing (grey) subjects.
Deaf participants show significantly lower percentage of correct responses compared with hearing participants in temporal but not spatial bisection. * $p< 0.001$ after Bonferroni correction.

Turning attention to the neurophysiological results, the omnibus ANOVA on the lateralized ERP amplitude involving temporal areas in the 50-90 ms time window showed a strong interaction between Flash (S1, S2), Task (Space, Time) and Group (H, D; $F(1,27)= 234$, $p< 0.001$, GES= 0.59). Thus, we subsequently performed hypothesis-driven follow-up ANOVAs and post hoc comparisons. First, we hypothesized that S2 could specifically modulate the interaction between other factors. Therefore, we performed two separate ANOVAs (one for each flash), with Task as within subject factors, and Group as between subject factor. As expected, we found a significant interaction between these two variables for S2 ($F(1,27)= 277.1$, $p< 0.001$, GES= 0.8). On the contrary, this was not the case for S1, where we did not find any significant effects (for the interaction: ($F(1,27)= 2.4$, $p= 0.1$, GES= 0.01). Thus, we focused subsequent analyses on S2, separately evaluating the two Tasks (Space, Time). Therefore we performed two separate ANOVAs (one for Space, the other for Time), with Group as between subject factor. We found a significant difference between Group for the temporal bisection ($F(1,27)= 283.9$, $p< 0.001$, GES= 0.9), while not for the spatial one ($F(1,27)= 0.002$, $p= 0.9$, GES< 0.001). In the end, a post-hoc t-test revealed that S2 during the temporal bisection task evoked a higher response in contralateral temporal areas of hearing compared to deaf people ($t(38.1)= 16.8$, $p< 0.001$). This is evident in Figure 3.8, representing scalp maps elicited by S2 delivered from -4.5° (i.e. left, left panel) and +4.5° (i.e. right, right panel), independently of timing (±250 ms), for hearing (top panel) and deaf participants (bottom panel) during the temporal bisection task. A positivity appears in occipital areas contralateral to the stimulus position in space for both groups. However, in hearing individuals S2 also elicits strong negativity in fronto-central areas and a prominent positivity in contralateral temporal regions, which are absent in deaf individuals. Thus, the response in fronto-central and temporal areas during the temporal bisection task is specific for the hearing individuals. Moreover, while we previously demonstrated that a higher contralateral activation in temporal sites is associated with better performance in hearing people (r= 0.88, p<0.0001; see Fig. 3.5), here we showed that this is not the case for deafness (r= 0.2, p= 0.6).

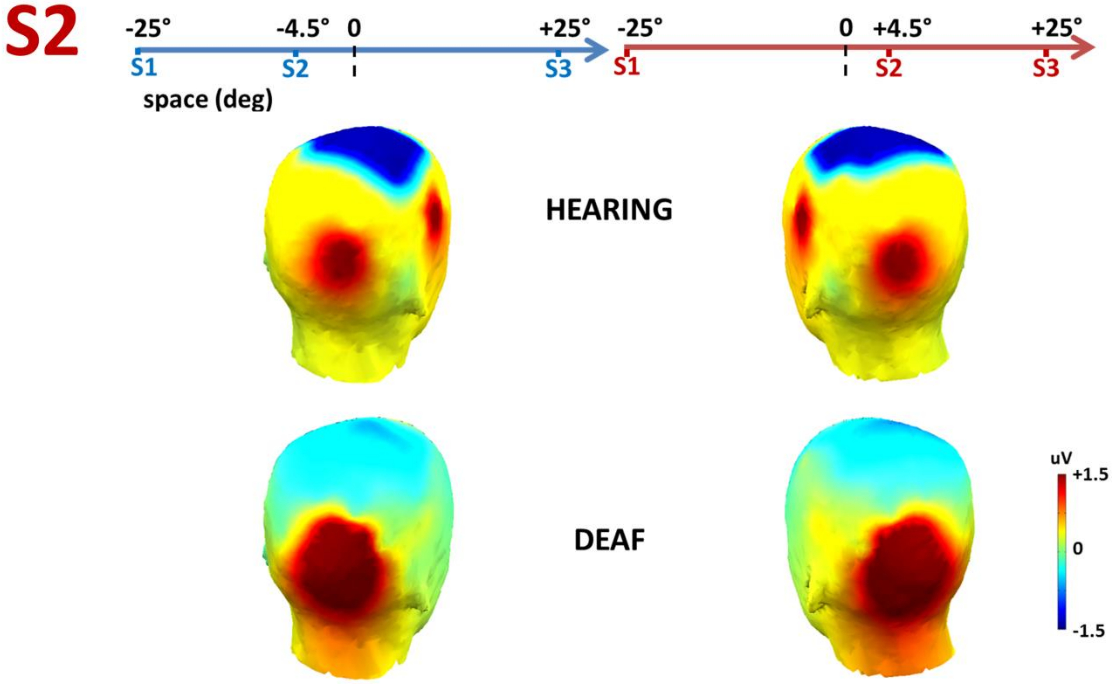

Figure 3.8 Scalp maps of the mean ERP amplitude in the selected time window (50-90 ms) after the second flash of the temporal bisection task, for hearing (top) and deaf (bottom) groups.
Left and right panels of the figure report the conditions in which S2 was presented from either left (i.e. - 4.5°, see left panel) or right (i.e. +4.5°, see right panel), respectively, independently of timing (±250ms). A contralateral occipital activation is always present independently of the group. A fronto-central and contralateral temporal activation is observed only for hearing participants.

As for occipital areas, an interaction between Flash (S1, S2), Task (Space, Time) and Group emerged from the omnibus ANOVA too (H, D; F(1,27)= 10.1, p= 0.003, GES= 0.02). Hypothesis-driven follow-up ANOVAs revealed significant main effects of Task (F(1,27)= 9.7, p= 0.004, GES= 0.1; Space, mean±SEM: 0.394±0.007 µV; Time: 0.385±0.006 µV) and Group (F(1,27)= 667.4, p< 0.001, GES= 0.9 H: 0.35±0.001 µV; D: 0.44±0.005 µV) for S1. The main effect of Task for S1 is likely driven by very low standard errors, as S1 was always delivered from the same position in space and thus precision was high. For S2, the hypothesis-driven follow-up ANOVA showed a significant interaction between the two variables (F(1,27)= 7.3, p= 0.01, GES= 0.02; see Fig. 3.9). Specifically, for S2, post-hoc t-tests showed a significant difference between groups for both the temporal (t(26.8)= -7.6, p< 0.001) and the spatial (t(22.1)= -6.3, p<0.001) bisection tasks, while similar activation between the tasks within the hearing group (t(16)=1.3, p= 0.4), and the deaf group (t(11)= -2.1, p= 0.1). A slightly bigger difference between the temporal with respect to spatial bisection task in deaf individuals is probably what is driving the interaction Task X Group for S2. To sum up, independently of the flash sequence, visual stimuli seem to elicit a higher response in occipital areas of deaf participants compared to hearing, and this occipital recruitment is even slightly higher for S2 during the temporal bisection.

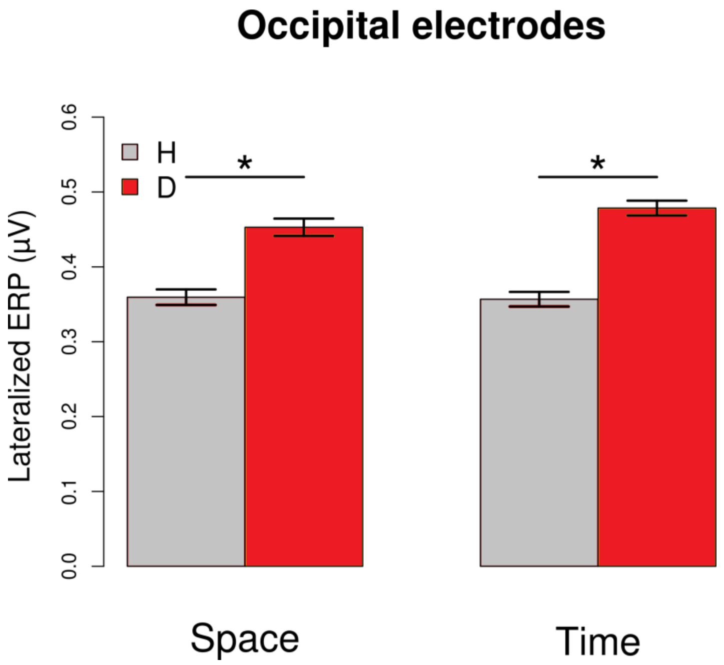

Figure 3.9 Lateralized (contralateral-minus-ipsilateral) ERP amplitude (mean±SEM) in occipital (O1/O2) scalp sites in the time window between 50-90 ms after the second flash of spatial (left) and temporal (right) bisection task.
In grey, hearing participants; in red, deaf participants. The star indicates a significant difference between the groups (p<0.001)

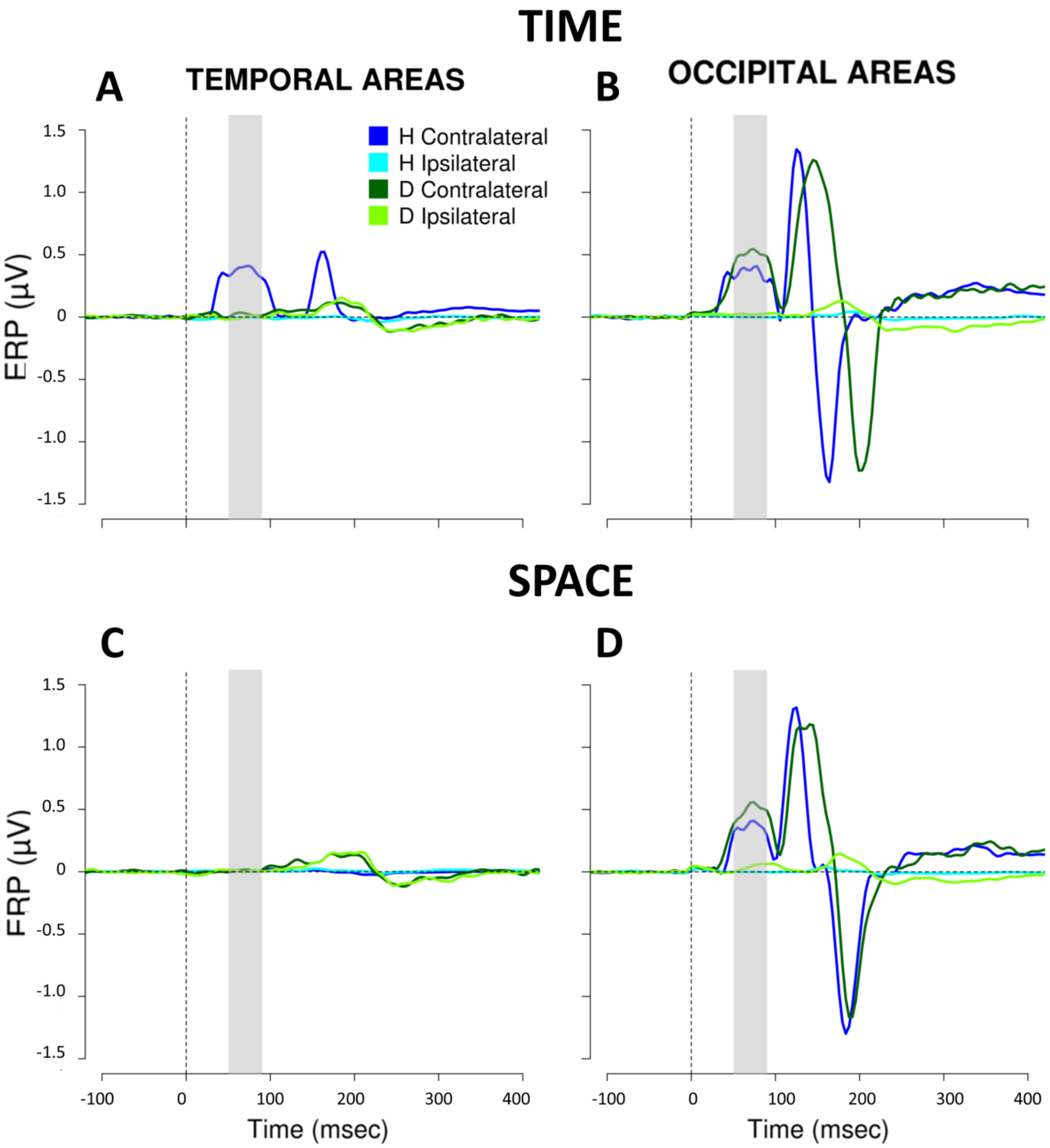

Figure 3.10 ERPs elicited by S2 during the temporal (top) and spatial (bottom) bisection tasks in temporal (left) and occipital (right) areas.

ERPs collapsed over temporal (i.e.T7/T8)/occipital (i.e. O1/O2) scalp sites contralateral to the spatial side of S2 presentation are in dark blue and dark green for hearing and deaf groups respectively. ERPs collapsed over temporal/occipital scalp sites ipsilateral to the spatial side of S2 presentation are in cyan and light green for hearing and deaf groups respectively. On the x-axis, t = 0 is stimulus onset. The shaded area delimits the selected time window (50–90 ms).

For both hearing and deaf groups, we report ERP waveforms recorded over the temporal (Fig. 3.10, left panel) and occipital (Fig. 3.10, right panel) scalp contralateral and ipsilateral to S2, for temporal (top panel) and spatial (bottom panel) bisection. Since, waveforms for hearing people are identical to those described in Section 3.1, here we focus on differences between the two groups. For both groups typical visual ERP components are observed in the initial 200 ms following cue onset, but the amplitude of the the C1 (50–90 ms) components is higher for deaf individuals for both tasks (Fig. 3.10B and 3.10D).

More interesting, only for hearing and not for deaf people we observed a positive early component over temporal scalp regions in the hemisphere contralateral to the cued location in space during the temporal bisection (Fig. 3.10A). The time window considered in the analyses was the first one presenting a task-related modulation. However, also a later activation (P140) selective for the temporal bisection occurs in temporal areas of hearing and not deaf participants, and other latency differences emerge between the groups in occipital areas during temporal bisection. The differences between the two groups did not derive from eye-movements. The average response of the eye deviation measured by EOG did not significantly differ between the two groups (for temporal bisection: t(14.7)= -0.24, p= 0.8; for spatial bisection: t(14)= -0.21, p= 0.8). Moreover, as for hearing individuals (see Section 3.1), within the deaf group there was no difference in eye deviation between the two tasks (t(11)= 1.38, p= 0.2).

By comparing the groups at source level, we confirmed that the response of interest was involving generators likely in the auditory cortices for hearing but not deaf individuals. Indeed, as evident in Figure 3.11, S2 during the temporal bisection task elicited a cortical response in the temporal region contralateral to the physical position of the stimulus in hearing and not in deaf people. The same experimental condition also evoked a response in the occipital region contralateral to the physical position of the stimulus for both groups, as expected for the processing of visual stimuli. However, in line with the statistical results involving the occipital electrodes, even the source analyses revealed that the recruitment of visual areas increases following deafness.

Discussion of results

This experiment investigated how auditory deprivation impacts on complex visual temporal skills and neural correlates. First of all, we observed a deficit for visual temporal bisection task in deaf individuals. More interesting, we reported the possible neural correlates of this deficit: visual temporal bisection elicits in hearing but not in deaf individuals an early response compatible with an activation of the auditory cortex, which shows many features compatible with the auditory-evoked N1 (see Section 3.1). Unlike hearing participants, complex temporal representation of visual flashes does not elicit any early responses in temporal areas of deaf participants, for which only the visual cortex results activated during the task.

