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THE SOUND OF SCOTOMA
A multisensory integration approach for individuals with Macular Degeneration

by

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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.

Hafsah Ahmad
March 2020

Abstract

Audio-spatial representation reorganizes in the absence of visual inputs, as in case of blind individuals. However, it is not clear how this spatial reorganization works. Although blindness is an ideal condition to understand how other sensory modalities react in absence of vision, there are some limits in using it as a modal. The main limit is that blindness can be considered a *stable* model of cortical organization and it does not allow to understand the mechanisms which cause this reorganization. To understand this process, we have studied a unique group of individuals suffering from Macular Degeneration (MD) for whom loss of visual inputs due to a progressive scotoma is an ongoing process. In this dissertation I decided to focus on understanding auditory spatial representation in MD individuals and to develop technnological solutions for them incorporating multisensory integration. First, we developed a device called ARENA which is an audio-tactile matrix of speakers to study audio-spatial localization in MD individuals. Our findings show that visual loss brings an immediate change in the processing of audio-spatial percept by attracting the lateral sounds towards scotoma positions in the center, producing a strong auditory spatial perception bias. To recaliberate this audio-spatial bias and to give MD individuals an understanding of their own scotoma to develop an effective pseudo fovea, we have designed a rehabilitation protocol called Intelligent Audio Visual Thumble Training (IVATT). A multisensory feedback device Audio Visual Thumble (AVT) is developed for this training. Our findings show that this technique is effective to overcome the audio-spatial bias and can improve the precision towards visual stimuli in peripheral visual field. This work concludes that development of scotoma alters the audio-spatial representation and hence focus of rehabilitation techniques can be extended to bring-in multisensory modalities in order to utilize residual vision of MD individuals.

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Chapter 1

Introduction and Literature review

1.1 Aim of the study

One important feature in our everyday life is to understand the environment surrounding us. To achieve this goal, we use mainly vision and the integration of it with all the other senses. However, what does happen to spatial representation in absence of vision? To answer this question until now, blindness has been used as a model for understanding neural reorganization. Although blindness is an ideal condition to understand the role of spatial representation, the limit is that it is a stable cortical organization. In this dissertation, I will propose and investigate a new model to investigate spatial representation that is Macular Degeneration (MD) disease. The first research question is: how does spatial representation reorganize when partial visual inputs are lost in patients with MD? Second, if there is a spatial reorganization, can we develop a rehabilitation protocol to overcome this bias using multisensory integration? From literature review, we found a research gap in understanding the multisensory representation reorganization with the partial loss of vision and we found that the rehabilitation techniques available for MD individuals focus on visual modality only, unlike blind individuals for whom many sensory substitution devices are available in market. The aim of this study is to understand auditory spatial representation in MD individuals and to develop technical solutions for them incorporating multisensory integration.

1.2 Multisensory Integration

Our perception of environment around us is based on various sensory feedbacks from the external world and it is processed by multiple sensory systems. In order to create a coherent representation of these sensory inputs, our brain binds the related sensory inputs together and the unrelated ones are segregated (Stein and Meredith (1993)). Hence, *Multisensory Integration* is defined as the ability of the brain to quickly and efficiently integrate the sensory inputs coded by possibly independent sensory systems. Multisensory integration is a basic perceptual function and where, when and how these sensory systems integrate together is a matter of deep research.

The conventional elementary theory of cortical association is that separate regions of the cortex discretely receive visual, auditory, tactile, gustatory and olfactory sensory inputs. These sensory regions are supposed to be self-regulating and are thought to show projections that congregate on sensory association regions (for example, parietal region). These sensory association regions then empowers the binding among separate senses. This conventional concept of binding between senses was overturned in the last decade of 20th century. Advanced functional imaging techniques (Foxe and Simpson (2002), Martuzzi et al. (2006), Macaluso et al. (2000), Calvert (2001)) and development of electrophysiological research on humans and animals (Giard and Peronnet (1999), Foxe et al. (2000), Molholm et al. (2002), Gomez-Ramirez et al. (2011), Murray et al. (2004)) opened new dimensions towards multisensory integration phenomenon. These evidences changed the paradigm of scientific research in cognitive neuroscience, opening doors to an idea that the primary sensory regions are entirely sensitive to sensory input from only one sensory modality. This idea gave birth to a hypothesis that multisensory integration is present nearly in all cortices, even in early cortical stages of sensory processing as well (Murray et al. (2016), Ghazanfar and Schroeder (2006)). However, this new paradigm of sensory interaction is a prevalent breakthrough in research and the debate on existence of multisensory integration in early sensory areas (Kayser (2010)) and the mechanisms underlying this sensory integration is still a significant research question (Schroeder and Lakatos (2009), Mercier et al. (2013)). Research is in progress now and some studies have shown the complex and heterogeneous behaviour of multisensory integration effects (Yu et al. (2019), Mercier et al. (2015), Mercier et al. (2013)).

Despite the fact that early anatomical research on different primary sensory modalities could not provide an evidence for strong anatomical linkages between these sensory regions (Jones and Powell (1970)), with the advancement of techniques in last couple of decades

we have seen some novel insights on this aspect. In the following section, the anatomical connectivity between sensory cortices (vision and audition) is discussed.

1.2.1 From auditory cortex to early visual cortex

During last 20 years, many studies on animals have found a coherent evidence showing monosynaptic (direct projections) from different areas of the auditory cortex towards early visual cortex. However, before 2002 we have seen no evidence showing direct pathway from A1 to V1 areas in monkeys. The possible absence of anatomical connections in monkeys became very controversial since the presence of this pathway in Mangolian gerbil as shown by Budinger et al. (2000), and because early visual cortex are recruited ny non-visual inputs as seen in blindness (Büchel et al. (1998), Sadato et al. (1996), Cohen et al. (1999),Weeks et al. (2000)). The influential study from Falchier and colleagues in 2002 (Falchier et al. (2002)) is the first evidence for presence of this pathway in macaque monkeys. They used retrograde trackers at different portions in early visual cortex and found the paternal neuron for these pathways at the sixth layer of core called the belt and parabelt regions of auditory cortex. They demonstrated a very important aspect of these projections showing that the peripheral region, that represent the peripheral visual field of primary visual cortex, received these projections in moderate density while the central regions that essentially represent the central visual field, received these projections in less density. Interestingly, later studies supported their finding that peripheral regions of early visual cortex have connectivity with auditory regions, however their finding about central regions of primary visual cortex showed sparse connectivity with auditory regions and the later finding could not gain support.

One year after Falchier et al. (2002) published their crucial findings, Rockland and Ojima (2003) partially conformed their findings. They found an evidence that belt area of auditory cortex connects to peripheral regions of V1 and V2. These connections were dispersed in VI and compact in V2. On the other hand, Rockland and Ojima (2003) could not find an evidence for connectivity between the belt and parabelt regions of auditory cortex and the central region of V1 and V2.