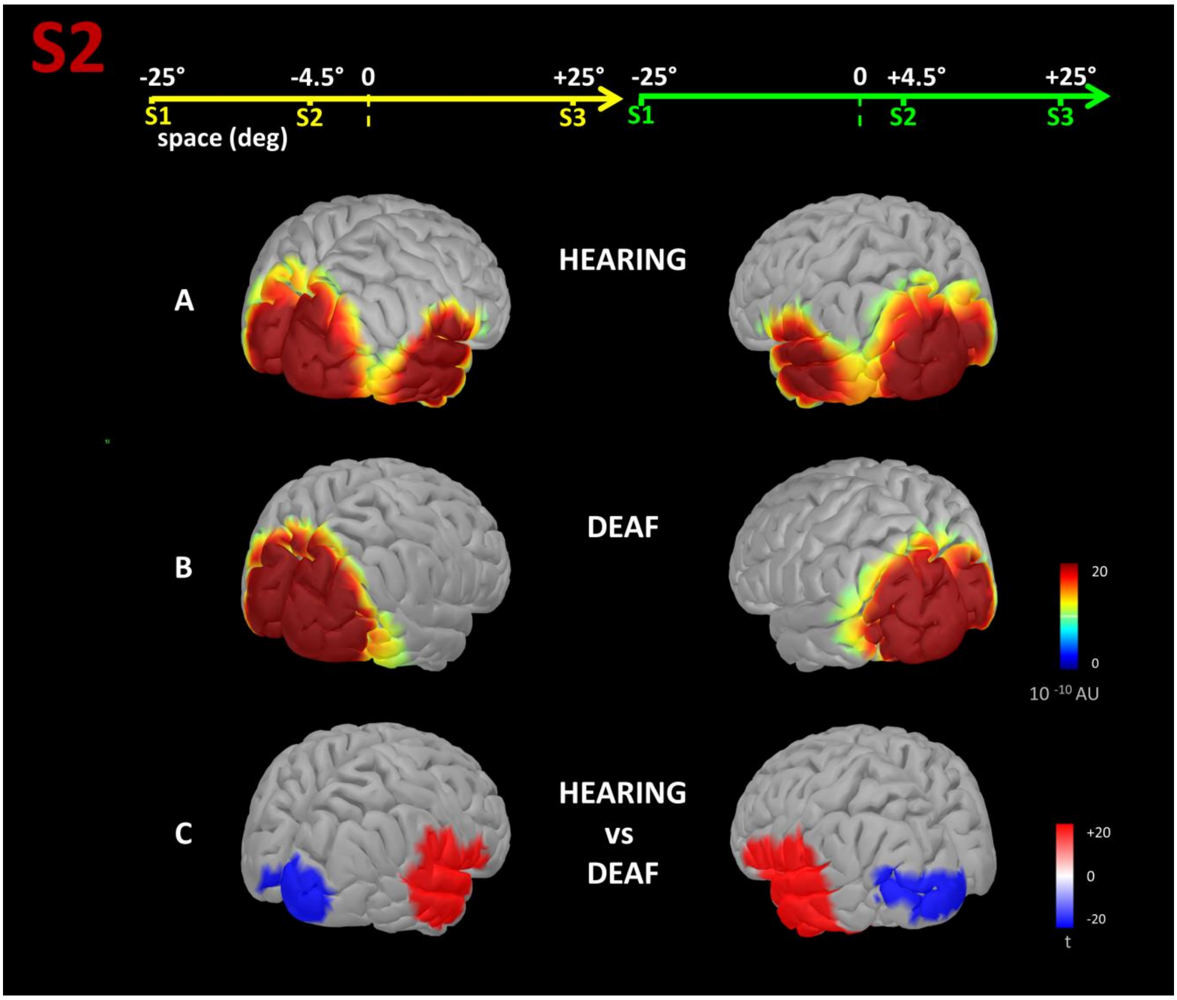

Figure 3.11 Average source activities within the 50-90 ms time window after S2 of the temporal bisection task, are compared between hearing and deaf participants.
Left and right panels report the conditions in which S2 was delivered from the left (i.e. -4.5°) or the right (i.e. 4.5°), respectively. Average normalized source activation for hearing **(A)** and deaf **(B)** groups is reported in arbitrary (normalized) units (AU). Last line **(C)** reports the results of paired two-tailed t-tests; the scale is in terms of t-statistics. Significant values of t-statistics are displayed: reddish and bluish colors indicate stronger activations in temporal and spatial bisections, respectively, while the intensity indicates the magnitude of t (i.e. the strength/significance of the difference). Only t-values corresponding to p< 0.0001 after FDR correction are displayed.

The deficit in temporal bisection following deafness was expected since it is a complex task in terms of temporal memory and attention, it involves the construction of complex temporal representation and we know from previous studies that audition plays a strong dominant role on it (Gori et al., 2012b, Gori et al., 2017). We exclude that it derived from a deficit in memory per se in the group of deaf individuals as there was no difference in performance between the two groups for the spatial bisection task. However, the main insight of the present study regards the neural correlates of the deficit, which seem to correspond to the lack of both an early negativity in fronto-central sites and an early positivity in temporal sites contralateral to the stimulus position in space. The fact that in deaf individuals the early response likely involving the auditory cortices is absent could indicate that auditory experience mediates its development in hearing people. In addition, the link between the early activation and temporal bisection abilities is confirmed by the fact that in hearing but not in deaf people we observed a strong correlation between behavioral performance at the temporal task and the amplitude of the early ERP response in contralateral temporal areas.

As expected (Bottari et al., 2011, Hauthal et al., 2014b), independently of the task, deaf people show a higher activation in occipital areas compared to hearing participants. Specifically, this activation is slightly more enhanced after the second flash of the temporal bisection task, likely suggesting some attempts of compensation in the occipital brain for the lack of involvement of the temporal regions during the task. This is in line also with the study of Bologningi et al. (2012), suggesting that the recruitment of occipital areas following deafness is not always adaptive.

To conclude, this study reveals a key role of auditory experience in complex temporal representation within the visual modality, suggesting that domain-specific supramodal organization of the auditory brain can be partially dependent on sensory experience. By showing that the impairment in building complex temporal representation following deafness is likely due to the lack of activation of the temporal cortex, results presented in Chapter 3 also increase knowledge about underlying neural processes involved in temporal deficits caused by auditory loss.

Chapter 4

Space vs. time

“Space is a still of time, while time is space in motion” (Piaget, 1927, p.2). It has been almost one hundred years since Piaget argued that temporal metric is strictly related to spatial metric. Yet, a century later, we still do not know how exactly space and time interact in the human brain, and in particular how they interact during development.

Two main theories address how the concepts of space and time are linked in the human mind: the Conceptual Metaphor Theory (CMT, Lakoff and Johnson, 1999) and the Theory of Magnitude (ATOM; Walsh, 2003). According to CMT, temporal representations depend asymmetrically on spatial representations. This means that space unilaterally affects time, whereas the opposite is not possible. The metaphorical language is mentioned to sustain this hypothesis (Boroditsky, 2000, Clark, 1973), suggesting that spatial metaphors are necessary to think and talk about time. Support for CMT comes also from several psychophysical studies (e.g. Casasanto and Boroditsky, 2008, Merritt et al., 2010). By contrast, Walsh et al. (2003) introduced a different perspective by proposing a Theory of Magnitude (ATOM), which does not predict any cross-domain asymmetry. ATOM states that space and time, together with numbers, are represented in the brain by a common magnitude system and are thus symmetrically interrelated (Bueti and Walsh, 2009, Burr et al., 2010, Lambrechts et al., 2013). Different behavioral (e.g. Bueti and Walsh, 2009, Dormal et al., 2008) and neuroimaging works (e.g. Fias et al., 2003, Pinel et al., 2004, Dormal and Pesenti, 2009) agree with the ATOM theory, highlighting interferences between the two domains and the activation of overlapping areas in the parietal lobe during magnitude processing. In this context, two effects have been extensively studied over the years: Kappa and Tau effects (e.g. Kawabe et al., 2010, Sarrazin et al., 2007, Bill and Teft, 1972). According to Kappa effect on the one hand, space affects the perception of time (e.g. time judgments increase as a function of spatial separation between stimuli). According to the Tau effect on the other hand, time affects the perception of space (e.g. space judgments increase as a function of temporal separation between stimuli). The Imputed Velocity Theory (Huang and Jones, 1982) states that

Kappa and Tau effects exist because humans intuitively attribute constant velocity to a single object apparently moving through space over time. Thus, if people assume a constant velocity of motion, they ascribe a greater duration to the two points that are further apart spatially, and conversely, a greater spatial separation between the two points that are temporally farther apart. These effects are often reported as examples of bidirectional interference between space and time, in favor of the ATOM theory (Benussi, 1913, Bill and Teft, 1969, Cohen et al., 1953, Collyer, 1977, Helson and King, 1931, Jones and Huang, 1982, Price-Williams, 1954, Sarrazin et al., 2004).

As explained in previous chapters, research suggests that different sensory modalities are more appropriate to process specific environmental proprieties. Specifically, vision is typically the most accurate sense for spatial representation (e.g. Alais and Burr, 2004), offering in a single frame an immediate and complete representation of the surrounding layout. As well as vision is crucial to represent space, audition is generally considered the most accurate sense to represent temporal information, prevailing in audio-visual temporal tasks (e.g. Bresciani and Ernst, 2007). A recent review (Loeffler et al., 2018) points out the importance of keeping in mind notions about the different roles of sensory modalities when addressing the link between space and time. Indeed, different sensitivities of sensory modalities to temporal and spatial information might explain the apparently contradictions between empirical evidence supporting either the CMT or the ATOM theory. In the review by Loeffler and colleagues, results indicate that most studies in favor of an asymmetric time-space mapping, and hence of the CMT, applied visual tasks for both temporal and spatial representations (e.g. Boroditsky, 2000, Xue et al., 2014, Merritt et al., 2010, Bottini and Casasanto, 2013, Casasanto et al., 2010). Instead, studies supporting the symmetry hypothesis, and thus the ATOM, predominantly used visual tasks for the spatial domain, and auditory task for the temporal domain. The tasks used varied across the studies, for instance they could involve duration and distance judgments (Bottini and Casasanto, 2013), ambiguous temporal and spatial questions (Boroditsky, 2000), temporal (e.g., which of two tones lasted longer) and spatial (e.g., which of two lines was longer) discrimination (Hyde et al., 2013), or incongruent vs. congruent audio-visual length-time pairings (Agrillo and Piffer, 2012). The authors of the review concluded that contradictory findings across studies may be related to task-dependent modality-specific processing, which may play a significant role for interrelations between temporal and spatial representations. Even a recent study supporting asymmetrical interference between space and time (Reali et al., 2019) can be re-read in this perspective. Researchers observed that the time influence on space disappeared when the illusion of imputed velocity was reduced, but actually they tested only the visual modality.

Within this framework, in this Chapter, we used results from Chapter 2 and 3 as neuroscientific bases to build up new experiments investigating possible mechanisms underlying the interaction between temporal and spatial representations, taking into account the specific role of vision and audition. Indeed, although both temporal and spatial representations are essential for human functioning, the mechanisms underlying these interrelations are far from being well understood. The bisection task used in the previous chapters turned to be a useful paradigm to investigate this topic. It consists of relative comparisons between spatial distances (i.e. spatial bisection) or temporal intervals (i.e. temporal bisection) between three stimuli. It requires strong skills in terms of memory and attention, and it taxes a sophisticated and well-calibrated spatial or temporal representation. Yet, what we think is special about the bisection is that it naturally combines spatial with temporal representations. Both spatial and temporal gaps are determined by the first and the third stimuli, and the spatial and temporal coordinates of the second stimulus can be independently modulated with respect to the other two stimuli. In Section 4.1, I present a study where the bisection task is used to investigate the interaction between the spatial and the temporal domains within the auditory modality during development. Indeed, no studies have explored the interaction between the two domains within the auditory modality in children (e.g. for the visual modality Bottini and Casasanto, 2013, Casasanto et al., 2010). Then, in Section 4.2 and 4.3, auditory and visual bisection tasks are used to study the interaction between space and time when one sensory modality, such as vision or audition, is missing. One of the goals of Chapter 4 is to investigate a possible role of temporal information to decode spatial information and vice-versa. Specifically we test weather when spatial or temporal skills are poor, such as during development, in blindness or deafness, people could benefit from coherent spatiotemporal information. In agreement with the ATOM (Walsh, 2003), results show both a temporal influence on spatial representations in childhood and blindness, and a spatial influence on temporal representations in deafness. Findings of Chapter 4 present new opportunities for developing sensory substitution devices and rehabilitation technologies for people who are blind or deaf. Indeed, one could simultaneously manipulate spatial and temporal cues to convey richer information.

4.1 Exp. 1: Time attracts auditory space during development

According to the cross-sensory calibration theory, during development, the most accurate sense for a given perceptual task is used to calibrate the other senses (see Chapter 1). Thus, results suggest that during development the visual system could have a crucial role to calibrate the auditory system for spatial representation, while the auditory system to calibrate the visual one for temporal representation (e.g. Gori et al., 2012b, Loomis et al., 1998, Da Silva, 1985). For the developing child, cross-sensory calibration processes seem to be more important than optimizing perception by integration, and therefore audio-visual integration develops gradually from early childhood (e.g. Bahrick, 2001, Streri, 2003, Lewkowicz, 2000) to adolescence (e.g. Gori et al., 2012b, Adams, 2016). Although many studies have investigated the development of audio-visual integration considering the spatial and the temporal domain separately, few studies to date have explored the interaction between the spatial and the temporal domains within a single modality during development (e.g. for the visual modality Bottini and Casasanto, 2013, Casasanto et al., 2010). Since during development the different sensory modalities interact, we may expect that during the sensory calibration processes also the temporal and spatial domains interact. Children may use spatial and temporal properties of stimuli to process different sensory environmental information. Since audition is fundamental for temporal representation, in this study we hypothesized that temporal cues could influence spatial representation development within the auditory modality (see Amadeo et al., 2019b).

To address this topic, we evaluated how children at different ages deal with congruencies and incongruences between the spatial and temporal domains during spatial estimation in the auditory modality. Auditory spatial representation was tested in a group of healthy children aged between 11 and 14 years using different auditory spatial bisection tasks. Spatial bisection consists of listening to a sequence of three consecutive spatially-separated sounds and judging the relative spatial position of the second stimulus. We manipulated time delays, together with space distances between the three sounds, in order to investigate the abilities of children to evaluate spatial features of auditory stimuli, when conflicting or non-conflicting spatial and temporal cues were delivered. A temporal bisection task, which involved judging the presentation timings of three sounds, was performed as a control experiment.

Method

Experimental paradigm

A group of 52 children aged between 11 and 14 years, along with 15 adults, took part in the study. Children were recruited from intermediate schools in Imperia (Italy), while adults were contacted from a list of volunteers in Genova (Italy). To test the developmental trend of auditory spatial skills, children were split into three groups according to their school grade (assessed by the national curriculum). 7 children and 2 adults were excluded from statistical analysis because they were defined as outliers (i.e. score in at least one task differing more than two standard deviations from the mean score of the group). Thus, the final sample consisted of 18 children aged approximately 11 years old (yo; 1st level of intermediate school, mean age±SD: 11.28±0.46 yo; F= 10), 14 children aged approximately 12 years old (2nd level of intermediate school: 12.14±0.36 yo; F= 6), 13 children aged approximately 13 years old (3rd level of intermediate school: 13.38±0.51 yo; F= 6), and 13 adults as control subjects (32.85±12.47 yo; F= 7). Based on mean age, for the sake of clarity, we will refer to these subsamples as “11-year-old group”, ”12-year-old group”, “13-year-old group”, and “adults”. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained prior to testing.

Figure 4.1 Photo of setup used for the bisection tasks.

Setup was identical to other Experiments described in Chapter 2 and 3 (Fig. 2.7A and Fig. 4.1). Participants were seated blindfolded in front of the center of an array of 23 speakers placed at a distance of 180 cm and spanning ±25° of visual angle (with 0° representing he central speaker, negative values on the left, and positive values on the right). They performed three spatial bisection tasks, as well as one temporal bisection task as a control. The order of spatial and temporal blocks was counterbalanced across subjects in order to take into account possible confounds (e.g. the influence of performing the temporal bisection task first). During each task subjects listened to a sequence of three consecutive sounds (500 Hz, 75 ms duration, 60 dB Sound Pressure Level (SPL)) for a trial duration of 1500 ms. Each spatial bisection task, and the temporal bisection task, consisted of 42 trials. In spatial bisection tasks, participants judged verbally whether the second sound (S2) was spatially closer to the first sound (S1; −25°, 0 ms) or to the third sound (S3; +25°, 1500 ms). S2 could occur randomly at an intermediate position from -25° to +25° in space, determined through the method of constant stimuli. In order to evaluate the role of temporal cues on space performance, temporal intervals between the three sounds were manipulated to originate three different spatial bisection tasks (Fig. 4.2, top panel): *independent time*, *coherent time* and *opposite time* spatial bisection tasks, with time intervals that could be independent, coherent or opposite with respect to space distances respectively.

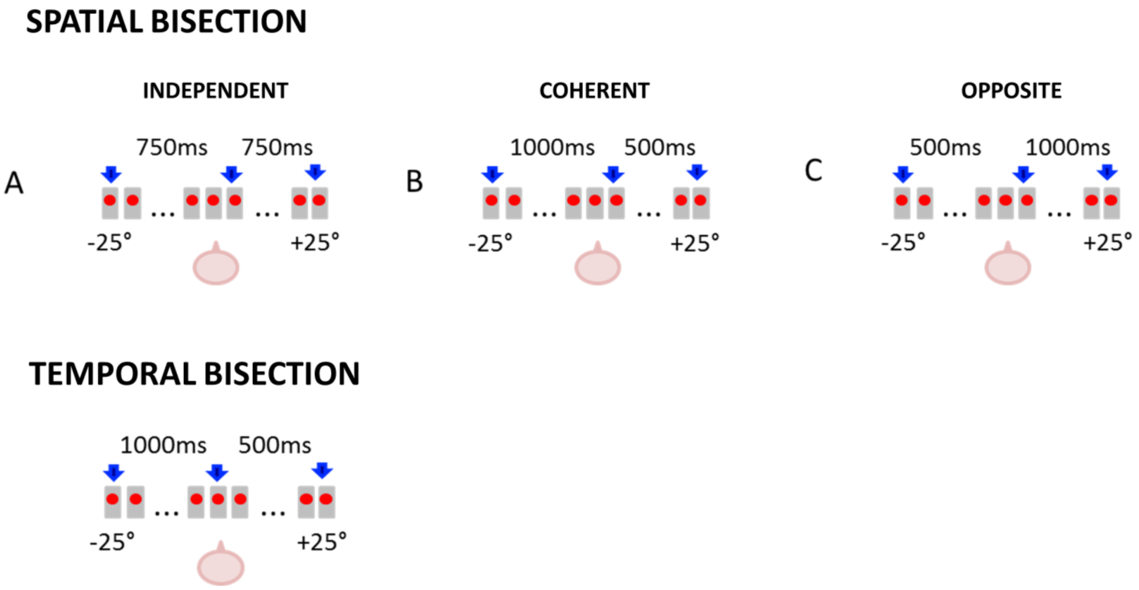

Figure 4.2 Illustration of the three spatial bisection tasks (top panel) and the temporal bisection task (bottom panel).
Participants were aligned with the central speaker (0°). The first and the second stimuli were always delivered at -25° and +25° respectively. For spatial bisection tasks (top panel), the second stimulus occurred randomly from -25° to +25°. **(A)** *Independent time* spatial bisection task: the time interval between the first and the second sound (750 ms) was independent to the time interval between the second and the third sound; **(B)** *Coherent time* spatial bisection task: spatial distances and temporal intervals between the three sounds were directly proportional (e.g. long spatial distance and long temporal interval); **(C)** *Opposite time* spatial bisection task: spatial distances and temporal intervals between the three sounds were inversely proportional (e.g. long spatial distance and short temporal interval). For temporal bisection tasks (bottom panel), the first and the second stimuli were always delivered at -25° and +25° respectively, while the second stimulus occurred from 0 ms to 1500 ms but always from the central speaker (0°). Milliseconds in the figure represent exemplar trials.

In the *independent time* spatial bisection, S2 was always delivered 750 ms after S1, which corresponded to the middle time of the temporal sequence between S1-S3. To correctly compute this task, children had to rely exclusively on spatial features since the three sounds were played with the same temporal delay between S1-S2, and between S2-S3 (as in the original work, Gori et al., 2014), making temporal aspects uninformative. Among spatial bisection tasks, the *independent time* one was always performed first to help children understand the spatial instructions, while the order of the other two spatial tasks randomly varied across participants. In the *coherent time* spatial bisection task, spatial distances between S1-S2 and S2-S3 were directly proportional to temporal intervals between the three sounds (e.g. a longer spatial distance between S1-S2 was associated with a longer temporal delay between the two sounds). In this case, temporal cues could be used by subjects to infer complex spatial representation. The exact temporal delay associated with each spatial position of S2 is reported in the upper horizontal axis of the central psychometric function in Figure 4.3. Considering that the total trial duration was 1500 ms and the number of speakers was 23, when S2 was for example delivered from the second speaker on the left it was associated with a delay of 65 ms, when it was delivered from the third speaker on the left with a delay of 130 ms (65+65 ms), and so on. Instead, space distances between the three sounds were inversely proportional to temporal intervals in the *opposite time* spatial bisection task (e.g. a longer spatial distance between S1-S2 was associated with a shorter temporal delay between the two sounds), making time informative but in the opposite direction with respect to space. Again, the exact temporal delay associated with each spatial position of S2 is reported in the upper horizontal axis of the psychometric function on the right in Figure 4.3. In this case for instance, when S2 was delivered from the second speaker on the left it was associated with a delay of 1435 ms (1500-65 ms), when it was delivered from the third speaker on the left with a delay of 1370 ms (1435-65 ms), and so on.

As to the temporal bisection task performed as a control experiment, participants were asked to verbally report whether S2 was closer to S1 or to S3 in the temporal domain (Fig. 4.2, bottom panel). Similarly to spatial bisection tasks, S1 and S3 were always delivered from −25° (0 ms) and +25° (1500 ms) respectively. Differently to spatial bisection tasks, S2 occurred randomly from 0 ms to 1500 ms after S1 but it was always delivered from 0° in space, by the central speaker. Hence, exclusively temporal cues could be used to perform this task. As for S2 position in the spatial bisection tasks, the timing of S2 in the temporal bisection task was determined using the method of constant stimuli.

To be sure the children understood the instructions correctly, a short training session with feedback was conducted before each condition. The experimental protocol began once we were sure they understood the tasks. All subjects were blindfolded before entering the experimental room so that the exact location and layout of speakers could not be seen. Before testing, all subjects were directed to maintain a stable head position and to fixate straight ahead. However, head and body orientation were continuously monitored during the experiment by the researchers (no differences emerged between groups). Participants were informed from the beginning that S1 was always produced by a speaker placed on their left, whereas the last sound by a speaker on their right (as in Gori et al., 2014). No feedback was given during experimental sessions.

Data analysis

For each task, we calculated the proportion of trials where the second sound was perceived as closer to the third sound and data were fitted by cumulative Gaussian functions. Following standard psychophysical procedure (Kingdom and Prins, 2010), PSE and threshold estimates were obtained from the mean and standard deviation of the best fitting function, and standard errors for the bisection PSE and threshold estimates were calculated by bootstrapping (Efron and Tibshirani, 1993). Specifically, we used a custom algorithm that has been previously validated in many published papers involving children (e.g. Gori et al., 2008) and clinical participants (e.g. Gori et al., 2010, Gori et al., 2017) whose performance was far from being optimal and similar deficits in bisection tasks were reported. The algorithm is based on Bootstrap technique; it automatically verifies the goodness of fit of the psychometric function and, when it is not significant, it assigns as threshold the worst value one subject can get (i.e. max threshold). In our case, two subjects were interpolated in the *opposite time* condition, and seven subjects were interpolated in the *independent time* condition.

Some subjects within the younger group based their answers on temporal features in the *opposite time* spatial bisection task (i.e. when time intervals were incoherent with respect to space distances), exhibiting inverted psychometric functions. These corresponded to thresholds assuming negative values, with thresholds closer to 0 meaning good precision but in the temporal domain. In order to consider these results together with those of children that performed the opposite time task without inverting the psychometric function, we applied a conversion to negative thresholds. Given thresholds (t) for the opposite time spatial bisection task, negative values t_{neg} were converted to: $t'_{neg} = t_{neg} - \min(t) + \max(t)$. This transformation allowed us to treat thresholds as a continuum, ranging from low thresholds, representing good precision in the spatial domain, to high thresholds representing poor spatial performance but good precision in the temporal domain. Analyses were subsequently conducted using R (R Core Team, 2017).

To investigate spatial bisection precision, statistical comparisons between thresholds were performed with two-way ANOVA, considering spatial thresholds (i.e. spatial precision) as dependent variable, Group (11 yo, 12 yo, 13 yo, adults) as a between-subjects factor, and Task (Independent, Coherent, Opposite) as a within-subjects factor. Post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction, i.e. after multiplying each p-value for n. of total comparisons which was 12 (i.e. 3 comparisons across tasks x 4 groups) and 18 (i.e. 6 comparisons across groups x 3 tasks). Then, to take into account possible confounds linked to the experimental sequence (e.g. the influence of first performing the temporal bisection task or the coherent time spatial bisection task), we separately added in another between-subjects factor to the ANOVA analysis: i) Block order with two levels (Spatial block first, Temporal block first), and ii) Spatial condition order with two levels (Coherent time first, Opposite time first). Thus, we performed a three-way ANOVA, considering Group and Block or Spatial condition order as between-subjects factors, and Task as a within-subjects factor.

In regards the temporal bisection task, thresholds were analyzed with a one-way ANOVA with Group (11 yo, 12 yo, 13 yo, adults) as a between-subjects factor.

Furthermore, Pearson correlational analyses (with a 95% confidence interval) were conducted to investigate the relationship between the performance at the *opposite time* spatial bisection task, and the performance at the other spatial bisection tasks (i.e. *coherent time* and *independent time*), and at the temporal bisection task. We focused on the *opposite time* condition because it is the one where the time influence can be better disentangled and the temporal attraction isolated. A positive correlation between the *opposite time* condition and the *independent time* one would indicate that the more subjects were not able to perform the spatial bisection task, the more they were attracted by temporal cues. Differently, the correlation between the *opposite time* condition and temporal bisection task gives us important information about the understanding of the instructions. If subjects were influenced by temporal cues during the *opposite time* spatial bisection task simply because they were wrongly performing a temporal task, their performance at the *opposite time* spatial bisection task should correlate with their performance at the temporal bisection task. Similarly, if younger participants simply performed a temporal instead of spatial bisection task, maybe due to a misunderstanding, their performance at the *opposite* condition should be associated with their performance at the *coherent* one since the two tasks contain exactly the same temporal information. These analyses were conducted considering both all participants involved in the study independently of age groups, and on the younger 11-year-old group.

Results

Our data demonstrate that children are attracted by temporal cues during complex auditory spatial estimations they are not able to solve. Figure 4.3 reports the psychometric functions of a 11-year-old subject showing strong temporal attraction (red) and a typical 13-year-old subject (blue) for spatial bisection tasks with *independent* (Fig. 4.3A), *coherent* (Fig. 4.3B) and *opposite* (Fig. 4.3C) time intervals. The proportion of trials where the second stimulus was reported to be closer to the third sound is plotted as a function of the position of the second sound, which was respectively directly or inversely proportional to the second sound delay in the *coherent time* and *opposite time* spatial task.

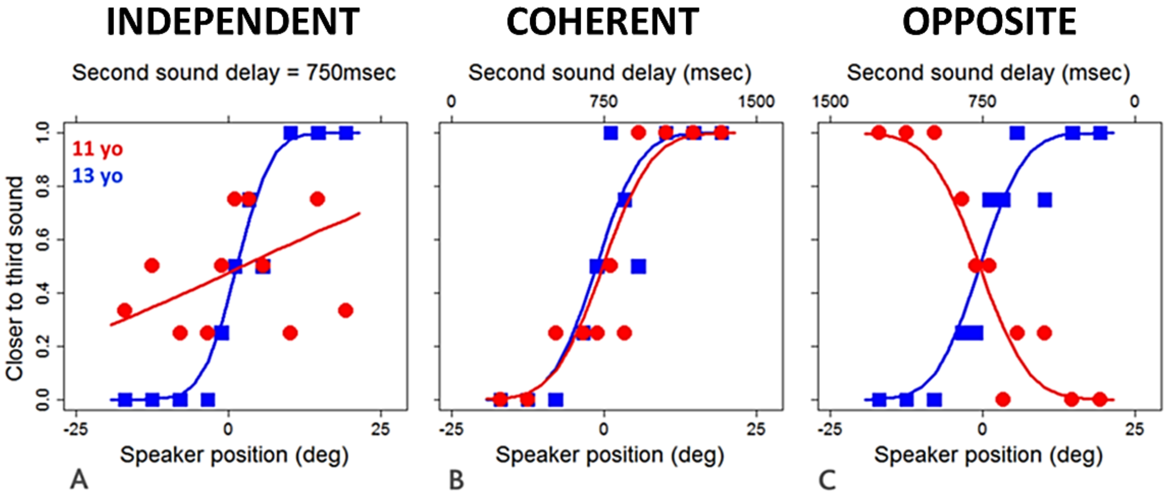

Figure 4.3 Results of a 11-years old child showing strong temporal attraction (red) and a typical 13-years old child (blue) for (A) independent time spatial bisection task, (B) coherent time spatial bisection task and (C) opposite time spatial bisection task.

The proportion of trials in which the second sound was judged as "closer to the third sound" is plotted against the speaker position for the second sound. Data are fit with the Gaussian error function. Points represent the 11 speaker positions that can be assumed by the second sound during the task.

In the *independent time* spatial bisection task (Fig. 4.3A), the 13 year old exhibits the typical psychometric function, whereas random responses and no psychometric function appear for the younger subject, meaning strong impairment in the task. However, results in the *coherent time* spatial bisection task (Fig. 4.3B) are different as the two psychometric functions are almost superimposed. The psychometric function of the 11-year-old individual is as steep as that of the older subject, reflecting similar precision. This finding suggests that temporal features are used by the younger child to improve performance in the spatial bisection task. Results from the *opposite time* spatial task further support this hypothesis (Fig. 4.3C). Indeed, the psychometric function of the typical 13-year-old child is constant, whereas the 11-year-old individual displays a well-shaped psychometric function but in the direction opposite than expected, meaning that his answers were based on the virtual position of the second sound determined by its temporal delays. Thus, for the younger child, there is a strong temporal dominance under this condition, suggesting that temporal cues are attracting the spatial auditory response during the spatial bisection task. We report the mean and standard deviation (SD) of R^2 of the psychometric functions for the spatial conditions of each group, without considering participants whose thresholds have been interpolated. For the *coherent time* spatial bisection, 11-year-old group: R^2 (mean±SD)= 0.50±0.16; 12-year-old group: R^2 = 0.49±0.21; 13-year-old group: R^2= 0.60±0.21; adults: R^2= 0.68±0.12. For the *opposite time* spatial bisection, 11-year-old group: R^2= 0.40±0.19; 12-year-old group: R^2= 0.37±0.19; 13-year-old group: R^2 = 0.52±0.18; adults: R^2= 0.65±0.12. For the *independent time* spatial bisection, 11-year-old group: R^2 = 0.36±0.24; 12-year-old group: R^2= 0.37±0.18; 13-year-old group: R^2= 0.54±0.18; adults: R^2= 0.70±0.11.

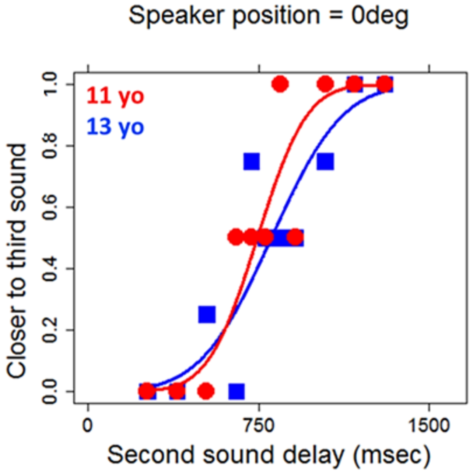

Figure 4.4 Results of a typical 11-years old child (red) and a typical 13-years old child (blue) for the temporal bisection task.

The proportion of trials in which the second sound was judged as "closer to the third sound" is plotted against the speaker position for the second sound. Data are fit with the Gaussian error function. Points represent the 11 delays that can be assumed by the second sound during the task.

Similarly, Figure 4.4 shows the psychometric functions of a typical 11-year-old (red) and 13-year-old subject (blue) for the temporal bisection task performed as a control experiment. We plot the proportion of trials where the second sound was reported as closer to the third one as a function of the presentation timing of the second sound. As expected, no differences emerge from the psychometric functions of the two children. For the psychometric functions of the temporal bisection, 11-year-old group: R^2= 0.54±0.16; 12-year-old group: R2= 0.6±0.2; 13-year-old group: R^2= 0.55±0.16; adults: R^2= 0.57±0.2.

In Figure 4.5, we report the results for the three spatial bisection tasks for all subjects involved in the present study, split into 4 age groups (11-year-old group: red, 12-year-old group: green, 13-year-old group: blue, adults: purple). As suggested by the individual psychometric functions, there are evident differences between younger and older children, with the 11-year-old group performing worst in the *independent* and *opposite time* conditions compared to the others. The two-way ANOVA with spatial thresholds (i.e. spatial precision) as dependent variable claims a significant interaction (F(2,112)= 9.02, p< 0.001, GES= 0.06) between Group (11 yo, 12 yo, 13 yo, adults) and Task (Independent, Coherent, Opposite). Post-hoc t-tests reveal that the performance of 11-year-old children is statistically more impaired in the *independent time* (t(17)= 4.7, p= 0.002 after correcting for 12 comparisons) and *opposite time* (t(17)= -4.42, p= 0.005 after correcting for 12 comparisons) bisection task compared to their own performance in the *coherent time* condition.

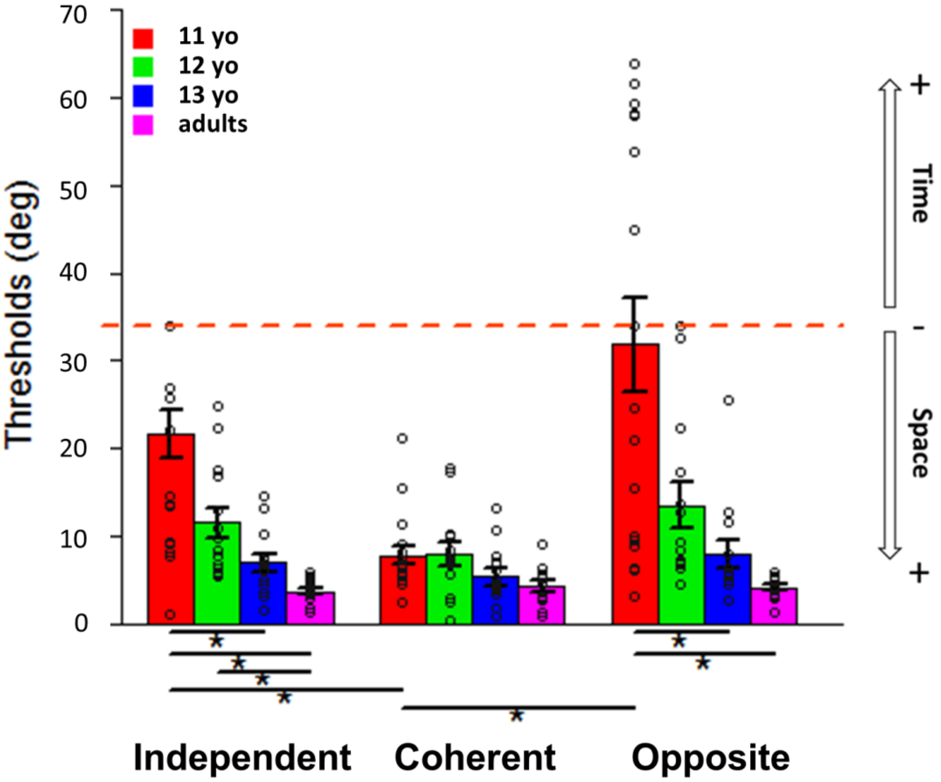

Figure 4.5 Average thresholds (±SEM) in the three spatial bisection tasks for each age group. Dots represent individual data; dots above the red line indicate subjects with inverted psychometric function. * p<0.01 after Bonferroni correction**.**

Dots above the red line in Figure 4.5 represent subjects whose psychometric function is inverted, which means subjects who are answering referring to time features of auditory stimuli although performing a spatial estimation task.