Above findings were supported by several other studies conducted on other mammals. For example, Henschke et al. (2015) also showed that A1 has a mild projection on V1. This was also supported by Cappe et al. (2009) who could not find an evidence for anatomical pathway connectivity from the auditory regions to central V2 regions. This result indirectly supports the idea of heteromodal pathways between peripheral representations from visual cortex. Another study on cats by Hall and Lomber (2008) found the parental neurons for

these pathways in posterior part of auditory cortex. This study used retrograde tracers for retinotropic representations of V1 and V2 in center and periphery. They also tested a second group of cats by using tiny deposits in more precise locations of visual cortex namely central, paracentral and peripheral visual fields. For this second group of cats with more precise locations, the results showed that parental neurons in posterior part of auditory cortex targets the neurons in peripheral visual field. This study (Hall and Lomber (2008)) provides an evidence for organization of heteromodal connectivity in cats which is in line with the findings for monkeys. An important point they found about neurons in the peripheral auditory cortex is that they show a lower retinotropic organization. This is in line with the work of Morrell (1972) which is a neurophysiological study, showed a presentation of audio-spatial inputs on primary visual cortex of cats.

Based on these studies, now it is known that in primates brain, auditory cortex regions of belt and parabelt regions have moderate projections to the peripheral visual field of V2 and dispersed projections for V1 peripheral fields. These studies are proof that there is multisensory integration among sensory cortices even when they are receiving perfect inputs. The study from Alais and Burr (2004) is an example of the hiraricy of how these sensory inputs are ordered by our brain. They have provided an evidence that when visual and auditory information are presented at the same time, the visual modality dominance over audition in the spatial domain. However, in the absence of vision, the high weightage of visual inputs (which is impaired for blind individuals) is shifted towards the auditory cortex and the visual cortex is recruited by auditory to form a multisensory integration. There are also some studies showing that in the absence of vision, the visual cortex of blind individuals process tactile and auditory inputs (Rauschecker et al. (1995), Collignon et al. (2009), Collignon et al. (2013), Voss et al. (2004)).

1.3 Low vision and cortical plasticity

Anatomy of vision, typically the early visual pathways, changes significantly as a result of a disease or an injury. These changes show an immediate effect on both anatomical and behavioural visual functionality tests. As an example, Macular Degeneration (MD), causes an observable change to visual acuity due to retinal damage and forms a scotoma on the retina. This change in visual field due to scotoma may be adapted by the visual system in such a way that effects the characteristics of neural pathways and perceptions. These changes can be either spontaneous or gradual depending upon the subsequent experience or training of the effected person. An analogy for these changes could be the traffic blockage on a busy street

inside the city which directly effects the flow of traffic on that street, which is similar to the blockage to flow of visual information towards the optic nerve due to Macular Degeneration. However, the blockage of traffic on busy street also effects the neighbouring streets as the drivers tries to find their way through unblocked streets thus producing a subsequent traffic jam in uneffected streets as well, hence adapting to the behaviour of blocked street. Similarly, flow of visual information adapts to the functional visual pathways at an early anatomical stage like retina or optic nerves. These plastic changes in visual anatomy can be found by testing either the anatomy, neural processing or visual behaviour.

1.3.1 Methods for measuring plasticity in low vision

Behavioural tests

To examine plasticity in people with low vision, three kinds of tests are used. 1) Comparing the difference in visual perception between low vision and sighted people to check plasticity, 2) tracking the visual functionality over a long period of time to measure attributes that are not directly related to underlying disease and 3) a training or perceptual learning method with a focus on improving a specific attribute affected by given pathology (Legge and Chung (2016)). Studying plasticity using these methods rely on various outcome measures.

Among the most common outcomes used for evaluating changes in visual functionality are visual acuity tests, contrast sensitivity tests and visual field tests. To measure visual acuity in a research setting, normally modern letter charts are used. These charts follow robust design techniques and they have a high reliability for test-retest settings. Among the best known visual acuity techniques are the Bailey-Lovie letter chart (Bailey and Lovie (1976)) and ETDRS chart (Ferris III et al. (1982)). Letter chart technique is used to measure contrast sensitivity as well. Among the commonly used methods are the Pelli-Robson chart (Elliott et al. (1990)) and MARS chart (Arditi et al. (2005)). Contrast Sensitivity Function (CSF) provides a more in-depth characterization of low-vision (Chung and Legge (2016)). However, CSF is not used commonly for low vision measurements because it requires more patient time and is technically difficult, although a user friendly CSF method has been developed that can be used in clinical settings (Lesmes et al. (2010)).

Another widely used outcome for measuring low vision plasticity is visual field perimetry. This parameter is used in pathologies involving visual field loss such as in Macular Degeneration. In case the pathology is hemianopia i.e. causes peripheral field loss, an instrument called Humphrey Visual Field Analyzer is commonly used. For the pathology involving central field loss, a test called Humphrey 10-2 test is used which covers the central 10 degrees

of visual field. Microperimetry (Nidek MP-1 and MAIA) is also an advanced technique to analyse sensitivity and focus of central visual field. These microperimeters are capable of presenting stimuli at known retinal locations with a reduced noise even with high eye movements. They use imaging and track landmark positions on retina for measurement to reduce the noise due to eye movements. Another advantage of using microperimeters is that they can measure the visual field which is an effective outcome in measuring the visual field deficits.

There are certain other outcomes used to measure plasticity in low vision which are focused towards measuring a certain attribute that concern real world challenges for these patients. Reading performance, for example, is an attribute commonly effected due to central visual field loss. There are several tests to assess the performance in reading, for example Bailey-Lovie near-vision chart (Bailey and Lovie (1976)), MNREAD visual acuity chart (Calabrese et al. (2016)), IReST reading tests (Trauzettel-Klosinski and Dietz (2012)) and the Radner reading test (Radner et al. (2002)). Among the other parameters to measure performance in outside world include face recognition (Bailey and Lovie (1980)), visual search task (Wiecek et al. (2012)), pedestrian mobility test (Soong et al. (2004)), letter recognition (Kwon et al. (2007)) and predicting the driving ability using visual field (Chaparro et al. (1998)).

Imaging tests

During the last 3 decades, imaging has been used to study the cortical and anatomical changes in low vision. The initial Scanning Laser Ophthalmoscope (SLO) was developed in 80s that acquired retinal images whiles simultaneous stimuli were presented (Mainster et al. (1982)). SLO became an essential instrument for measuring the pseudo fovea of patients with central visual loss. Another technique used for measuring pseudo fovea and fixation is the advanced fundus camera (White and Bedell (1990)). Other imaging tools used in low vision research include Nidek MP-1, OCT/SLO, MAIA (Seiple et al. (2013)), adaptive-optics SLO (Roorda and Duncan (2015)) and tracking SLO (Braaf et al. (2013)). Spatial resolution and field size of these instruments varies and therefore, the choice of instrument depends upon the research in question.