In addition, spatial thresholds of 11 year olds are significantly higher than those of 13 year olds and adults in the *independent* (11 vs. 13: t(21.5)= 4.9, p= 0.001; 11 vs. adult: t(17.7)= 6.33, p< 0.001 after correcting for 18 comparisons) and *opposite time* (11 vs. 13: t(20.2)= 4.25, p= 0.007; 11 vs. adult: t(17.2)= 5.16, p= 0.001 after correcting for 18 comparisons) tasks, highlighting a clear improvement in performance associated with age. This developmental trend is in line with previous findings (Gori et al., 2012a) and is further confirmed by the 12 year olds, who exhibit a mean threshold in between the younger and older groups for both tasks. Only in the *independent time* spatial bisection, 12 year olds are statistically less precise than adults (t(14.5)= 4.41, p= 0.01 after correcting for 18 comparisons). The role of time cues in inferring complex spatial representation is also evident by low thresholds and no statistical differences between different groups in the *coherent time* spatial bisection task.

We can exclude that the effects simply derived from confounds associated with the experimental session sequence. The three-way ANOVAs with spatial thresholds as dependent variable, including Block order or Spatial condition order, reveal neither a significant interaction between Group, Spatial task and Block or Spatial condition order (for block order: F(2,108)= 0.14, p= 0.9, GES= 0.001; for spatial condition order: F(2,108)= 0.006, p= 0.9, GES= 0.00004), nor a main effect of Block or Spatial condition order (for block order: F(1,54)= 0.3, p= 0.5, GES= 0.003; for spatial condition order: F(1,54)= 0.4, p= 0.5, GES= 0.003). However, in both cases a significant interaction between Group and Task is still evident (when including block order: F(2,108)= 8.7, p< 0.001, GES= 0.06; when including spatial condition order: F(2,108)= 8.9, p= 0.0002, GES= 0.06).

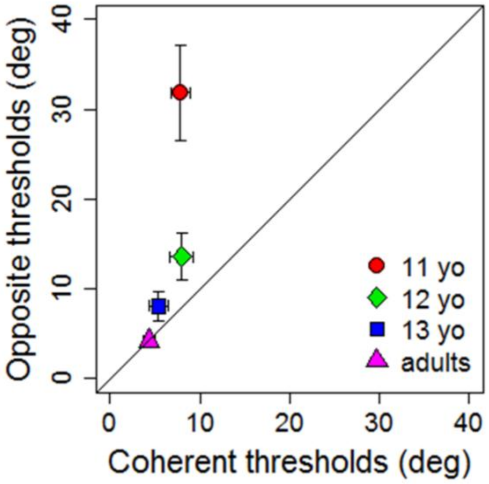

Figure 4.6 Relationship between coherent and opposite spatial bisection tasks across different age groups.

Average data (±SEM), plotting *opposite time* spatial bisection threshold against *coherent time* spatial bisection thresholds.

In Figure 4.6, the average threshold in the *coherent time* spatial bisection task is plotted against the average threshold in the *opposite time* spatial bisection task for each group. Adults and subjects in the 13-year-old group show low thresholds and similar performances for both tasks, whereas the 11 and 12-year-old groups display discrepancies between thresholds in the two tasks. Especially, the younger group shows an average threshold similar to that of the other subsamples in the *coherent time* condition, but a deep decrease in precision when time and space are incongruent in the *opposite time* task.

In agreement with previous results (Gori et al., 2012b, Vercillo et al., 2016), all participants were able to perform the temporal bisection task and similar precision is observed between age groups (F(1,56)= 0.06, p= 0.8, GES= 0.001).

As to the correlational analyses between the spatial tasks, we found a significant association between performance at the *independent time* and *opposite time* spatial bisection tasks both considering all subjects together (r= 0.88, t(56)= 13.92, p< 0.001), and focusing on the 11-year-old group (r= 0.84, t(16)= 6.3, p< 0.001; Fig. 4.7A). Furthermore, there was no significant association between the *opposite time* spatial bisection task and the temporal task performed as control either for all participants independently of their ages (r= 0.07, t(56)= 0.5, p=0.6) or for the younger group (r= 0.04, t(16)= 0.18, p= 0.9; Fig. 4.7B). Similarly, performance at the *opposite time* spatial bisection task was not associated with the performance at the *coherent time* spatial bisection task (considering all participants: r= 0.19, t(56)= 1.4, p= 0.1; considering the younger group: r= 0.02, t(16)= 0.09, p= 0.9; Fig. 4.7C).

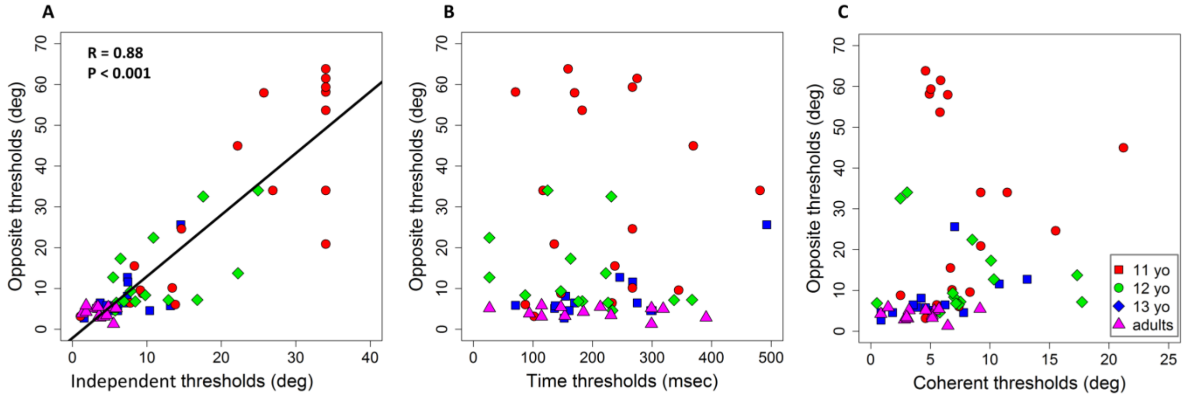

Figure 4.7 Results of correlational analyses.
(A) Correlation between *opposite time* spatial bisection and *independent time* spatial bisection; **(B)** Correlation between *opposite time* spatial bisection and temporal bisection; **(C)** Correlation between *opposite time* spatial bisection and *coherent time* spatial bisection.

Discussion of results

In this study we investigated how the spatial and the temporal domains interact during the development of auditory spatial representation. We measured spatial discrimination thresholds in children and adults, when conflicting and non-conflicting spatial and temporal cues were presented during auditory spatial bisection tasks. We showed that younger children are influenced by temporal cues when inferring complex spatial coordinates within the auditory modality.

Specifically, we observed that children younger than 12 were not able to decode the spatial relationships between sounds when they were played with the same temporal interval, making the temporal domain uninformative about space. However, when the spatial information was coherent with the temporal information children of all age became able to perform the task. When spatial and temporal cues were incongruent, children younger than 12 were attracted by the temporal instead of spatial information, while older participants resulted unaffected by the cross-domain conflict.

The later emergence of auditory spatial bisection skills is not surprising as spatial bisection is a complex task. The differences in performance across children of different age is likely due to the ongoing maturation of audio-visual integration and the effect of cross-sensory calibration of the visual modality on the auditory one for spatial representations

(Gori, 2015, Da Silva, 1985, Loomis et al., 1998). The clear developmental trend observed around 12 years of age is supported by many studies claiming that audio-visual integration reaches mature levels around 11-14 years old (e.g. Adams, 2016, Nardini et al., 2016, Brandwein et al., 2011). However, younger children benefited from spatiotemporal coherence and improved their performance when temporal information was available. This suggests that temporal cues could be used by children to face complex spatial representations they were not able to deal with. In this direction, we also reported a strong correlation between performance at the *independent time* and performance at the *opposite time* spatial bisection tasks not only for younger children, but considering participants of all ages. Hence, there is a specific influence of time on spatial judgments within the auditory modality, which is stronger for young children, but present also at older ages when people have difficulties in building spatial representations. This suggests that the temporal attraction could be a general mechanism supporting the processing of spatial representation when spatial skills are poor. Specifically, temporal feedback may help the developing child to build complex spatial representations within the auditory modality.

Our results seem to rule out the possibility that younger participants misunderstood the task. Indeed, if the strategy of the younger group was exclusively based on the temporal cue (i.e., performing a temporal task even tough asked to perform a spatial task), all the psychometric functions in the *opposite time* condition should be perfectly inverted. This is not the case, suggesting that there exists a bias but participants are not performing a temporal task completely ignoring the spatial instructions. Figure 4.3 shows the psychometric function for an 11-years old participant showing a strong temporal attraction. Furthermore, no correlation appeared between the performance at the *opposite time* spatial bisection task and the performance at the temporal task, suggesting that younger children were not attracted by the temporal cues in the incongruent conditions simply because they performed a temporal task using the easier discriminable dimension for them (i.e. time). In this direction, we also checked whether there exists a correlation between the *opposite time* spatial bisection task and the *coherent time* spatial bisection task. If younger participants simply performed a temporal instead of spatial bisection task, their performance in the *opposite time* condition should be associated with their performance at the *coherent time* one, since the two tasks contain exactly the same temporal information.

To conclude, this study shows a strong interaction between the temporal and spatial domains in children, raising the hypothesis that the human brain might use temporal maps to solve complex auditory spatial analysis when spatial reference is poor, as in young children. In these individuals, temporal processing of space for auditory signals weights more and might be used. This hypothesis would explain why younger participants are strongly enhanced when spatiotemporal coherent cues were presented, and show a temporal attraction when facing conflicting spatiotemporal information.

4.2 Exp. 2: Time to infer space in blindness

Visual experience is important for the development of complex spatial representations. In Chapter 2, we showed that early blind and late blind individuals with long blindness duration show a strong deficit in a spatial bisection task, likely due to a weaker and not lateralized activation of areas likely involving the visual cortex. One can wonder why blind individuals, who have higher auditory skills compared to sighted individuals for many spatial tasks, are not able to perform the spatial bisection task. Although this task requires complex attentional and memory skills, it is hard for blind individuals only in the spatial domain. Indeed, when they have to bisect stimuli in the temporal domain, their performance is as good as those of sighted individuals, as well as their cortical activations (Section 2.1 and 2.2). In Section 4.1, we demonstrated that when auditory spatial bisection abilities are low in young children, they are attracted by temporal information when performing complex spatial estimation within the auditory modality. Starting from this, with Piaget's idea in mind (Piaget, 1927), we hypothesized that when vision is not available, such as in blindness, temporal representation of events could be used to set auditory spatial representations. If this is the case, we expect auditory spatial representations of blind individuals to be strongly influenced by the temporal representation of events. Here we tested this hypothesis (see Gori et al., 2018). To this end, a group of 17 blind and 17 sighted individuals were tested with an auditory bisection task where conflicting and not conflicting spatial and temporal information was delivered.

Methods

Experimental procedure

A group of 17 blind participants (mean age±SD: 45.9±17.9 yo; F=9) and 17 age and gender-matched sighted participants (36.5±13.5 yo; F=9; t(32)= 1.74, p= 0.1) took part in the study (see Table 4.1 for details). All participants reported no history of neurological or cognitive deficits. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained prior to testing.

Stimuli and procedure were identical to those of the Experiment in Section 4.1. Participants performed three spatial bisection tasks (i.e. *independent time*, *coherent time* and *opposite time* spatial bisection tasks), and one temporal bisection task as a control (see Fig. 4.2). As in the previously described Experiment, in the *independent time* spatial bisection, S2 was always delivered 750 ms after S1, which corresponded to the middle time of the temporal sequence between S1-S3. To correctly compute this task participants had to rely exclusively on spatial features since the three sounds were played with the same temporal delay between S1-S2, and between S2-S3 (as in original work, Gori et al., 2014), making temporal aspects uninformative. In the *coherent time* spatial bisection task, spatial distances between S1-S2 and S2-S3 were directly proportional to temporal intervals between the three sounds (e.g. a shorter spatial distance between S1-S2 was associated with a shorter temporal delay between the two sounds). Thus, temporal cues could be used by subjects to infer complex spatial representation. Instead, space distances between the three sounds were inversely proportional to temporal intervals in the *opposite time* spatial bisection task (e.g. a shorter spatial distance between S1-S2 was associated with a longer temporal delay between the two sounds), making time informative but in the opposite direction with respect to space.

PARTICIPANT	AGE	GENDER	PATHOLOGY	BLINDNESS ONSET
S1	52	M	Retinopathy of Prematurity	Birth
S2	77	F	Retinis Pigmentosa	Birth
S3	62	F	Atrophy of the eyeball	Birth
S4	25	M	Leber amaurosis	Birth
S5	52	F	Retinis Pigmentosa	Birth
S6	58	M	Uveitis	Birth
S7	59	M	Glaucoma	Birth
S8	42	F	Glaucoma	Birth
S9	28	F	Retinopathy of Prematurity	Birth
S10	27	F	Retinopathy of Prematurity	Birth
S11	24	F	Glaucoma	Birth
S12	27	F	Microphthalmia	Birth
S13	29	F	Retinis Pigmentosa	Birth
S14	29	M	Glaucoma	Birth
S15	65	M	Retinis Pigmentosa	38
S16	58	M	Glaucoma	20
S17	67	M	Retinal detachment	51

Table 4.1 Clinical details of the blind group (N= 17).
The table shows chronological age at testing, gender, pathology and age of blindness onset for each participant.

Data analysis

Even data analyses followed closely those described in the Experiment performed in Section 4.1. First of all, PSE and threshold estimates were calculated for each task. Then, since some blind participants exhibited inverted psychometric functions in the *opposite time* spatial bisection task (like younger children), the conversion applied to negative thresholds in Section 4.1 was similarly used (i.e. negative values t_{neg} were converted to $t'_{neg} = t_{neg} - \min(t) + \max(t)$).

To investigate spatial bisection precision, statistical comparisons between thresholds were performed with an omnibus two-way ANOVA, considering Group (Sighted, Blind) as a between-subjects factor, and Task (Independent, Coherent, Opposite) as a within-subjects factor. For each group, a follow-up one-way ANOVA was carried out with the

Task (Independent, Coherent, Opposite) as a within-subjects factor. As regards the temporal bisection task, thresholds were analyzed with a one-way ANOVA with Group (Sighted, Blind) as a between-subjects factor. Post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction.

Results

Figure 4.8 (lower panels) plots the proportion of answer “second sound closer to the third sound” as a function of the position of the second sound, for one typical blind subject (in red) and one age-matched typical, sighted control (in grey). The size of the dots is proportional to the number of trials at each position. Figure 4.8A reports the results for the *independent* bisection condition, Figure 4.8B for the *coherent* bisection condition and Figure 4.8C for the *opposite* bisection condition. In the *independent* bisection condition (Fig. 4.8A), the sighted individual shows the typical psychometric function. Contrarily, the blind subject shows almost random responses with no psychometric function, reflecting strong impairment in this task (in agreement with previous findings, Gori et al., 2014). As regards the *coherent* bisection task (Fig. 4.8B), the results are quite different: here the psychometric function for the blind individual is present and as stepper as that of the sighted participant, meaning similar precision. This result suggests that a temporal cue can be used by blind individuals to improve their performance in the spatial bisection task. In the *opposite* spatial bisection task (Fig. 4.8C), the response of the sighted subject is identical to the response in the other two conditions. Differently, the blind individual shows a well-shaped psychometric function but in the opposite direction than expected (in grey). The performance of the blind individual reveals a strong temporal dominance for the spatial bisection task under this condition, suggesting that in this blind subject, while not in the sighted one, the temporal cue is attracting the spatial auditory response.

While for sighted individuals the manipulation of the temporal cue during spatial bisection does not affect the response, it strongly influences the response of blind participants. Figure 4.9 shows the results for all subjects involved in the study. Averages and individuals data for the three spatial bisection tasks and for the temporal bisection task are reported for blind (in red) and sighted (in gray) individuals. Dots represent individual data, those above the red dashed line indicate subjects with inverted psychometric function. As previously suggested by the psychometric functions reported in Figure 4.8, the average threshold of blind participants (red bar) is higher than the one of sighted participants for the *independent* spatial bisection (in agreement with previous findings, Gori et al., 2014), but average thresholds become similar between the groups for the *coherent* spatial bisection, suggesting that blind individuals benefit from the temporal cue during spatial judgments.