In past, it was not possible with the available techniques to study the cortical changes underlying low vision. Thanks to the development of non-invasive cortical imaging techniques as a result of which now it is possible how structure and function of brain reacts to onset of low vision. Whole-brain magnetic resonance imaging voxel-based morphometryhas been used to study the structural imaging by observing the afferent projections to visual cortex of

blind people with no visual experience (Kupers et al. (2011)). This study showed a notable atrophy of the optic chiasm, optic nerve, optical radiations, primary and secondary visual areas and MT. Magnetic resonance imaging was used in another study to observe the atrophy of V1 area in Macular Degeneration patients (Hernowo et al. (2014)). In another study, the diffusion tensor imaging method was used showing a reduction of white matter integrity during optic radiations in blindness compared to sighted individuals (Dietrich et al. (2015)). This studied showed a greater loss of white matter in late blind individuals (above 18 years of age) compared to congenital blind individuals.

Among the functional imaging methods to study cortical changes following low vision are the functional magnetic resonance imaging and positron emission tomography. To study the level of activation for different cortical regions commonly used method is the change in hemodynamic which is the measurement of the blood oxygen level dependent (BOLD) response. BOLD works on the concept that the active neurons need more supply of oxygen which creates a difference in oxyhemoglobin and deoxyhemoglobin levels in blood showing a cortical activity. Population receptive fields (PRFs) is a computational method that has been used to study changes in visual cortices as a result of different pathologies (Wandell and Winawer (2015)). PRF measures receptive field of a single neuron as fMRI analog. It can be an important method to study the cortical changes with vision loss.

1.3.2 Plasticity following early visual deprivation

Humans come to this world with an premature pattern vision. Behavioural measures for full-term new-born show that they have grating acuity of only 20/860 (Snellen chart) or 0.7 cycles/degree, whereas sighted adults have a grating acuity of approximately 10 cycles/degree (Brown and Yamamoto (1986)). Normal vision is achieved with growing age and visual experience. For example, infants that are born with dense cataracts are found to have reduced acuity in adult age, provided cataract is not surgically removed at an early stage. Visual function matures with growing age i.e. critical flicker fusion matures within 2 months, acuit and contrast sensitivity requires six to seven years of visual experience (Ellemberg et al. (1999)), visual span for reading at early school (Kwon et al. (2007)) and it takes almost a decade for face perception. In this context, the age of disease onset plays an important role as it effects the plasticity and the recovery of normal vision, provided any restorative treatment is available at a later stage in life.

Influence of early deprivation on visual cortex of kittens showed that visual function recovery after a long period of deprivation was absent in visual cortex (Hubel and Wiesel

(1965)). Case studies on people suffering from long term or congenital visual deprivation shows similar results of poor performance (Von Senden (1960), Gregory and Wallace (1963)). For instance, let's consider case study of a subject MM. MM was born with normal vision, but due to an accident at 3.5 years of age, he lost complete vision of one eye while the cornea other eye was also seriously damaged with only light perception without pattern vision. After four decades of accident, he has a surgery of limbal stem-cell and also had a corneal transplant. These surgeries gave him a better image formation at retina. He was tested for certain behavioural tests within two years of vision restoration. These tests showed an acuity of 20/500, close to normal perception of motion and colour and normal recognition of two dimensional objects. However, higher level visual abilities like identifying three dimensional objects and face recognition remained severely impaired (Šikl et al. (2013)). fMRI studies for MM showed that his visual cortex responded actively to motion stimuli, however ventral visual pathways did not revealed normal category specific activation for face and three dimensional stimuli. MM was tested again after 10 years and the results showed improvement neither in visual acuity nor in higher level visual cue recognition (Huber et al. (2015)). From MM's case study, a conclusion can be drawn that if the visual functions are not truly developed before the visual loss, after the vision restoration they do not develop with visual experience. Even some functions developed before visual deprivation; visual acuity for MM as an example; may also decline with time during long period of visual deprivation.

With advanced techniques in research, there are studies that have shown contrary results to case studies mentioned above i.e. they have found a greater plasticity in adults who have restored vision after a very long period of visual deprivation. Studies on adult patients with amblyopia have shown that some kinds of extensive visual exercises can improve the visual acuity at adult age (Hess et al. (2011), Levi and Li (2009)). Amblyopia is a pathology that effects acuity and contrast sensitivity of one eye resulting in lower reflective power for both eyes. A conventional thought about this pathology is that its treatment does not produce any positive results in terms of plasticity after a critical age of around seven years. However, these studies found an improvement in visual acuity even at adult age. Even if amblyopia is not considered among low vision pathologies, these studies are still a significant evidence showing plasticity of visual functionality at adult age.

Molyneux raised an interesting question in 1688. The question was that if a person is congenitally blind, so has no visual experience, if he regains his vision at adult age, will he be able to recognize shapes and sizes through vision? (Lievers (1992)). The answer to this question has been in search since it was originally proposed. A study on adults who were suffering from congenital early onset cataract and were surgically treated at later years in

life, reported an experiment in which soon after the surgery subjects were asked to match the shape of object presented either in their hand or shown, with a set of objects (either visual or touch) (Cohen and Matthen (2018)). Results of this study shows that subjects performed better in uni-modal cues i.e. matching touch-touch and vision-vision, but they showed poor results in cross modal matching i.e. touch-vision. These subjects were tested again after a certain period and it revealed that visual experience during this period have improved their cross modal skills and now they can perform better in matching touch-vision. This ability of learning to incorporate vision with touch at adult age provides another evidence for adult plasticity in visual deprivation. These results are indeed encouraging for visual rehabilitation.

1.3.3 Plasticity following late onset visual deprivation

The term *critical period* for vision refers to the developmental period of humans when the cortical organization for visual pathways develop depending on visual experience, either normal or impaired. After critical period, the cortical organization and neural pathways matures and become stable and becomes harder to adapt any changes in sensory inputs (Wandell and Smirnakis (2009), Fagiolini and Hensch (2000)). This is the reason why adults who suffer from visual deprivation at a later stage in life (such as cataract or age-related macular degeneration) are expected to show less plasticity to ongoing changes in sensory inputs. However, evidence are still present showing plasticity to some extent in adults (sighted or low vision) even after critical period.

The potential for plasticity in low vision depending on visual experience and onset age of disease has been studied since long time. The topic is of critical importance because it has direct implications of rehabilitation. For example, consider if there plasticity is totally absent in adult age, the person deprived of vision will not be able to adapt to changes in visual inputs and hence there will be no impact of any rehabilitation. In this case, the only possibility will be a cure that can restore vision to its normal state, which is practically impossible to-date especially for retinal diseases. In this scenario, it is important to understand the potential of an adult's brain to adapt to changes in visual experience and to understand how this potential decreases with growing age, typically at old age when the person is more prone to develop visual impairments (Huttenlocher (2009),Pascual-Leone et al. (2011)).

Visual experience of a person can be altered in several ways. The most common way is through perceptual learning or training techniques in which participants are repeatedly shown similar stimuli. It may take several days to several weeks of extensive training to teach a sighted person a new skill. For example, position judgment (Li et al. (2004)), face

identification (Sun et al. (2014)), orientation discrimination (Chen and Fang (2011)), texture identification (Okura et al. (2019)) and letter recognition (Schwab and Nusbaum (2013)). Another way that can limit the visual experience is by limiting synaptic normal visual experience of a person. After limiting the orientation-specific visual inputs of subjects for four hours, an increase in sensitivity towards limited orientation was observed in comparison with orthogonal orientation used as a control task (Zhang et al. (2010)). In another experiment, contrast sensitivity of subjects was reduced for four hour using specialized goggles (Kwon et al. (2009)). Subjects performed better in contrast discrimination tasks after the impaired contrast period. They also showed an increased V1 and V2 activity in fMRI BOLD signals. These results show an enhancement in response gain for visual cortex as a result of limitation in the normal visual environment. Findings from the study of Boroojerdi et al. (2000) are also consistent with the previous studies that limited visual functionality enhances the activity in visual cortex. They used TMS pulses to measure threshold amplitudes. TMS pulse were used to produce phosphenes that are the perception of flashing light when applied to visual cortex. Sensitivity towards phosphenes progressively increased during initial three hours of light deprivation which returned to baseline after three hours when light deprivation was eliminated (Boroojerdi et al. (2000)). Multisensory changes at cortical levels are also seen for light impairment. In another experiment reported, subjects were blindfolded for five days. When tested for a tactile discrimination task after 5 days, sighted subjects showed an improved performance reporting enhanced fMRI BOLD signals in occipital cortex for tactile simulations. The elevated BOLD signals returned to baseline after 24 hours of deprivation (Merabet et al. (2008)). These findings provide a solid ground for the presence of plasticity in normally sighted adults brain. However, the evidences discussed above represent brain plasticity when a specific visual attribute is artificially deprived for a few hours or for a few days and the subjects regain normal sight after a certain recovery period. This artificial deprivation can not replace natural visual impairments that occur gradually and sustains life-long with a gradual increment. Therefore, below we discuss the plasticity due to diseases like age-related cataracts and age-related macular degeneration.

One of the leading cause for blindness in elder ages is the age-related cataracts. Luckily, there is an effective treatment for the effected eye by surgically replacing the effected intraocular lens by an artificial one. It is possible to regain the visual functions like acuity and contrast sensitivity after surgery, even if the surgical procedure is performed years after the cataract occurred (Williamson and Seewoodhary (2013)). Some interesting biases in perception are related with the cataract condition and their perception after the surgery. Due to cataracts, the interocular lens blurs (impaired sharp details) and filters out the light with

short wavelengths (blue light). After cataract removal surgery, patients generally report of dominant perception of warm colours in their environment, while coolers colours are changed after surgery. During such a study on cataract patients, they were asked to set-up the visual stimuli in such a way that they appear to be achromatic. The set-up results were biased towards the bluish shades with cataract, while they shifted towards yellowish shades after cataract removal, hence compensating for the new short wavelength light at the retina (Delahunt et al. (2004)). Similarly, in pre-surgical phase, patients are reported to complain blurry environment even at their best focus, which becomes sharp in post-surgery phase (Parkosadze et al. (2013)). Thanks to cataract removal surgery, the acuity regains with in days after surgery while colour and sharpness takes weeks to months to return to normal. The retrieval of perception, acuity and sharpness after surgery shows that visual pathways are plastic and are capable of adapting any changes to visual inputs caused either by a disease or by a therapy even at adult age.

Age-related macular degeneration is another leading cause of visual impairments and blindness worldwide. Unlike cataracts, there is no treatment available to stop the irreversible damage caused by the disease till date. It has been shown that reading abilities are badly effected as a result of central visual loss in macular degeneration, and certain perceptual trainings have proved to be effective in improving reading skills by learning to use healthy retinal regions. A paradigm called rapid serial visual presentation (RSVP) developed to increase the reading speed has shown an improvement of 53% after six weeks of training session on participants suffering from age-related macular degeneration and Stargardt's disease (Chung (2011)). Further evidence of perceptual learning in improving reading speed using the RSVP paradigm was found by showing an increased performance with reduced print size in MD subjects (Coates and Chung (2014)). It has also been shown that using oculomotor task can be effective to increase reading speed in comparison with RSVP (Seiple et al. (2011)). Similarly, AMD subjects performed better for reading speed, visual acuity and fixation stability following an eccentric training task (Rosengarth et al. (2013)). The fMRI study during this eccentric training task showed an improvement in BOLD signal in V1, V2 and V3 areas. However, this increased activity persisted only during the training and not after the training. Similar performance improvements in reading abilities were found in sighted adults compared to AMD patients while performing a similar task showing the similar ability for perceptual learning in adult age (Chung et al. (2004)). Indeed, these results of perceptual learning are encouraging for rehabilitation techniques showing that it is possible to make use of residual vision of macular degeneration individuals.

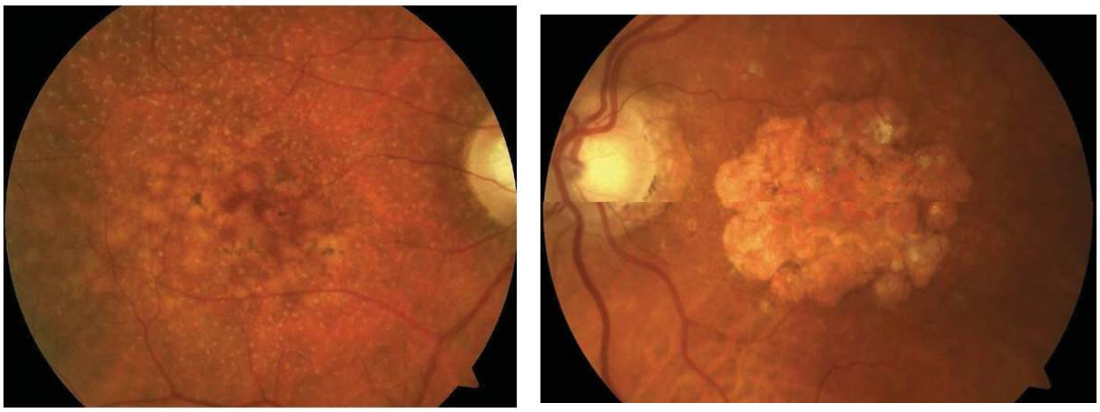

Figure 1.1 Examples of fundus images for different MD conditions. Left: Numerous Drusen (yellow-white spots) of different sizes, Right: Geographic atrophy

1.4 Macular Degeneration (MD)

Macular Degeneration (MD) is an irreversible, chronic and progressive disease and is among the leading causes for blindness worldwide. A study conducted in 2016 shows that around 6.2 million people were globally effected by the disease (Vos et al. (2016)). MD was ranked fourth among causes for blindness in a survey conducted in 2015; first three being Cataracts, preterm birth and Glaucoma (Vos et al. (2015)). Macular Degeneration can either be Age-related Macular Degeneration (AMD) cause with aging after around 60 years of age, or it can be hereditary or genetic called Juvenile Macular Degeneration (JMD). The number of population effected by AMD is expected to increase even more because of longer life expectancy.