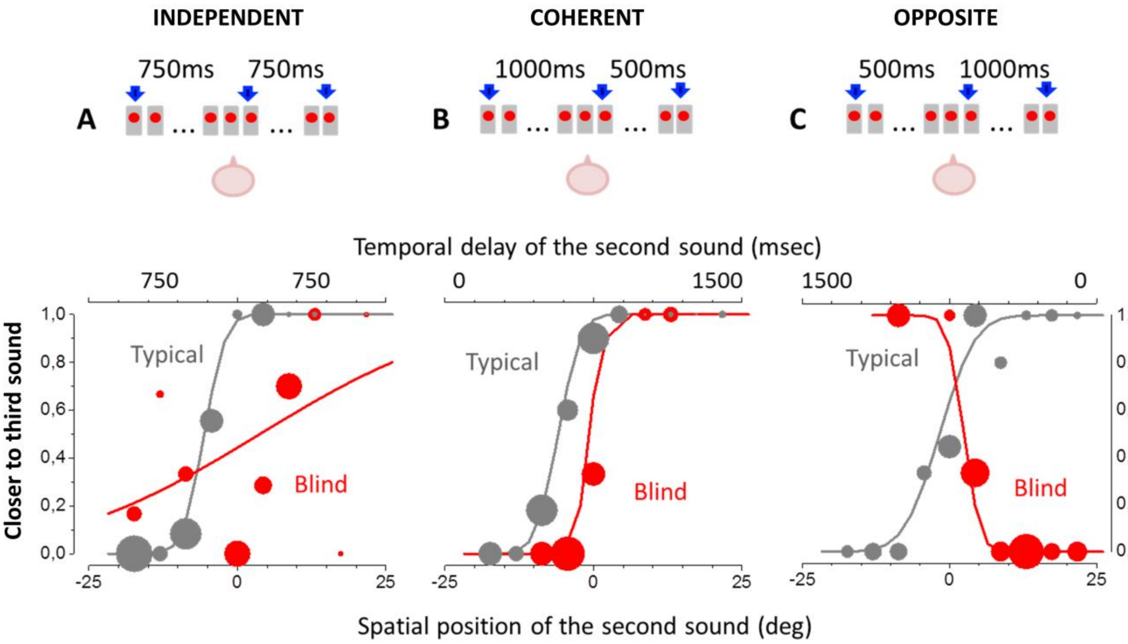

Figure 4.8 Results of the three spatial bisection tasks for a blind participant (red symbols) and a typical sighted control (grey symbols).

Subjects sat in front of an array of 23 speakers, illustrated by the sketches above the graphs. **(A)** *Independent time* spatial bisection. Top: the time interval between the first and the second sound (750 ms) was independent to the time interval between the second and the third sound. Bottom: proportion of trials judged “closer to the right sound source”, plotted against the speaker position for the second sound. The size of the dots is proportional to the number of trials at that position. Both sets of data are fitted with the Gaussian error function. **(B)** *Coherent time* spatial bisection. Top: spatial distances and temporal intervals between the three sounds were directly proportional (e.g. long spatial distance and long temporal interval). Bottom: same as for (A). **(C)** *Opposite time* spatial bisection. Top: spatial distances and temporal intervals between the three sounds were inversely proportional (e.g. long spatial distance and short temporal interval). Bottom: same as for (A) and (B).

The interaction between space and time seems to occur under threshold. The smallest difference between the temporal delays of S2 was of 65 ms for each speaker, while the temporal threshold obtained from the temporal bisection task was of 200 ms. Considering the *coherent* condition in Figure 4.9, we can observe that the spatial threshold is on average 3.5°, meaning less than two speakers. This spatial threshold corresponds to a temporal delay of about 130 ms, which is lower than the temporal threshold obtained in temporal bisection, suggesting subthreshold interaction between space and time. Importantly, the thresholds of blind participants increase in the *opposite* bisection task, with some participants inverting the psychometric function (i.e. those with thresholds above the red dashed line). This result implies a reduction of precision in the conflict condition. The two-way ANOVA with spatial thresholds as dependent variable claims a significant interaction (F(2,64)= 17.72, p< 0.001, GES= 0.23) between Group (Sighted, Blind) and Task (Independent, Coherent, Opposite). From follow-up one-way ANOVAs, significant differences among Tasks (Independent, Coherent, Opposite) emerge for the blind group (F(2,32)= 19.34, p< 0.001, GES= 0.4) but not for the sighted group (F(2,32)= 1.5, p= 0.2, GES= 0.03). Post-hoc t-tests reveal that the performance of blind individuals is statistically more impaired in the *opposite* time bisection task compared to their own performance in the *independent* time (t(16)= 3.7, p= 0.006) and *coherent* time (t(16)= -4.86, p< 0.001) condition. Still, their performance significantly improves from the *independent* time to the *coherent* time condition (t(16)= -4.21, p= 0.002). In addition, spatial thresholds of blind participants are significantly higher than those of sighted participants in the *independent* (blind vs. sighted: t(17.1)= 4.18, p= 0.002) and *opposite time* (blind vs. sighted: t(16.6)= 4.69, p< 0.001) conditions. The role of time cues in inferring complex spatial representation is also evident by low thresholds and no statistical differences between groups in the *coherent time* spatial bisection task (blind vs. sighted: t(32)= -0.45, p= 1). In agreement with previous results (Gori et al., 2012b, Vercillo et al., 2016), all participants were able to perform the temporal bisection task and similar precision is observed between sighted and blind groups (Fig. 4.9 right panel; F(1,32)= 0.29, p= 0.6, GES= 0.009).

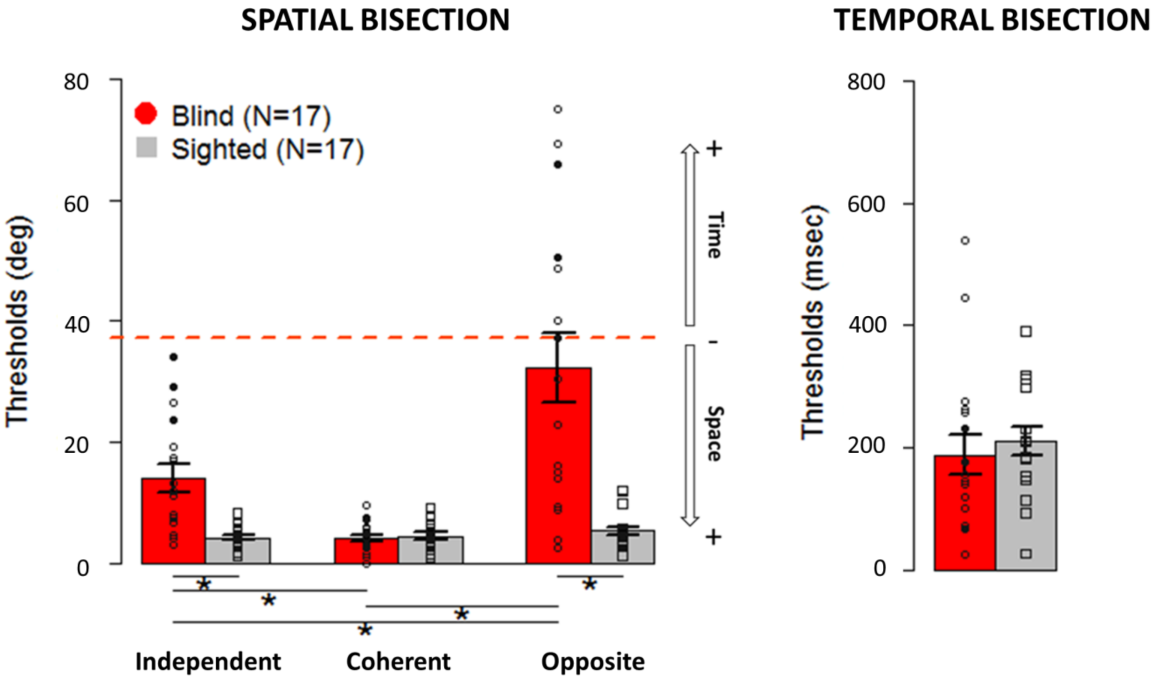

Figure 4.9 Group performance in auditory bisection tasks.
Average thresholds (±SEM) of the three spatial bisection tasks (left panel) and the temporal bisection task (right panel) for blind (red) and sighted (grey) participants. White dots (early blind), black dots (late blind) and squares (sighted) represent individual data; dots above the red line indicate subjects with inverted psychometric function. * p<0.01 after Bonferroni correction.

In Figure 4.10 individual thresholds in the *coherent time* spatial bisection task are plotted against individual thresholds in the *opposite time* spatial bisection task for the sighted (in grey) and blind (in red) group. Sighted participants show similar performances for both tasks, with all the individual data laying in the equality line, whereas blind participants display discrepancies between thresholds in the two tasks. In this latter group, all dots lay up the equality line suggesting lower performance for the *opposite time* than the *coherent time* task.

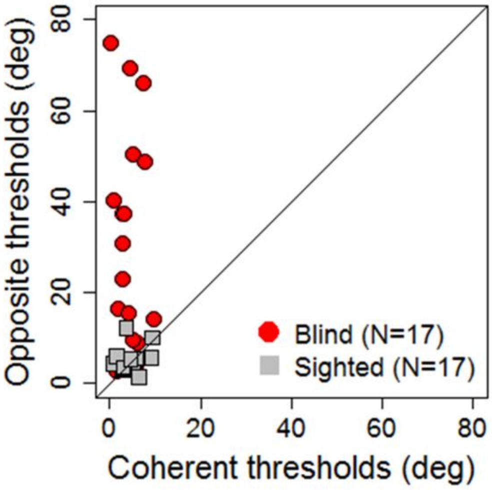

Figure 4.10 Relationship between coherent and opposite spatial bisection tasks for blind and sighted participants.
Individual data, plotting *opposite* thresholds against *coherent* thresholds (calculated from the width of individual psychometric functions). Red and grey dots represent blind and sighted individuals respectively.

Discussion of results

In this experiment, we studied the interaction between space and time when visual input is missing, testing whether time attracts auditory space for visually impaired individuals. In particular, we hypothesized that in blind individuals, temporal cues could be used to determine the spatial relationships of events within the auditory modality. Thus, sighted and blind individuals performed various spatial bisection tasks, in which spatial and temporal coherent and conflicting information was presented. As predicted, we observed a strong attraction towards temporal cues during spatial bisection in blind but not in sighted individuals. In blind participants, the spatial bisection deficit disappeared when coherent temporal and spatial cues were presented (e.g. short space associated with short time) and increased for conflicting spatial and temporal stimuli (e.g. short space associated with long time).

To check that the attraction towards the temporal cue during the spatial bisection task was not simply because participants used the easier available cue to solve the task, we also run a pilot preliminary experiment with two blind participants. Specifically, we have tested the attraction towards a pitch cue during an auditory spatial bisection task. A paradigm similar to the used in here was applied in the pitch study, by substituting the time cue with a pitch cue. Indeed, early blind subjects have enhanced skills in auditory pitch discrimination (Gougoux et al., 2004). If blind people in the experiment described in this Section were simply attracted by the other available information (i.e. time) because they had no sensitivity for space, then they should show an attraction towards the pitch cue during the pilot pitch study, as we observed for time here. In two preliminary blind participants, we observed that they were both able to perform the pitch task independently of space, but they did not use the pitch cue to interpret space in conflicting conditions.

These results provide two important points of discussion that will be deeper addressed in Chapter 5. The first one extends the findings of Section 4.1: temporal and spatial representations may be strictly linked. Indeed, in blind individuals the modification of temporal cues alters spatial bisection performance. Specifically, we observed a subthreshold interaction between space and time. Since subthreshold facilitation is an evidence of functional interaction at early levels of sensory processing (Gori et al., 2011a), we think that the interaction between space and time we observed occurs at early sensory level. The second implication is that visual experience seems to be crucial for the development of independent spatial and temporal representations: temporal attraction of space is evident only for blind and not for sighted adults, who can dissociate the two cues without any problem. Since the visual experience is important for the development of complex spatial representations, when vision is not available it seems that independent temporal and spatial maps cannot develop. This possibility would explain why blind individuals strongly benefit from spatiotemporal coherence, and invert the psychometric function when facing conflicting spatiotemporal information. They follow the virtual position of the sound suggested by its temporal delay, using temporal cues to make specific auditory complex spatial estimations. In line with results about young children, this study suggests that in some cases the brain may use temporal cues to decode auditory spatial coordinates of the environment.

4.3 Exp. 3: Space to infer time in deafness

Auditory experience is important for the development of complex temporal representations. In Chapter 3 we report impaired temporal bisection skills in deaf people, caused by the lack of activation in area likely involving auditory cortices during the task. Moreover, we reported a strong interaction between spatial and temporal representation during development (see Section 4.1), and when the visual experience is missing (see Section 4.2). Specifically, we showed that when vision is not available, such as in blindness, subjects are not able to build complex spatial representations and are strongly attracted by temporal cues. Based on this evidence showing a strong link between spatial and temporal representation, we hypothesized that when audition is not available, not only complex temporal visual representations is impaired, but also visual spatial representation of events could be used to build a complex temporal representation (see Amadeo et al., 2019c). To test this hypothesis, 17 deaf and 17 hearing individuals were tested with visual temporal tasks where conflicting and not conflicting spatiotemporal information was delivered.

Methods

Experimental procedure

A group of 18 deaf participants (mean age±SEM: 35.7±3.5 yo; F=9) and 18 age and gender-matched hearing participants (32.4±1.5 yo; F=9; t21.2= 0.86, p=0.4) were recruited to take part in the study. Deaf participants were recruited at the National Association for Deaf (Ente Nazionale per la protezione e assistenza dei Sordi), in Genova, Italy. prior to testing. One deaf and one hearing participant were excluded from statistical analysis because they were identified as outliers (i.e. score in at least one task differing more than three standard deviations from the mean score of the group), giving rise to a final sample of 17 subjects per group. All participants reported no history of neurological or cognitive deficits, they had normal or corrected-to-normal vision and they were right-handed by self-report. All deaf participants had bilateral moderate to profound hearing loss, and did not receive a cochlear implant (see Table 4.2 for details). The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained.

Setup was the same as in Experiments in Section 4.1 and 4.2. However, participants performed three visual temporal bisection tasks (*independent space, coherent space,* and *opposite space*), and one visual spatial bisection task as a control. Indeed, the same technological device allows delivering auditory or visual stimuli. In each task, subjects see a sequence of three consecutive flashes (2.3° diameter, 75 ms duration) for a fixed trial duration of 1500 ms. For deaf participants, a hearing person fluent in Italian sign language was involved for instructions and questions. Procedure was similar to previous experiments investigating auditory spatial bisection abilities in children (Section 4.1) and blind participants (Section 4.2): - participants were warned to maintain a stable head position straight ahead throughout testing; - a short training session with feedbacks was conducted; - participants were informed from the beginning that the first flash was always produced by a device placed on their left, whereas the last flash by a device on their right; - no feedbacks were given during experimental sessions. Similarly, the order of spatial and temporal blocks was counterbalanced across subjects, and among temporal bisection tasks, the *independent space* one was always performed as the first one, with the order of the other two tasks randomly varying across participants.

PARTICIPANT	AGE	SEX	AGE AT DEAFNESS DETECTION	HEARING AID USE	AGE AT SIGN LANGUAGE FIRST EXPOSURE
S01	56	F	From birth	Uses currently	26 years old
S02	42	M	From birth	Uses currently	Unknown
S03	34	F	From birth	Uses currently	6 years old
S04	33	F	From birth	Uses currently	From birth
S05	23	F	From birth	Used in the past	From birth
S06	28	F	7 years old	Uses currently	18 years old
S07	24	F	From birth	Used in the past	15 years old
S08	37	F	5 years old	Uses currently	13 years old
S09	60	M	From birth	Used in the past	From birth
S10	21	F	13 years old	Never used	19 years old
S11	26	F	From birth	Used in the past	From birth
S12	29	M	3 years old	Used in the past	6 years old
S13	21	F	From birth	Uses currently	From birth
S14	37	F	From birth	Uses currently	3 years old
S15	73	M	6 years old	Never used	7 years old
S16	35	M	From birth	Used in the past	6 years old
S17	28	M	From birth	Uses currently	25 years old

Table 4.2 Clinical details of the blind group (N= 17).
The table shows chronological age at testing, gender, pathology and age of blindness onset for each participant.

In temporal bisection tasks, participants judged verbally whether the second flash (S2) was temporally closer to the first flash (S1; -25°, -750 ms considering 0ms the halfway point of the trial duration) or to the third flash (S3; +25°, +750 ms). S2 could occur randomly at an intermediate time point between -750 ms (corresponding to the trial start time) and +750 ms in time (corresponding to the trail end time), determined through the method of constant stimuli. With the same ratio behind the experiments previously described in this Chapter, to evaluate the role of spatial cues in time perception, spatial distances between the three flashes were manipulated to create three different temporal bisection tasks (Fig. 4.12, upper panels from left to right): *independent space*, *coherent space* and *opposite space* temporal bisection tasks, with spatial distances between visual stimuli which could be independent, coherent or opposite with respect to time intervals respectively. In the *independent space* temporal bisection, S2 was always delivered from 0° in space, which corresponded to the central light-emitting device (as in the temporal bisection task performed as control experiment in Section 4.1 and 4.2; see also Fig. 4.2). To correctly compute this task participant had to rely exclusively on temporal features since the spatial distance between S1-S2 was identical to the spatial distance between S2-S3, making spatial aspects entirely uninformative. In the *coherent space* temporal bisection task, temporal intervals between S1-S2 and S2-S3 were directly proportional to spatial distances between the three flashes (e.g. a shorter temporal delay between S1-S2 was associated with a shorter spatial distance between the two flashes). The spatial and temporal features of this condition correspond to those in the *coherent time* spatial bisection in Section 4.1 and 4.2. The exact spatial position associated with each temporal delay of S2 is reported in the upper horizontal axis of the central psychometric function in Figure 4.12. Considering that the total trial duration was 1500 ms and the number of light-emitting devices was 23, when S2 was for example presented at -682 ms (i.e. with a delay of 68 ms from S1) it was delivered from the second device on the left; when it was presented at -614 ms (i.e. with a delay of 136 ms from S1) it was delivered from the third device, and so on. In this condition, spatial cues could be used by subjects to infer complex temporal representation. Instead, in the *opposite space* temporal bisection task time intervals between the three lights were inversely proportional to space distances (e.g. a shorter temporal delay between S1-S2 was associated with a longer spatial distance between the two flashes), making space informative but in the opposite direction with respect to time. The spatial and temporal features of this condition correspond to those in the *opposite time* spatial bisection in Section 4.1 and 4.2. Again, the exact spatial position associated with each temporal delay of S2 is reported in the upper horizontal axis of the psychometric function on the right in Figure 4.12. In the opposite space temporal bisection task, S2 was delivered from the second device on the left when it was presented at +682 ms (i.e. with a delay of 1432 ms from S1), it was delivered from the third device on the left when it was played at +614 ms (i.e. with a delay of 1364 ms from S1), and so on.

In the spatial bisection task performed as control experiment, participants were asked to verbally report whether S2 was closer to S1 or to S3 in the spatial domain (as in the *independent time* spatial bisection in Section 4.1 and 4.2; see also Fig. 4.2). Differently to temporal bisection tasks, S2 occurred randomly at an intermediate position from -25° to +25° in space but it was always presented at 0 ms (i.e. 750 ms after S1, which corresponded to the middle time of the temporal sequence between S1-S3). As for the S2 position in the temporal bisection tasks, the spatial position of S2 in the spatial bisection task was determined using the method of constant stimuli.

Data analysis

Similarly to the other experiments in this chapter, we calculated the proportion of trials where the second flash was perceived as closer to the third flash and data were fitted by cumulative Gaussian functions for each task. PSE and threshold estimates were obtained from the mean and standard deviation of the best fitting function (Kingdom and Prins, 2010), and standard errors for the bisection PSE and threshold estimates were calculated by bootstrapping (Efron and Tibshirani, 1993). The same custom algorithm was used, and two subjects were interpolated in the *opposite space* condition, and one subject was interpolated in the *independent space* condition. Similar to younger children and blind people, also some deaf participants based their answers in the *opposite space* temporal bisection task on spatial features (i.e. when space distances were incoherent with respect to time intervals), resulting in inverted psychometric functions with threshold expressed by negative values (values closer to 0 meaning good precision but in the spatial domain). Thus, in order to include these results together with those of deaf individuals who performed the *opposite space* task without inverting the psychometric function, we applied the conversion to negative thresholds as previously done (Section 4.1 and 4.2). Given thresholds (t) for the opposite space bisection task, negative values t_{neg} were converted to $t'_{neg} = t_{neg} - \min(t) + \max(t)$. This transformation allowed us to treat thresholds as a continuum, ranging from low thresholds representing good precision in the temporal domain to high thresholds representing poor temporal performance but good precision in the spatial domain.

To investigate temporal bisection precision, statistical comparisons between thresholds were performed with an omnibus two-way ANOVA, considering Group (Hearing, Deaf) as a between-subjects factor, and Task (*Independent*, *Coherent*, *Opposite*) as a within-subjects factor. For each group, a follow-up one-way ANOVA was carried out with the Task (*Independent, Coherent, Opposite*) as a within-subjects factor. To control whether an early exposure to sign language was impacting on the performance, deaf participants were also split into early and late based on sign language first exposure (cut-off: three years old) and a permutation ANOVA with Group (Early, Late) as a between-subjects factor, and Task (*Independent, Coherent, Opposite*) as a within-subjects factor was run. To perform this analysis, we applied the *aovp* function of the lmPerm package in R (Wheeler, 2010). For the spatial bisection task, thresholds were analyzed with a one-way ANOVA with Group (Hearing, Deaf) as a between-subjects factor. For both bisection tasks, post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction.

Moreover, for the group of deaf individuals Pearson correlational analyses were carried out to evaluate the relationship between the performance at the three conditions (*independent space*, *coherent space* and *opposite space*) of temporal bisection task and the performance at the spatial bisection task.

Results

Averages and individuals data for the three temporal bisection tasks and for the spatial bisection task are reported for deaf (in red) and hearing (in gray) individuals in Figure 4.11.

The two-way ANOVA with temporal thresholds as dependent variable shows a significant interaction (F(2,64)= 9.39, p< 0.001, GES= 0.2) between Group (Hearing, Deaf) and Task (*Independent*, *Coherent*, Opposite). Post-hoc t-tests reveal that deafness impairs temporal bisection abilities, as evident from the higher thresholds of deaf people in the *independent space* temporal task compared to hearing participants (deaf vs. hearing: t(19.7)= 2.86, p= 0.03). Moreover, while for hearing individuals (in grey) the manipulation of the spatial cue during temporal bisection slightly influences the response (i.e. similar performance for the three temporal conditions; see Fig. 4.11), it strongly affects the response of deaf participants (in red). Indeed, from follow-up one-way ANOVAs significant differences among Tasks emerge for both deaf (F(2,34)= 14.96, p< 0.001, GES= 0. 2) and hearing participants (F(2,34)= 6.53, p= 0.004, GES= 0. 01), but post-hoc t-tests reveal only a small difference between the *coherent* and the *opposite* conditions for hearing participants (t(16)=2.87, p= 0.03), whereas the performance of deaf individuals results statistically more impaired in the *opposite space* bisection task compared to the *independent space* (t(16)= 3.29, p= 0.01) and *coherent space* (t(16)= 4.84, p< 0.001) conditions.

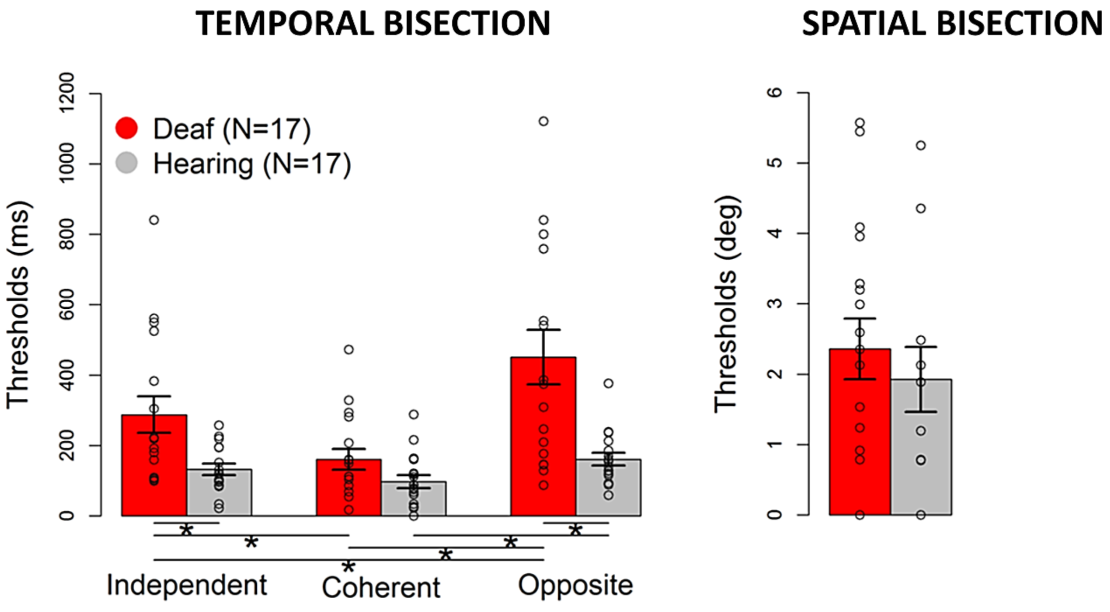

Figure 4.11 Group performance in visual bisection tasks.
Average thresholds (±SEM) of the three temporal bisection tasks (left panel) and the spatial bisection task (right panel) for deaf (red) and hearing (gray) participants. Dots represent individual data; *p< 0.01 after Bonferroni correction.

These findings indicate a strong reduction of precision in the conflict condition after auditory deprivation. Still, performance of deaf individuals significantly improves from the *independent space* to the *coherent space* condition (t(16)= 3.71, p= 0.005), suggesting that deaf individuals benefit from the spatial cue during temporal judgments. The average threshold of deaf participants (red bar) is also higher than the one of hearing participants for the *opposite space* temporal bisection (deaf vs. hearing: t(17.8)= 3.66, p= 0.005), but average thresholds become low and similar between the groups for the *coherent space* temporal bisection (deaf vs. hearing: t(26.9)= 1.82, p=0.2), in which temporal cues can be used by deaf participants to succeed at the task. The timing of sign language exposure does not impact on the results of deaf participants, as no significant differences across the tasks emerge between early and late sign language learners from the permutation ANOVA (n. permutation(1,45)= 429, p= 0.2).

As expected, all participants were able to perform the spatial bisection task and similar precision is observed between hearing and deaf groups (Fig. 4.11 right panel; F(1,32)= 0.47, p= 0.5, GES= 0.01). However, we can exclude that deaf subjects performed better at the *coherent space* temporal bisection task simply because they performed a spatial task using the easier discriminable dimension for them (i.e. space) as no correlation appeared between performance in the *coherent space* temporal bisection and performance in the spatial bisection (r=0.11, p= 0.7), and between performance in the *opposite space* temporal bisection and performance in the spatial bisection (r=0.11, p= 0.6). Similarly, there is no correlation between the *independent space* temporal bisection task and the spatial bisection task (r=0.08, p=0.7), supporting the interpretation that the spatial cue was not influencing the performance in the *independent space* temporal bisection.

Figure 4.12 (lower panels) plots the proportion of answer “second flash closer to the third flash” as a function of the temporal delay of the second flash, for one deaf subject (in red) and one age-matched hearing control (in grey). Figure 4.12A reports the results for the *independent* bisection condition, Figure 4.12B for the *coherent* bisection condition and Figure 4.12C for the *opposite* bisection condition. As suggested by group data, in the *independent* bisection condition (Fig. 4.12A) the hearing individual shows the typical psychometric function. Contrarily, the deaf subject shows more random responses without a well-shaped psychometric function, reflecting for the first time an impairment of deaf people in this task. As regards the *coherent* bisection task (Fig. 4.12B), the results are quite different: here the psychometric function for the deaf individual is present and as steep as that of the hearing participant, meaning similar precision. This result suggests that a spatial cue can be used by deaf individuals to improve their performance in the temporal bisection task. In the *opposite* temporal bisection task (Fig. 4.12C), the response of the hearing subject is identical to the response in the other two conditions. Differently, the deaf individual not only does not show a clear psychometric function but his pattern of responses is in the opposite direction than expected (in red). The performance of the deaf individual reveals a strong spatial influence for the temporal bisection task under this condition, suggesting that in this deaf subject, while not in the hearing one, the spatial cue is attracting the temporal visual response.

In Figure 4.13 individual thresholds in the *coherent space* temporal bisection task is plotted against individual thresholds in the *opposite space* temporal bisection task for the hearing (in grey) and deaf (in red) group. Hearing participants show similar performances for both tasks, with all the individual data laying in the equality line, whereas deaf participants display discrepancies between thresholds in the two tasks. In this latter group, almost all dots lay upper the equality line suggesting lower performance for the *opposite space* than the *coherent space* task.

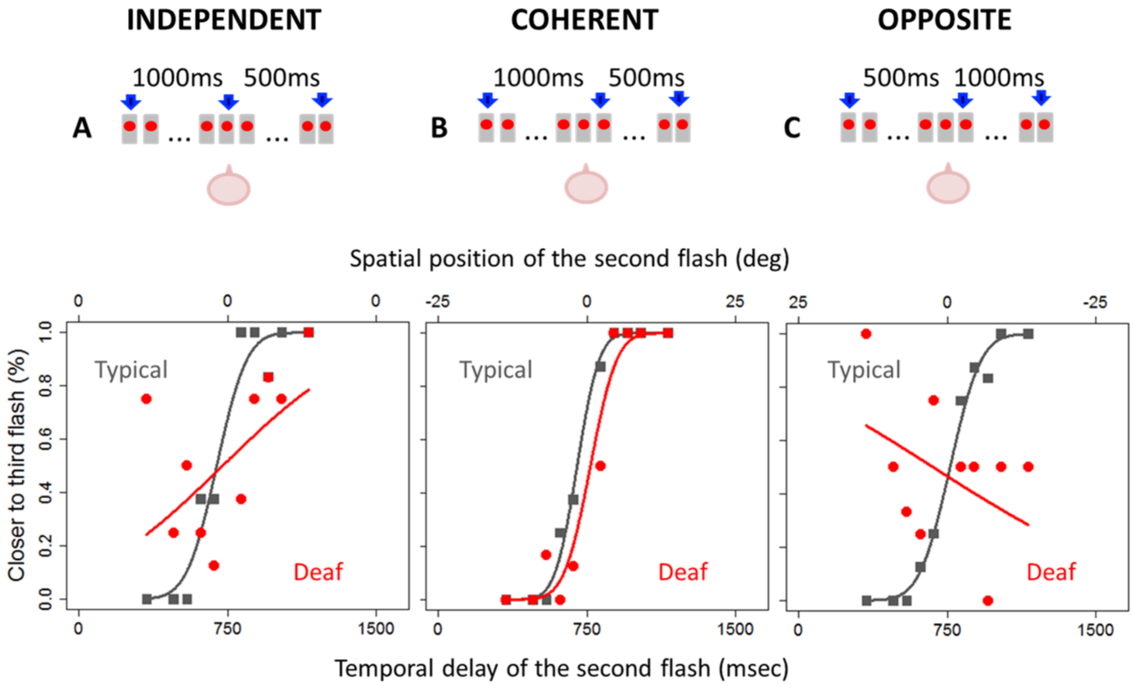

Figure 4.12 Results of the three temporal bisection task for a deaf participant showing strong spatial attraction (red) and a typical hearing control (gray).
Subjects sat in front of an array of 23 LED, illustrated by the sketches above the graphs. **(A)** *Independent space* temporal bisection. Top: the space distance between the first and the second flash (25 deg) was independent to the space distance between the second and the third flash . Bottom: proportion of trials judged ‘‘closer to the third flash source’’ plotted against the temporal delay for the second flash. Both sets of data are fitted with the Gaussian error function. **(B)** *Coherent space* temporal bisection. Top: temporal intervals and spatial distances between the three flashes were directly proportional. Bottom: same as for (A). **(C)** *Opposite space* temporal bisection. Top: temporal intervals and spatial distances between the three flashes were inversely proportional. Bottom: same as for (A) and (B).

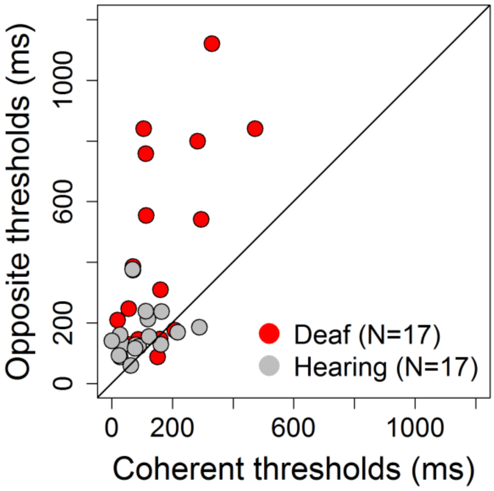

Figure 4.13 Relationship between coherent and opposite temporal bisection tasks for haring and deaf participants.
Individual data, plotting *opposite* thresholds against *coherent* thresholds (calculated from the width of individual psychometric functions). Red and gray dots represent deaf and hearing individuals, respectively.

Discussion of results

Here we studied the interaction between space and time when the auditory input is missing, testing whether space influences visual time for individuals with auditory impairment. In particular, we hypothesized that in deaf individuals, for whom the construction of complex temporal representation is impaired, spatial cues could be used to determine the temporal relationships of visual events. Deaf and hearing subjects were tested with a visual task where conflicting and not conflicting temporal and spatial information was delivered. As predicted, we observed a strong attraction towards spatial cues during temporal bisection in deaf but not in hearing individuals. Indeed, the deficit of deaf individuals in complex temporal representation disappeared when coherent temporal and spatial cues were presented (i.e. *coherent space* temporal bisection task), and increased for conflicting temporal and spatial stimuli (i.e. *opposite space* temporal bisection task). On the contrary, hearing participants were unaffected by the cross-domain coherence or conflict showing similar performances for the three conditions.

In line with our study during development and in blindness, the current findings provide further evidence that temporal and spatial representations may be strictly linked in the human brain, and sensory experience may be crucial for the development of independent spatial and temporal representations.

In order to better understand what was the strategy used by deaf participants we run some additional correlational analyses. The lack of correlation between spatial performance (i.e. spatial bisection) and temporal performance when coherent (i.e. *coherent space* temporal bisection) and conflicting (i.e. *opposite space* temporal bisection) spatiotemporal cues were presented suggests that the improved and impaired temporal performance of deaf individuals under these conditions was not simply due to the use of the spatial cue. Indeed, if they just performed the spatial task with temporal information injecting noise, at least their performance in the *coherent space* temporal bisection should be as good as in the *independent space* temporal bisection. Furthermore, if deaf participants were simply performing a spatial task even tough asked about time, in the *opposite space* temporal bisection the psychometric functions should be always perfectly inverted. Instead, in the *opposite space* condition we observed a biased and not a complete inversion, suggesting that the strategy of the group was not exclusively based on the spatial cue but there exists a dominance of spatial over temporal information. Also, performance in the *independent space* temporal bisection task did not correlate with that in the pure spatial bisection, further supporting the lack of weight assigned to the spatial cue in the independent space temporal task. Thus, although we cannot completely exclude deaf participants used space as it was the easier discriminable dimension, our results suggest that participants were not simply performing a spatial task instead of a temporal judgment.