Macular Degeneration, as the name suggests, is the permanent degeneration of Macula. Macula is the central part of retina at the back of the eye. Its function is providing inputs for sharp details and brightness of visual scenes in surrounding environment. A person effected by the disease, undergoes a constant, destructive and irreversible changes in their macula with growing age as a result of which visual acuity decreases. During the early stages of the disease, yellow-white spots called retinal or subretinal drusen or retinal pigments are formed on macula. Once started, chances are that this disease will lead to an end stage of

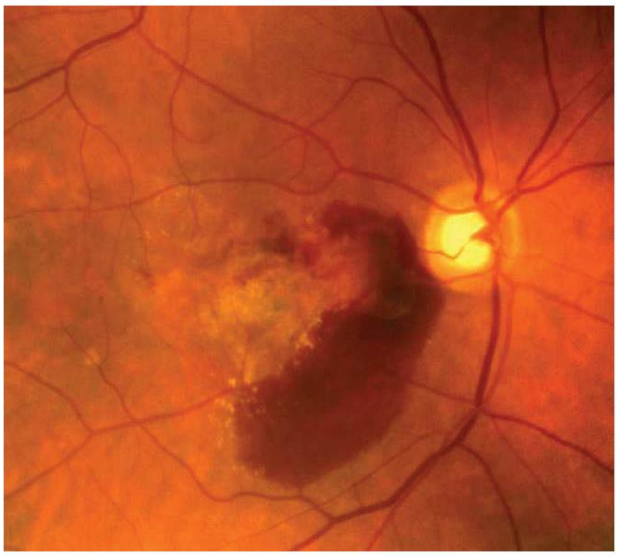

Figure 1.2 Fundus image for non-vascular AMD

retinal damage. End-stage AMD can be of two types; neovascular AMD (nvAMD) and geographic atrophy (GA) (Bressler et al. (1988)). Figures 1.1 and 1.2 shows examples for fundus images obtained through microperimetery for different MD conditions from Tromso Eye Study in Norway. As can be seen on left side of Figure 1.1, during the early stages of MD, yellow-white spots appear on the retina that can feel like *flashing* on the eyes or in the form of *salt and pepper noise*. The right side of Figure 1.1 shows an advanced stage MD in which a clear scotoma or blind spot appears on retina.

During the early stages of Macular Degeneration, a person may not experience any visual loss. With advancement of disease, at GA stage, visual inputs are lost at damaged retinal positions and blind spots or scotoma appears in visual fields. These scotoma appear due to permanent loss of retinal pigment epithelium and photoreceptors (Curcio et al. (1996)). A condition of MD called Wet Macular Degeneration occurs due to neovascularisation inside or beneath the retina, which causes leakage of fluids and.or blood in macula. If left untreated, there will be a rapid degradation of eye cause of retinal destruction and eventually lead to blindness.

1.4.1 Challenges for MD individuals

Patients suffering from advanced stages of MD have great challenges to face. Particularly they have reading impairments and problems with brightness. They lose vital information for seeing a scene like sharpness, brightness and fine details. They have problems in recognizing facial features, even from a small distance because of loss of central fixation point. This impairment of facial recognition significantly limits the social life of these individuals. Figure 1.3 shows a typical example of how a daily life scene may be perceived by a person suffering with Macular Degeneration. Since the macula is lost, the fixation stability of these individuals is severely impaired. Face recognition, driving, finding a dropped object on floor, differentiating similar toned colours and poor vision at night are just to name a few challenges which significantly effects the social life of these individuals. In case of peripheral visual loss, there are problems in walking, climbing stairs and can not see any obstacle on their way which is invisible due to peripheral scotoma (Stelmack (2001), Slakter and Stur (2005)). But the most difficult challenge from all of the ones mentioned, is knowing that this damage is irreversible and progressive and above all, to-date there is no treatment possible, so the small blind spot they see today could become a big scotoma tomorrow.

Figure 1.3 Examples of visual inputs as seen by a retina, Wet Macular Degeneration and Dry Macular Degeneration

1.4.2 Preferred Retinal Locus (PRL)

Our brain is capable of adapting to changes in environment, thanks to the plastic nature of our brain. As a result of MD, fovea (responsible for fixation stability and focus) is lost. Naturally, to fulfil this damage, an adaptive strategy is built by the brain by trying to see through the residual vision in periphery. Eccentric fixations in MD individuals has been described for more than fifty years (Von Noorden and Mackensen (1962)). MD patients learn to use eccentric retina at a discrete area called the *Preferred Retinal Locus (PRL)* (Crossland et al. (2005)). It can also be described as a distinct area of retina that contains the central target of an image for greater than 20% of fixation interval (Whittaker et al. (1988)). It is possible that a patient of MD use more than one PRL depending upon the task (Lei and Schuchard (1997), Fletcher and Schuchard (1997), Guez et al. (1993), Crossland et al. (2005)). The location of PRL is subject and task dependent and it is not possible to predict its position as it may also change from time to time (Erbezci and Ozturk (2018), Denniss et al. (2017)). Figure 1.4 is a nice example of demonstrating PRL taken from a study by MIT about the changes in brain as a result of PRL formation. In the figure, a blind zone is shown within 10 degrees of visual angle at the central visual field. Since the central visual field is damaged, the fovea is also damaged and hence the subject is unable to fixate using fovea. Thanks to the natural ability of developing a PRL, subject has developed a PRL in the healthy part of retina (outside 10 degrees and inside 20 degrees of visual angle).

1.5 Rehabilitation techniques for Macular Degeneration

MD is one of the leading causes of blindness, particularly in adult population due to Age-related macular degeneration or AMD, all over the world including developed countries (Wykoff (2019), Sabel et al. (2019)). Unfortunately, to-date there is no effective treatment for the disease. therefore, along with finding a solution to bring the damaged retina back in form, most of the focus of studies related to MD is on either minimizing the progressive damage through drugs, nutrition or exercises (Keenan et al. (2019), Chew et al. (2012), Martin et al. (2012)) or developing rehabilitation techniques to minimize the effects of impairment (Nguyen et al. (2009), Palmer et al. (2010), Park (1999), Daibert-Nido et al. (2019)). Since, the medication and surgery have not shown any worth mentioning improvements, therefore, the focus is always on low-vision rehabilitation options. Among the typical rehabilitation techniques used for MD are the assessment of residual functional retina and vision (Şahlı and İdil (2019), Morimoto et al. (2006), Hanout et al. (2015)), identifying preferred retinal locus

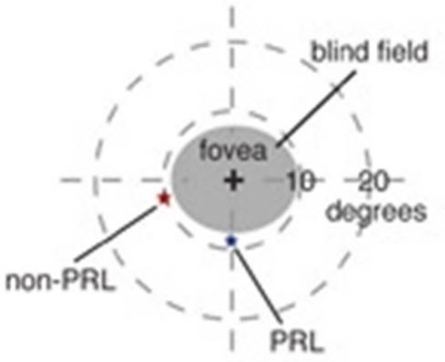

Figure 1.4 Presentation of PRL outside the blind zone

(PRL) and training for its active use as a pseudo fovea (Deruaz et al. (2002), Rohrschneider et al. (2008), Seiple et al. (2011)) and certain rehabilitation programs offered at specialized centers for specific skills like driving or education (Radvay et al. (2007), Hooper et al. (2008)). These examples are just a few from the massive research already in progress for this disease. These techniques have proven to bring a small change in life of these patients especially in terms of learning to use their residual vision that has improved their reading and orientation skills and learning to move their eyes to an extent where they can see the missing information due to scotoma. However, the focus of these rehabilitation techniques is mainly on visual modality only i.e. learning to use residual vision by means of visual aids and visual search techniques.

Around four decades ago, Paul Bach-y-Rita and his team published a short article that presented a natural, but yet, novel idea: people deprived of one sensory modality (vision, for example) can gain access to the missing sensory information, thanks to another intact sensory modality by transforming the missing information in the remaining one (Bach-y Rita et al. (1969)). Bach-y-Rita believed in the idea that *"We see with our brain, not with our eyes"*, and this was proved by him in his later works that if the missing information is provided by another modality, our multi-sensory brain capable of calibrating itself to translate the transformed information. In sighted persons the multi-sensory brain is hardwired to integrate the information coming from visual, auditory and spatial sensory modalities to build a nice

picture of environment around us. In several studies it has been shown that visual cortex of blind persons is recruited by auditory cortex to represent audio-spatial information received (Rauschecker (1995), Collignon et al. (2013), Voss et al. (2004)). As intuited by Bach-y-Rita and colleagues (Bach-y Rita et al. (1969)) the concept of seeing through brain has been taken ahead and now-a-days blind people can actually see through their brain by using certain assistive rehabilitation devices that make them able to perceive the space around them as better as a sighted person can do. For example, "ABBI", which is an Audio Bracelet for Blind Interaction. It can be wore on hand as bracelet and provides audio feedback enabling blind children to explore their body dimensions in space (Finocchietti et al. (2015)), "The vOICe", which converts visual information from images into audio information for blind people (Ward and Meijer (2010)), similarly Johnson and Higgins (2006) have presented a device for blind individuals that can convert visual information into tactile information (Johnson and Higgins (2006)) and "EyeMusic", which is another visual to auditory sensory substitution device for blinds (Abboud et al. (2014)) to name a few.

Combining the above two concepts i.e. rehabilitation for Macular Degeneration and development of multisensoy integration techniques for rehabilitation, we have taken an idea to do a multisensory rehabilitation for patients suffering from MD. To-date all the rehabilitation protocols available for MD focus on effective development of PRL using visual tasks and training protocols. Knowing that our brain is capable of doing multisensory integration and that even in sighted people there is some sort of multimodal integration and peripheral regions of visual cortex gets mild recruitment from auditory cortex, in this study we have presented a rehabilitation protocol that aims to develop an effective PRL by integrating sound and proprioception along with residual vision.

1.6 Objective of thesis

In light of the state-of-art described in first chapter of this dissertation, in the first part, technical details of devices used in the following parts is provided. We have presented two devices: (I): ARENA to understand the role of audio modality on space representation due to a central scotoma. ARENA is a 2-D matrix (5x5) of speakers covered with tactile sensors. The device is capable of producing sounds and recording response positions; thanks to the tactile sensors. As an application, we have elaborated an application of ARENA in details in Chapter 3 for MD individuals; (II): AVT device which is designed to improve the audio and visual localization bias in MD patients. AVT is composed of an LED and a buzzer

which provides visual and auditory feedbacks respectively. AVT can be an effective device to develop PRL (Preferred Retinal Locus) or pseudo fovea in the residual healthy part of retina.

In the second part, an audio-spatial behavioural task to understand how audio and spatial representations are effected as a result of scotoma is MD patients is presented. ARENA device is used to perform an audio localization experiment with MD individuals and sighted controls. The results of this study shows that audio and spatial perception is altered as a result of scotoma and sounds are biased towards the scotoma positions in audio-spatial maps of these individuals.

In the third part of this dissertation we have described a rehabilitation protocol called Intelligent Audio Visual Thumble Training (IVATT) that involves audio, visual and proprioceptive feedbacks from visual field in peripersonal space to help MD individuals develop an effective PRL, thanks to audio and proprioceptary feedbacks from the Audio Visual Thumble (AVT) device designed to provide multisensory feedback while exploring the space for rehabilitation of MD individuals.

Chapter 2

Seeing, Hearing and feeling scotoma through technology

2.1 We see with our brain, not with our eyes

Around four decades ago, Paul Bach-y-Rita and his team published a short article that presented a natural, but yet, novel idea: people deprived of one sensory modality (vision, for example) can gain access to the missing sensory information, thanks to another intact sensory modality by transforming the missing information in the remaining one (Bach-y Rita et al. (1969)). Bach-y-Rita believed in the idea that *"We see with our brain, not with our eyes"*, and this was proved by him in his later works that if the missing information is provided by another modality, our multi-sensory brain capable of calibrating itself to translate the transformed information. In sighted persons the multi-sensory brain is hardwired to integrate the information coming from visual, auditory and spatial sensory modalities to build a nice picture of environment around us. In several studies it has been shown that visual cortex of blind persons is recruited by auditory cortex to represent audio-spatial information received (Rauschecker (1995), Collignon et al. (2013), Voss et al. (2004)). As intuited by Bach-y-Rita and colleagues (Bach-y Rita et al. (1969)) the concept of seeing through brain has been taken ahead and now-a-days blind people can actually see through their brain by using certain assistive rehabilitation devices that make them able to perceive the space around them as better as a sighted person can do. For example to name a few of them, "ABBI", which is an Audio Bracelet for Blind Interaction. It can be wore on hand as bracelet and provides audio feedback enabling blind children to explore their body dimensions in space (Finocchietti et al. (2015)). Another one is "The vOICe", which converts visual information from images into audio information for blind people (Ward and Meijer (2010)). Similarly Johnson and Higgins

(2006) have presented a device for blind individuals that can convert visual information into tactile information (Johnson and Higgins (2006)) and "EyeMusic", which is another visual to auditory sensory substitution device for blinds (Abboud et al. (2014)).

Taking the idea further, we designed two new technologies for individuals with Macular Degeneration (MD). With this pathology they develop a central scotoma or blind spot on their retina. In this chapter, we present the two devices that are; 1). ARENA which is an audio-tactile matrix of speakers covered with tactile sensors, and is used to understand the audio-spatial representation in MD participants, and we found an audio localization bias in these participants using ARENA device (Ahmad et al. (2019)), and 2). AVT or Audio Visual Thumble device which is a small, low technology device used as a rehabilitative training to improve audio and visual localization bias.