To sum up, these results suggest deaf people benefit from spatiotemporal coherence during visual time estimations, introducing the idea that in some cases the brain may use spatial cues to decode temporal coordinates of the environment.

Chapter 5

General discussion

The overall aim of the current thesis is to investigate how sensory modalities, such as vision and audition, impact the development of some aspects of spatial and temporal representation in the human brain. To this end, the project involves the study and comparison of different populations, such as children and adults without sensory disabilities as well as blind and deaf people. After a general introduction about the complexity of our multisensory world and its relationship with the perception and coding of spatial and temporal information (Chapter 1), I illustrated neural mechanisms underlying some complex auditory spatial (Chapter 2) and visual temporal (Chapter 3) skills. Subsequently, I reported possible mechanisms of interaction between spatial and temporal representations (Chapter 4).

5.1 Vision and audition in space and time

In Chapter 2 and Chapter 3, I focused on the role of vision and audition on spatial and temporal representation, respectively. This thesis used blindness and deafness to deeper disentangle the contribution of the two sensory modalities on underlying neural mechanisms involved in spatial and temporal perception, trying to disambiguate why both a “sensory compensatory hypothesis” and a “perceptual deficiency hypothesis” have been proposed to explain perceptual skills following sensory deprivation.

Our results agree with a supramodal organization of the visual cortex (see Ricciardi et al., 2014). Indeed, first of all we demonstrated that lateralized changes in visual activity following sounds represent an amodal signature of spatial orienting auditory attention (Section 2.1). This happens independently of visual experiences. Specifically, we demonstrated that the lateralized enhancement in parieto-occipital regions by peripheral sounds (i.e. ACOP) previously observed in sighted individuals (McDonald et al., 2013) is also present in people who are congenitally blind; substantially, visual deprivation enhances this cortical response (see Section 2.1). All previous research on the ACOP only looked at sighted individuals, finding that a larger ACOP is associated with better visual discrimination accuracy at the sound's location (McDonald et al., 2013, Feng et al., 2014). One interesting possibility that arises from our results is that the ACOP is not only associated with enhanced visual processing at the sound's location, but it is also associated with overall enhanced auditory spatial processing. Considering that several studies have reported that enhanced spatial hearing abilities of blind individuals are subserved by cross-modal plasticity (see also Voss, 2016), we may speculate that an increased ACOP amplitude following visual deprivation may reflect the enhanced abilities of individuals who are congenitally blind to reflexively orient spatial attention to the sound's location. This would help blind individuals process information in multisensory environments. However, the main insight of this experiment (Section 2.1) is that the auditory-evoked activation of contralateral visual areas does not need visual experience to develop.

Researchers have identified several anatomical routes that may mediate auditory responses in the occipital cortex in sighted people, including direct pathways between lower-level unimodal regions (Falchier et al., 2002, Rockland and Ojima, 2003), and indirect feedback connections from higher multisensory regions to unimodal sensory regions (Stein and Meredith, 1993, Driver and Noesselt, 2008). Given the late onset of the ACOP signal (i.e. 250 ms after the auditory cues) and the relatively late stage in the visual processing hierarchy to which it has been localized, ACOP is probably not mediated by direct pathways between the auditory and visual cortices. Instead, the data are consistent with the involvement of longer hierarchical pathways and higher-level multisensory regions prior to visual cortex activation. Although we cannot infer which exact cortical structures underlie the ACOP, the fact that we observed an ACOP in blind people in the first place suggests that the specific pathways involved in eliciting the ACOP do not require visual input to develop. Instead, sensory impairment enhances those pathways. The present findings add evidence to the hypothesis of mutual interaction between supramodal organization and cross-modal plasticity of the brain – these are the "yin and yang" of brain development according to Cecchetti and colleagues (Cecchetti et al., 2016a). Specifically, the occipital activation to sounds previously observed in sighted individuals and found here in blind individuals supports the idea that several visual brain regions can develop even in the absence of any visual experience, and those areas can also respond to specific perceptual information independently of the each sensory modality that conveys the input (i.e. supramodal organization). At the same time, the stronger response in blind compared to sighted people suggests that the lack of visual experience can drive cross-modal reorganization within brain areas deprived of normal visual inputs. Indeed, the brain areas can start responding more strongly to non-visual stimuli (i.e. cross-modal plasticity). The spatially lateralized pattern of occipital activation that we observed in blind people enriches the recent body of literature which reports that retinotopic organization principles are preserved in blind people (e.g. Striem-Amit et al., 2015, Butt et al., 2013, Bock et al., 2013). Previous studies based their conclusions on analyses of resting state or anatomical connectivity without actually demonstrating a contralateral activation of the visual cortex of blind people in response to auditory stimulation. Recently, Sourav et al. (2018) used EEG to demonstrate that one basic feature of retinotopic organization (i.e. upper versus lower visual field organization) is present in people who were born with total bilateral cataracts and subsequently underwent cataract-removal surgeries. Using the results from our experiment, we assert that the visual cortex retains another fundamental aspect of retinotopic organization (i.e. laterality of visual field) without needing visual input. In this way, our data strengthen the notion that some basic features of retinotopic processing are independent of sensory experience, supporting the account of sensory cortices' supramodal organization (Cecchetti et al., 2016a).

At this point, a question naturally arose as to what extent the visual experience is really necessary for the visual brain to develop and function. From a previous study, we know that acoustic recruitment of the visual brain plays an important role in the auditory spatial task of spatial bisection (Campus et al., 2017). The latter requires relative comparisons between external spatial distances. Considering that vision interferes with spatial bisection abilities (Gori et al., 2014), we addressed to what extent visual experience is necessary for developing recruitment of occipital areas observed during auditory bisection tasks. We found a key relationship between visual experience and human ability to build complex spatial representation, as required by spatial bisection. Indeed, we demonstrated in this case that the specific occipital response to sounds does not develop when visual experience is missing (Section 2.2). Also, it is lost after prolonged blindness in people who became blind later in life (Section 2.3). It therefore seems that the sensory-independent supramodal organization of visual areas is, at least in some cases, dependent on visual experience. Thus, supramodal brain areas respond to a given perceptual task independently from the sensory modality that conveys the input (i.e. sensory-independent supramodal organization), but sensory experience may be in some cases necessary to develop this supramodal architecture.

This result may appear to conflict with the results previously reported in the context of reflexive auditory spatial attention, but there are differences between the tasks used to explain such results. The latter study used a difficult spatial bisection task requiring spatial representations in Euclidian coordinates, strong spatial skills in terms of memory and attention, and finally a sophisticated, well-calibrated spatial-auditory map. In contrast, the task used in the other experiment does not stress the construction of complex spatial maps. We can speculate that the lack of vision impairs the projection of complex multi-sensory maps on the retinotopic maps used by the visual cortex. This could be a plausible explanation that agrees with previous studies highlighting neuroplasticity limits. In this regard, it is important to note that the ERP component, which we found blindness attenuates, reflects early perceptual effects, far from the later cognitive effects (e.g.

attention and expectation) reflected by the ERP component investigated in the ACOP experiment (McDonald et al., 2013, Feng et al., 2014).

The ACOP is elicited by unpredictable sounds and characterized by a late time window (250-400 ms). By estimated sources, it is localized to the ventrolateral extrastriate visual cortex (Brodmann’s area 19). In contrast, the ERP component that the spatial bisection evokes consists of a strong response in the same early time window as a visual-evoked C1 (50-90 ms), with generators likely involving visual cortex (Campus et al., 2017). Considering that vision is important for aligning neural representations of space deriving from different sensory modalities (e.g. King, 2014, King, 2009), our hypothesis in the current thesis is that visual deprivation interferes with re-alignment of the brain’s complex auditory spatial information. In sighted people, the auditory external frame of reference is anchored to the visual system (Foley et al., 2015). External representations, like those required by the spatial bisection task, seem to originate from the spatial alignment of auditory and visual signals in oculocentric (eye-centred) coordinates (Pouget et al., 2002, King, 2009, Jay and Sparks, 1984, Cohen and Andersen, 2002). Unlike the first experiment we ran as well as more traditional sound localization tasks, the bisection experiment requires spatial judgment that depends on two external auditory landmarks; it is more anchored to an external perception of the surrounding space (Gori et al., 2014). Visual deprivation may therefore impact the processes related to codifying auditory space, impairing the building of external spatial representations. We see no conflict with other previous studies showing a preserved retinotopic organization in blind and sight-recovery individuals (Striem-Amit et al., 2015, Sourav et al., 2018) . For example, Striem-Amit and colleagues (Striem-Amit et al., 2015) revealed that, when using functional connectivity MRI indices, a certain level of large-scale retinotopic organization is retained in the visual cortex of the blind, while in the bisection experiment we focused on a very early time window that we measured with EEG. It could be that a certain level of retinotopic organization is preserved but nevertheless attenuated in cases of blindness, or it may be that it is not evident in our data because it does not involve the earliest pathways of visual processing. As for Sourav and colleagues’ (Sourav et al., 2018) study, we can hypothesize that other features maybe associated with retinotopic organization require visual input to develop. An alternative explanation could be that the construction of complex auditory spatial representation that we test in the current study reflects a peculiar ability for which retinotopic organization of the striate cortex is not a prerequisite.

Another possible interpretation about spatial bisection skills and neural correlates involves differences in spatial imaging strategies between sighted and blind individuals. In recent years, a growing body of research has employed the mental scanning paradigm as a tool to investigate the metric properties of mental spatial images in the blind population (Cattaneo et al., 2008, Cattaneo et al., 2007, Iachini and Ruggiero, 2010, Afonso et al., 2010). In one study (Afonso et al., 2010), the authors claimed that only blindfolded sighted and late blind people can create metrically accurate spatial representations of small-scale spatial configurations by listening to a verbal description or haptically exploring the configuration. On the other hand, early and late blind participants, but not sighted individuals, can generate accurate spatial mental images using locomotor exploration of a full-scale navigable environment. These results highlight that spatial imagery in early and late blind people differs from spatial imagery among sighted individuals (Afonso et al., 2010). Although spatial imagery is sensitive to visual experience, it does not seem to explain our results because the observed component we consider here involves a very early time window (50-90 ms). This more likely reflects perceptual rather than imaging processes.

Symmetrically, some past studies have supported a sensory-independent supramodal organization of the auditory cortex too, suggesting one might extend the supramodal principle to other sensory regions. Although this kind of research is much more limited in deafness compared to blindness, several studies showed sensory-independent task-selective recruitment of the auditory brain. For instance, the auditory language network mostly maintains its distinctive properties in the brain independently of the sensory modality being used as input. Researchers have repeatedly reported sign language processing to recruit the same auditory regions typically recruited by spoken language processing in deaf adults during both sign production (e.g. Corina et al., 2003, Emmorey et al., 2003) and sign comprehension (e.g. Neville et al., 1998, MacSweeney et al., 2002). Apart from activations related to language, studies have only clearly documented task-selective recruitment in auditory cortices for the perception of visual rhythm (Bola et al., 2017). Specifically, regardless of the sensory modality involved, perception of rhythms peaked in the same anatomic auditory regions – that is, the posterior and lateral parts of the high-level auditory cortex. Interestingly, other results showed that the large-scale topography of auditory cortex does not differ between hearing and deaf individuals. Tonotopic-like large-scale functional connectivity patterns can emerge and be retained through life in prelingually deaf humans without auditory experience (Striem-Amit et al., 2016). In addition, studies in deaf cats revealed that the auditory cortex mostly preserve anatomic connectivity patterns (Barone et al., 2013, Chabot et al., 2015, Meredith et al., 2016). Similar to blindness, it follows that large-scale anatomic and functional connectivity patterns seem to be preserved following deafness in humans.

Therefore, as for the visual context, one might wonder to what extent auditory experience is necessary for the auditory brain to develop and function. A number of psychophysical studies have revealed a strong audition’s role in temporal bisection tasks, which require subjects to encode presentation timings of stimuli, keep them in mind, extract the relative time intervals between them, and compare estimates (Gori et al., 2012b, Gori et al., 2017). Similar to our studies involving spatial bisection, we wondered whether recruitment of the auditory brain may be necessary for temporal bisection regardless of sensory modality tested. Moreover, since this was the case for the visual modality, our subsequent question regarded to what extent auditory experience is necessary for this neural circuit to develop. In hearing people, we demonstrated the existence of an early ERP response compatible with activation of the auditory cortex specifically elicited by the construction of complex temporal representation during a purely visual temporal bisection task. Differently, deaf participants could not perform the same visual task, and the specific cortical activation observed in hearing people appears to be missing. This means that a lack of audition seems to impact development of some visual temporal skills and underlying neural circuits, impairing one's ability to understand complex temporal relationships such as those involved in solving temporal bisection tasks.

Our results in typical hearing individuals (Section 3.1) suggest a supramodal organization of the auditory brain: audio-visual cortical interaction seems to occur at very early stages of processing. Auditory regions could support complex visual temporal representation. Our results in deaf individuals (Section 3.2) add that this aspect of supramodal organization is dependent on sensory experience: the auditory experience seems crucial in developing an early fronto-central and temporal scalp response specific for time perception of the visual stimuli. Although rhythmic temporal patterns can be coded in various sensory modalities, our study suggests that the auditory domain could process such stimuli most efficiently. Deaf participants show a deficit in temporal bisection, which agrees with existing literature that shows how auditory experience is necessary for developing some timing abilities in other modalities. For instance, deaf adults were found to be impaired in estimating visual temporal durations in the range of seconds (Kowalska and Szelag, 2006) and tactile temporal durations in the range of milliseconds (Bolognini et al., 2012).

Far from studies showing cross-modal plasticity following deafness, our findings suggest a key relationship between auditory experience and the human ability to build complex temporal representation. It is important to highlight that the ERP component we found to be attenuated by deafness reflects early perceptual effects. Indeed, it appears between 50-90 ms after the visual stimulus and it mimics some characteristics compatible with the auditory-evoked N1 component. We can therefore speculate that cortical activations similar to those underlying the N1 ERP component play a fundamental role in constructing complex temporal representation in visual modality; however, this mechanism may depend on the auditory experience. The impaired functional specialization we observed in temporal regions of deaf humans complements our study on auditory spatial bisection processing among people who are blind. The spatial metric of sounds elicits an early response likely involving the visual cortex in sighted but not in blind individuals, mimicking many aspects of the visual-evoked C1 (see Chapter 2). Similarly, the temporal metric of flashes elicits an early response likely involving also the auditory cortex in hearing but not in deaf individuals, which mimics some aspects of the auditory-evoked N1 (see Chapter 3). Taken together, these results suggest that some properties of large-scale supramodal organization of human sensory cortices are domain-specific and do not develop without sensory experience in a given modality.

To sum up, the findings of the current thesis contribute to the debate about two hypotheses ("sensory compensatory hypothesis" vs. "perceptual deficiency hypothesis") previously proposed to explain enhanced and impaired skills following sensory deprivation. The available evidence suggests that the two hypotheses are not mutually exclusive, but also that behavioural and brain modifications in blind and deaf individuals can cause adaptive (compensatory) and maladaptive (deficiency) features. Our results are in line with a supramodal organization of sensory cortices, adding that this could be partially explained by a domain specific organization at the cortical level. The two domains could be space and time. A speculation is that the visual cortices are involved in spatial processing and the auditory cortices are involved in temporal processing, all independent of sensory modality delivering the signal. In line with the "sensory compensatory hypothesis", our results claim that some aspects of supramodal organization do not crucially rely upon sensory experience-dependent developmental mechanisms. The loss of one sensory modality could induce compensatory unmasking and/or strengthening of existing neural multisensory pathways (Rauschecker, 1995), such as for the ACOP. Conversely, in line with the "perceptual deficiency hypothesis", we show that in some cases adequate sensory experience may be necessary to unmask multisensory neural connections. These are not automatically recoverable through plasticity. This could be at the base of the deficits following sensory deprivation, such as those we reported in complex spatial and temporal representation that rely on early and low-level stages of sensory processing.

Our findings provide strong evidence for cross-sensory calibration theory (Gori, 2015). The theory states that, during development, sensory channels communicate with each other and can calibrate the sensory signals. In this line of though, the most robust, accurate sensory can calibrate the other sensory signals. Actually, the hypothesis behind the design of thesis is derived from previous behavioural results on audio-visual spatial and temporal multisensory skills development in typical children. A few years ago, our research group showed that young children used only the visual information to estimate the multisensory spatial position of the stimulus in an audio-visual multisensory spatial bisection task (Gori et al., 2012b). After this age, they began integrating both modalities, resulting in the typical adult-like ventriloquist effect. Similarly, in the same bisection task but focused on the temporal domain, children followed auditory modality without integration and, interestingly, researchers did not observe integration in adults as well (Gori et al., 2012b).