2.2 ARENA - An audio-spatial matrix

ARENA is an audio-tactile device capable of providing audio-spatial feedbacks. The device consists of a 5x5 matrix (dimension 50x50x10 cm) of 25 blocks (each block dimension 10x10 cm). Each block consists of a speaker in center covered by 16 haptic pads. These blocks are interconnected in cascade through USB terminals. The blocks are compact placed in the form of a vertical 2-D board. ARENA is shown in Figure 2.1, where the left side shows image of device in form of 2-D vertical blocks and on the right are shown a subsection of four blocks. Each block in Figure 2.1 is highlighted by numbers $1, 2, 3$ and 4 for the ease of understanding.

2.2.1 Design

Each block of ARENA is connected in cascade fashion to another via two types of cables. One set of cables are cylindrical connectors that are responsible for power transfer from one block to the other as shown in Figure 2.2A and the other set of cables are micro-USB cables that are responsible for data transfer in cascade design of blocks (Figure 2.2B). Next section explains how data and power are supplied to the cascaded block network.

2.2.2 Building Blocks

ARENA device has a modular architecture and works as a composition of three main modules that are shown in the form of a block diagram in Figure 2.3. The three main modules are: PC, HOST and SLAVE module as discussed below.

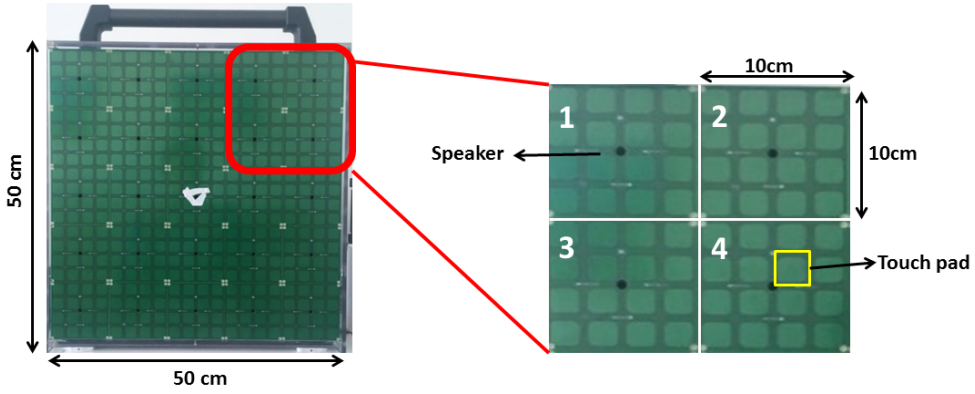

Figure 2.1 The ARENA. It is a 2-D matrix (5x5) of 25 blocks, each block consists of a speaker in center covered by 16 tactile sensors. On the left is represented the device in its entirety, while the right part of the figure represent a subsection of it, in which each block is highlighted by numbers 1, 2, 3 and 4 for the ease of understanding.

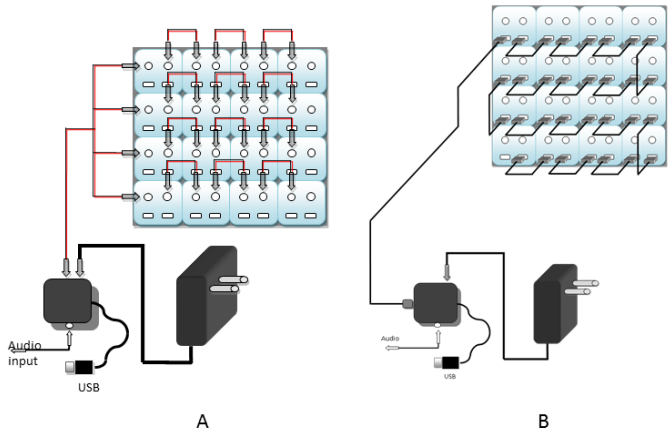

Figure 2.2 Cabling System. A. Power connections (micro-USB connectors). B. Data connections (cylindrical connectors)

PC (Windows / LINUX)

Commands from the PC are sent via serial port (RS232) to the HOST module. Commands to run the speakers are produced using MATLAB (Mathworks.Inc) software. Sound card of PC is used to send sounds to HOST module via AUX cable.

HOST

HOST is responsible for data exchange with PC via serial network (RS485) interface that guarantees a great reliability for the distance. All the modules are in parallel on the same line (multi-drop configuration). A wire from either of end terminals of compact blocks matrix is connected to one interface of HOST and the other interface to the PC. Hence, the commands are sent by the PC through a virtual serial port to the speakers through a RS485 interface. With Windows, it is possible to identify this serial port by opening the device manager, by looking at which port is activated when the USB is connected to the PC. The "HOST" card is connected to the 220Vac power supply, to the PC using the appropriate USB connector, and to an audio source (whether it is the same PC or not). The USB port also provides power to the module.

SLAVE

Each SLAVE unit consists of a NTS board and a CBM 8x8 which together makes a single haptic block. NTS or New Tactile Sensor board produces vibrations by Vibrating DC Coreless Motor. CBM board is 10x10 cm in size and it reads the sensitive capacitors matrix and makes them available to the NTS board. Each module has 16 capacitive tactile sensors. Auditory signals generated by PC are processed by a 3W class C amplifier. This is led by a digital potentiometer for volume modification. A DSPIC33FJ128MC802 microcontroller controls both the amplifier and potentiometer. All connected devices are connected via I/O ports and the CBM board by a 12C port. This system is provided with an external power source.