These results on typical development suggest that the modalities play a crucial role during development; namely, the visual modality is crucial for developing multimodal spatial bisection skills, and the auditory modality is crucial for developing multimodal temporal bisection skills. More importantly, these results have allowed us to make some predictions regarding the implications of the lack of one sensory signal for developing these skills. As predicted, we found that blind individuals have problems in understanding the auditory spatial bisection task, likely due to a weaker and not lateralized activation of the area likely involving the visual cortices. Deaf individuals reveal a strong deficit in the visual temporal bisection task, likely due to the lack of activation in areas possibly involving auditory cortices. Thus, the model of studying the development of multisensory integration and sensory dominance in children can be a good way to specifically predict sensory impairment in individuals with a disability. A similar prediction was done in the past for blind and dyskinetic children. Starting from the observation of sensory dominance on multisensory tasks in typical children (Gori et al., 2008), research has indicated specific impairments on haptic orientation estimation in blind children (Gori et al., 2010), and on visual size estimation in dyskinetic children (Gori et al., 2011b).

5.2 Space, time, and speed

In Chapter 4, I investigated possible interactions between spatial and temporal representation. I first demonstrated that when visual calibration of space continues to occur, such as during development, or it is impossible, such as in blindness, complex auditory spatial representation is impaired and the brain uses temporal information to infer auditory spatial coordinates (Section 4.1 and 4.2). Second, I showed that when auditory calibration of time is impossible, such when an individual is deaf, complex visual temporal representation is impaired and the brain uses spatial information to decode visual temporal coordinates (Section 4.3). The deficit that we observed in children younger than 12 years old and blind adults during auditory spatial bisection, as well as the deficit we observed in visual temporal bisection of deaf adults, disappeared when coherent spatiotemporal cues were delivered, and such deficits increased in the wake of conflicting spatiotemporal information. Modification of spatiotemporal cues therefore alters spatial and temporal bisection performance in children, blind people and deaf people, whereas control adults can easily dissociate the spatial and the temporal cues in both tasks.

By showing both a temporal influence on spatial representations in childhood and blindness, and a spatial influence on temporal representations in deafness, our findings support the Theory of Magnitude (ATOM; Walsh, 2003). Indeed, the ATOM proposes the existence of an undifferentiated system of magnitude representation in the brain, predicting that space and time are symmetrically related. On the other hand, the Conceptual Metaphor Theory (CMT) predicts asymmetrical interactions between the spatial and temporal domains, assigning a dominant role to space (Lakoff and Johnson, 1999). According to the CMT, representations of time depend asymmetrically on representations of space. Casasanto et al. (2010) and Bottini et al. (2013) both investigated the interaction between the two domains during development within the visual modality. They found that children aged between 4-11 years could ignore temporal information when making spatial judgments, but they were influenced by spatial information when making temporal judgments. The authors interpreted their results as space-time asymmetry, supporting CMT

(Lakoff and Johnson, 1999). However, one can easily reconcile these results with our data in young children, given the dominant status of vision in performing spatial judgments (e.g. Alais and Burr, 2004). In agreement with a recent review (Loeffler et al., 2018), we think the main reason for asymmetric effects between space and time relies on the sensory modality involved rather than a genuine asymmetric mapping between the two domains. Stating the dominant role of vision when it comes to space perception and of audition for time perception (see Chapter 1), we support the claim that the direction of the mutual interaction between space and time strongly depends on the sensory modality. Indeed, this occurs with space influencing time estimations within the visual modality, and time influencing space estimations within the auditory modality. Our data reveal that this is particularly true when one sensory input is absent, such as for people who are blind or deaf people, where completely independent spatial and temporal representations seem not to develop.

Thus, our results regarding the influence of time in spatial representation suggest that temporal information can act as an alternative cue for reorganizing spatial representation subtending some more complex spatial abilities. Previous works showed that the spatial reference frames of blind individuals are fundamentally different from those of sighted individuals (Pasqualotto et al., 2013). In agreement with this idea, a recent studied showed that blind individuals enhance their skills in the spatial bisection task when they can use their bodies as references (Vercillo et al., 2018). While the retinotopic organization of the visual cortex may support the reorganization underlying some enhanced auditory spatial skills in blindness (such as the sound localization ability), it may be insufficient to guarantee the development of more complex spatial skills, such as those required for the auditory spatial bisection task. A possible explanation is that, when blind individuals must face complex spatial representations they cannot solve, they rely on alternative cues. One cue could be the body as a reference, while the other one could be time. Specifically, the fact that blind people were not attracted by a pitch cue when it substitutes the temporal cue in the bisection task we mentioned as preliminary control experiment in Section 4.2 indicates that the attraction of blind people towards another cue is specific for the temporal domain. Similarly, by showing an influence of space in temporal representation following deafness, we suggest that spatial information acts as an alternative cue for reorganizing temporal representation subtending certain complex temporal skills when auditory experience is missing. This leaves us with a few questions, such as how temporal information can support space processing in blindness, and how spatial information can support time processing in deafness. Both blind and deaf individuals benefit from coherence in spatiotemporal information.

The cross-sensory calibration theory (Gori et al., 2012b, Gori, 2015) suggests that the visual system’s calibration of the auditory system is fundamental for developing an auditory sense of space, and the reverse is the case for time. Humans could mediate these processes with pathways involving the superior colliculus (King et al., 1988, King, 2014).

Starting from our results, we could interpret that, for some complex spatial and temporal representations, the visual system calibrates the auditory sense of space, and the auditory system calibrates the visual sense of time, by processing the speed of the stimuli (and possibly assuming a constant velocity as expected default). Neurons that process speed information have been demonstrated for the visual modality in the visual cortex (Liu and Newsome, 2003). These neurons could be responsible for processing information during auditory spatial bisection tasks. In typical conditions, the visual system may facilitate transference of auditory processing from a temporal to a spatial coordinate system relying on speed processing. In a similar way, the auditory system could facilitate transference of visual processing from a spatial to a temporal coordinate system. When the visual or auditory inputs are unavailable, this transfer may not occur, resulting in auditory maps based only on temporal cues for inferring complex spatial representations when a person is blind, and visual representation based only on spatial cues to infer complex temporal features when a person is deaf. One might speculate, then, that the mediator between auditory time and visual space is velocity processing, which may represent a channel of communication between the two sensory systems. Figure 5.1 reports a graphical description of how vision and audition may collaborate to estimate space and time starting from the speed properties of an object.

Concerning typical individuals’, given the higher weight of vision in space estimation, the latter can be independent of the temporal coordinates of the stimulus for both coherent (Fig. 5.1A left) and conflicting (Fig. 5.1A right) situations. Similarly, given the higher weight of audition, time estimation in typical individuals can be independent of the spatial coordinates of the stimulus for both coherent (Fig. 5.1A left) and conflicting (Fig. 5.1A right) situations. At the same time, when the visual information is missing, the spatial counterpart seems unable to develop and blind individuals then rely only on temporal coordinates to infer complex spatial information (Fig. 5.1B). When the auditory information is unavailable, it is the temporal counterpart that seems not to develop and deaf individuals must accordingly rely only on spatial coordinates to infer temporal information (Fig. 5.1C). If this were the case, it would explain why blind individuals are sensitive to the temporal delay of the stimulus and not to its spatial position when information is conflicting (Fig. 5.1B right), and why under the same condition deaf individuals are sensitive to the spatial position of the stimulus and not to its temporal features (Fig. 5.1C right). It is worth wondering about the benefits of such a mechanism. Having a map that contains both spatial and temporal metric information could be useful, considering that objects usually move coherently in space and time. A possible speculation is that, when the visual or auditory networks for spatial and temporal perception are impaired, blind and deaf individuals assume constant velocity of environmental stimuli, thereby inferring space from time and vice-versa.

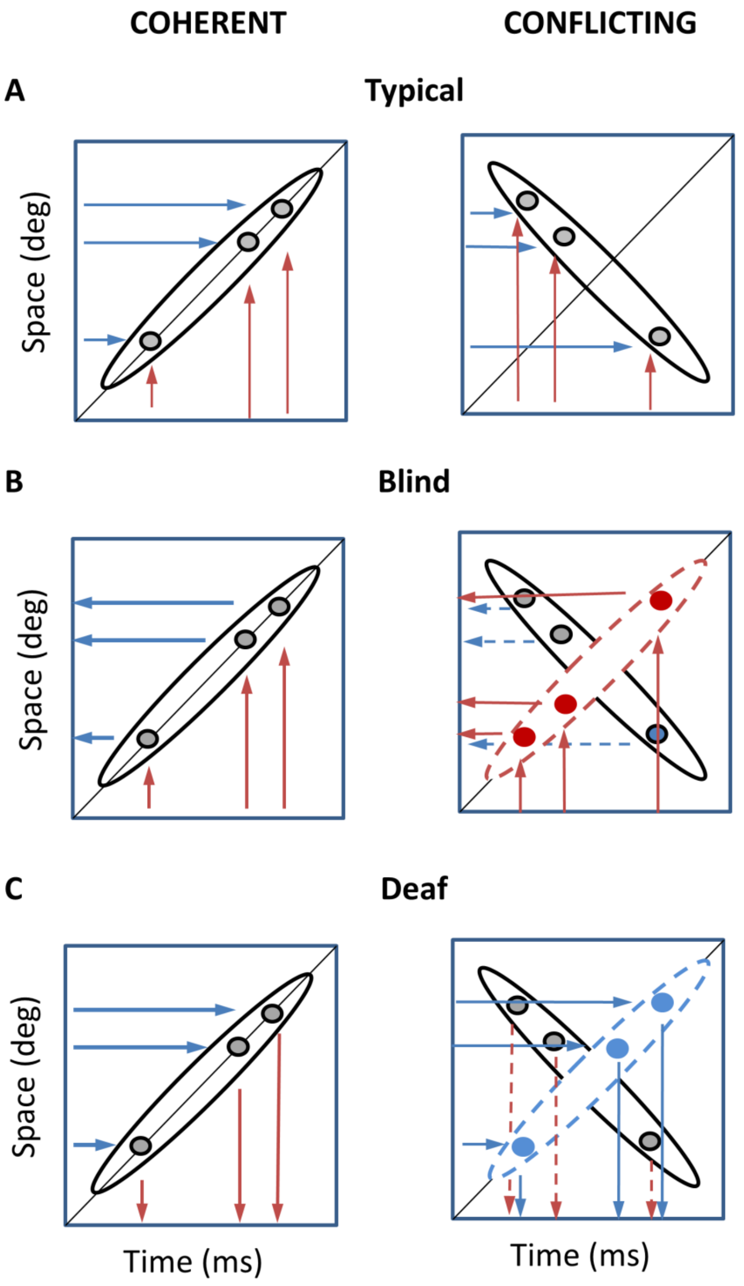

Figure 5.1 Graphical model of our theory.
In typical individuals **(A)**, spatial and temporal estimations are independent, for both coherent (left) and conflicting (right) information. In blind individuals **(B)**, spatial information may be inferred by the temporal coordinates of the stimulus, assuming constant velocity. When spatiotemporal coherent stimuli are presented, the spatial estimation could be successfully extracted by the temporal cue (left). On the other hand, when conflicting spatiotemporal information is provided, the temporal cue could be wrongly used to derive the spatial position of stimuli (right). In deaf individuals **(C)**, temporal information may be inferred by the spatial coordinates of the stimulus assuming constant velocity. When spatiotemporal coherent stimuli are presented, the temporal estimation could be successfully extracted by the spatial cue (left). On the other hand, when conflicting spatiotemporal information (right) is provided, the spatial cue could be wrongly used to derive the temporal delays of stimuli.

This is supported by the Imputed Velocity Theory (Huang and Jones, 1982), which researchers previously proposed to explain the Tau ad Kappa effects (Kawabe et al., 2010, Sarrazin et al., 2007, Bill and Teft, 1972). According to the latter, humans intuitively impute uniform motion to discontinuously displayed successive stimuli. This strategy could help blind and deaf people overcome metric problems by using unimpaired temporal or spatial maps to decode auditory spatial and visual temporal metric, facilitating interaction with others. On one side, this strategy would be adaptive and allow them to correctly process spatial or temporal information. On the other side, this strategy could be maladaptive when there is conflicting spatial and temporal information, as it would deceive sensory deprived individuals in the evaluation because of the wrong cue, thereby perceiving an illusory spatial position or temporal delay of the stimuli. This could be the reason why typical people do not develop this strategy: when spatial and temporal information is conflicting (e.g. during accelerations and decelerations) the temporal cue is uninformative for inferring space and vice-versa. It may be that the temporal attraction of space and the spatial attraction of time produce a misperception of the stimulus, impacting one’s capability to interact with the environment. Real-life situations where implicitly assuming constant velocity is potentially maladaptive involve all cases of accelerating or decelerating environmental objects. An example would be a motorcycle that suddenly increases speed – in this situation, hearing sounds closer in time does not necessarily indicate that one has travelled a shorter path. A final speculation is that the temporal sequence of events could be at the base of the development of spatial relationship understanding and vice-versa, and sensory experience seems crucial for this developmental mechanism to occur.

5.3 Concluding remarks

The current thesis points out that some spatial and temporal skills require the functional recruitment of areas likely involving the visual and auditory cortices respectively. Spatial orienting auditory attention and complex auditory spatial representation elicit specific activations in parieto-occipital areas, while complex visual temporal representation elicits a specific early activation in fronto-central and temporal scalp regions. Although future researchers should test cortical activations that are involved in spatial and temporal representation in other senses, such as in the tactile modality or a multisensory context, our results strongly suggest that some domain-specific proprieties characterize the organization of the visual and auditory cortices. In agreement with multisensory research showing a dominant role of vision in space perception (e.g. Alais and Burr, 2004) and audition in time perception (e.g. Bresciani and Ernst, 2007), visual and auditory cortices may be involved in building complex spatial and temporal representation, respectively. This may happen independently of the sensory modality delivering the input. Results from this thesis add further evidence: consider there are some domain-specific aspects in the supramodal organization of sensory cortices, sensory experience could be a prerequisite for developing at least some of them. Indeed, lack of vision hampers neural correlates underlying some complex spatial abilities and neural correlates, and the lack of audition hampers neural substrates of some complex temporal abilities. Besides shedding light on some limits of cortical reorganization following sensory deprivation, these findings offer important implications for understanding the neural underpinnings of temporal and spatial representations.

This thesis furthermore evidenced a strong interaction between spatial and temporal representation under certain circumstances. When auditory spatial skills are poor, such as for young children and blind people, there exists a strong attraction towards temporal information when performing auditory spatial judgments. Similarly, when visual temporal skills are poor, such as in the case of people who are deaf, there exists a strong attraction towards spatial information when performing visual temporal judgments. In some cases, the brain may therefore use temporal cues to infer an environment’s spatial coordinates and spatial cues to decode temporal features.

Because typical adults can successfully dissociate spatiotemporal information, the development of completely independent spatial and temporal representations may depend on visual and auditory sensory experience. We speculated that audio-visual calibration processes during development may rely on speed processing, where time and space require integration. Beside possible interpretations, this thesis agrees that sensory modalities interact during development, but it also suggests that spatial and temporal domains could interact. Moreover, sensory experience could impact this interaction. A future study should investigate complex visual temporal representation during development. This would be specular to the experiment in this thesis testing complex auditory spatial skills of children. Audio-visual integration gradually develops throughout childhood, so that based on our hypotheses we can expect spatial cues to influence younger children’s visual temporal estimation. Among others, a question that is still open pertains to whether temporal attraction of space and spatial attraction of time represent a general principle of spatial representation in blindness and deafness, respectively, or if they are specific for the spatial and temporal bisection tasks we performed. Although other studies have observed spatiotemporal interactions (e.g. Roder et al., 2004 for blind people), further research will be necessary to understand whether this kind of interaction represents a general principle of the brain. A possible way to answer this question could be to apply a similar approach to other tasks for which enhanced skills have been reported in blind or deaf individuals (i.e. the minimum audible angle for blind and some duration reproduction tasks for deaf). Future experiments involving cross-modality and cross-domain conflicts (such as audio-space vs. visuo-time, or visuo-space vs. audio-time) should also be planned to shed light on the interaction between auditory and visual modalities, as well as spatial and temporal domains in typical individuals.

Beyond theoretical relevance, the results of the current thesis may have repercussions for teaching and rehabilitation strategies following sensory loss. If in some cases time influences auditory space judgments and space influences visual time estimations, it behoves us to develop new techniques in which one can simultaneously manipulate spatial and temporal cues to convey richer information. For instance, congruent spatiotemporal information could help teach some spatial concepts at school, such as angles, shapes, distances, or scale (e.g. the difference between a centimetre and a meter could be explained by comparing short and long time intervals between sounds). The same could be thought for teaching some temporal proprieties, such as the rhythmic component of reading. As for rehabilitation, if blind and deaf individuals benefit from spatiotemporal coherence, there is potential to develop new technological devices by providing temporal cues to inform about spatial dimensions and vice-versa. Blind people rely strongly on auditory information to orient themselves in their environments. Sturdy spatial maps are clearly of paramount importance and their development in the absence of visual information must be understood and recovered if impaired. New techniques could be realized in this direction for helping visually impaired children by taking advantage of temporal cues to recalibrate spatial representation. Similarly, our findings present opportunities for developing sensory substitution devices and rehabilitation technologies for deaf children, where, in this case, spatial cues can recalibrate temporal representation. From a technological perspective, the hope is to exploit the neuroscientific results obtained by this thesis to think of new science-driven rehabilitation devices for improving impaired spatial and temporal abilities of blind and deaf individuals.

List of publications

Amadeo, M. B., Campus, C., and Gori, M. (2019). Impact of years of blindness on neural circuits underlying auditory spatial representation. *Neuroimage*, 191: 140-149.

Amadeo, M. B., Campus, C., and Gori, M. (2019). Time attracts auditory space representation during development. *Behav Brain Res*, 376: 112185.

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