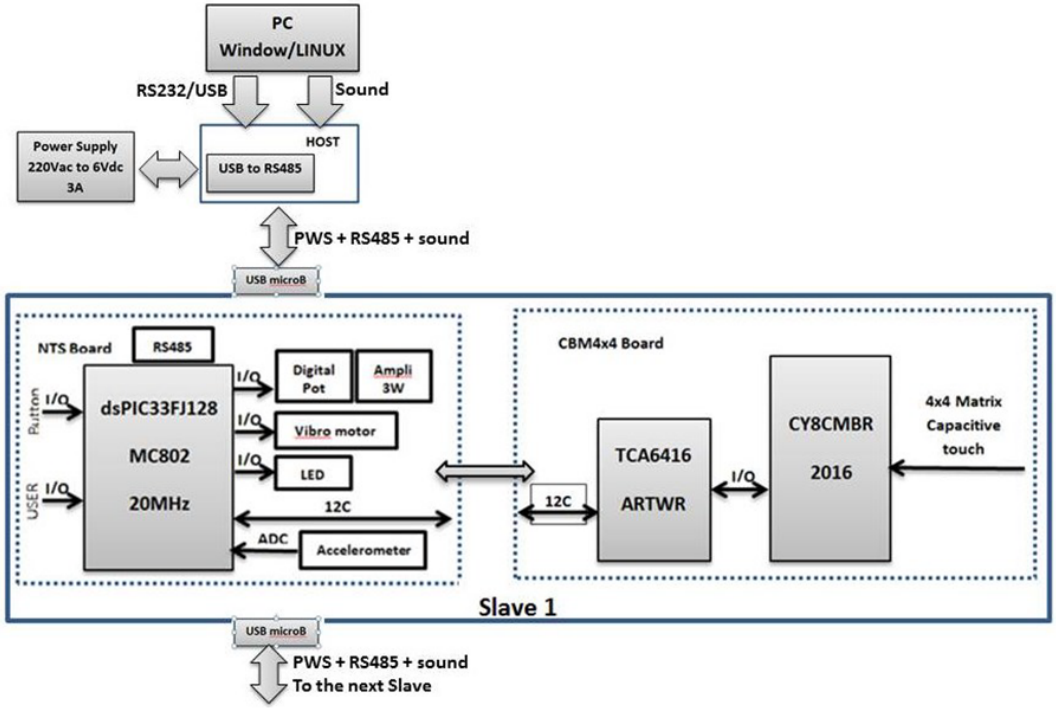

Figure 2.3 Schematic block diagram of ARENA. The three main building blocks are the HOST, SLAVE and a PC with Windows or LINUX.

2.2.3 Communication procedure

The high-speed communication protocol (250Kbaud) guarantees the execution of commands in a few tens of microseconds, must also allow the activation and deactivation of stimuli and the reading of haptic sensors independently and in any combination on the chain.

Therefore, the microcontroller must verify that the command is intended for its section, execute it and return an answer when requested. The NTs compute always the message after the end byte. If the same command has to be sent to all the boards connected to the BUS, it is sufficient to use the broadcast address. Otherwise, if you wish to control just some boards or if you want to send different commands to one or more boards, the commands have to be chained together one after the other. In this case, each command will have its own bytes of start, address and end but only the last command will have the end byte.

Hence, the communication procedure is based on the exchange of commands with a specific format:

- A starting byte.
- A byte that indicates the address of the board to which the message is intended.
- A byte indicating the command.
- An ending byte.

2.2.4 Applications

ARENA is a novel technological innovation that can constitute a starting point for new clinical procedures for blind and visually impaired adults and children. It allows understanding the spatial behaviour of these groups towards sounds. Its ability to record the responses (thanks to haptic blocks) makes it novel in the sense that unlike previous sound localization techniques, which rely on verbal response from the subject, it can actually record the positions of responses in the form of x, y coordinates. One major application of this device is discussed in Chapter 3 in detail where it is used to understand the audio-spatial localization for people with central scotoma. Another, significant application of this device is shown by Setti et al. (2018) where authors have studied spatial memory skills in blind individuals through the auditory modality. ARENA is used to produce different sounds from real world and subjects are asked to memorize the sequence of sounds produced and touch the device from where they perceived sounds were produced in the same order as auditory stimuli. There are many

other ways in which this device can be used to study audio-spatial and visual correlations in different groups of subjects.

2.2.5 Limitations

Being a preliminary device with the idea of studying effects of scotoma on auditory modality, ARENA comes with certain limitations. One of the limitations of the device is the serial reproduction of sounds: it is not possible to send multiple sounds at the same time. Other limitations are; the dimensions of this device covers only ±47.47 degrees of visual angle while sitting at a distance of 30 cm and that it is not a handy device to use with elderly population because the height of the device is not adjustable.

2.2.6 Future of ARENA

There is a big room for bringing improvements in the design, technology and applications of this device. For the design perspective, we are working to improve not only the size of ARENA (so it can cover larger visual angles) but also works are in progress to bring the depth dimension into the new design as well. For the technical perspective, works are in progress for developing new handy device on the similar concept of ARENA and also capable of processing multiple auditory stimuli at a time. From the applications perspective, visual feedbacks can also be added along with auditory and haptic modalities in order to better understand the multi-sensory integration phenomenon. Also, in a broader perspective, ARENA can be used to study sensory motor cognition, thanks to its audio spatial feedbacks.

2.3 AVT - An audio-visual ring with spatially and temporally congruent feedback

The Audio Visual Thumble (AVT), is a device that incorporates auditory and visual feedbacks, by means of a high integration buzzer and a high brightness red LED, respectively. The device was created to be worn on a phalanx, preferably the index, to allow people with visual dysfunctions to practice developing the ability to identify targets outside or at the edge of the visual field, associating the multisensory information coming from the device with the own movement. In other words, AVT is a multisensory rehabilitation device that allow integrating auditory, visual and proprioceptive (motion) information together. As a possible rehabilitative application of this device, we decided to use it in patients with with visual

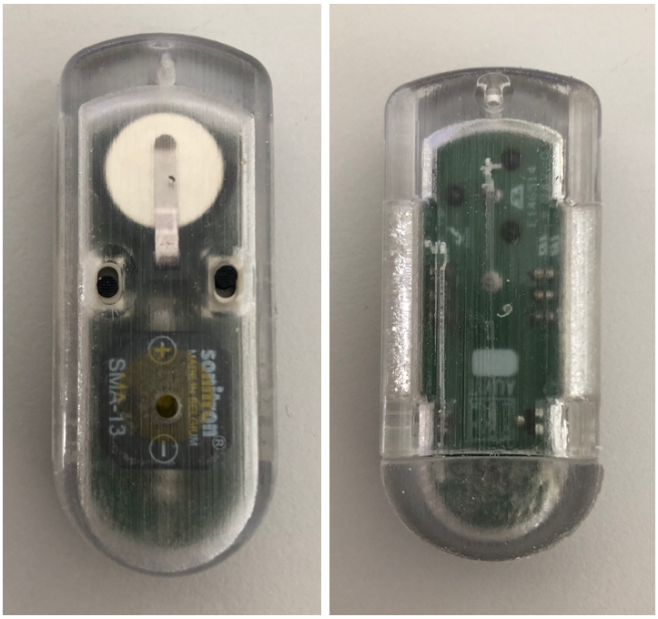

Figure 2.4 AVT device with housing for biocompatible material seen from above (left) and from below (right)

impairments, specifically with scotoma. In Chapter 4, I will describe how AVT has been used within a rehabilitation training, called Intelligent Visual Audio Thumble Training (IVATT). The device's front and back side with housing for biocompatible materials is shown in Figure 2.4. These multisensory modalities are aimed to make the patients suffering from Macular Degeneration (MD) aware of their own scotoma by exploring the space. As mentioned in Section 2.1, the idea of this device is to help develop a pseudo fovea by using audio and proprioceptry senses along with residual vision.

2.3.1 Design and working

AVT integrates two disposable 3V tablet batteries, a Buzzer (SMA-13 multi-application buzzer, sound pressure = 75 dB, operating voltage = 1.5 to 24 Vdc, operating current = 1.8 mA) integrated inside a driver to generate the square wave necessary for the production of a Tone and a red LED with high brightness (SMD chip LED lamp, 1.6 x 0.8 mm, 4W, Hyper red). The schematic diagram for AVT circuit is shown in Figure 2.5.

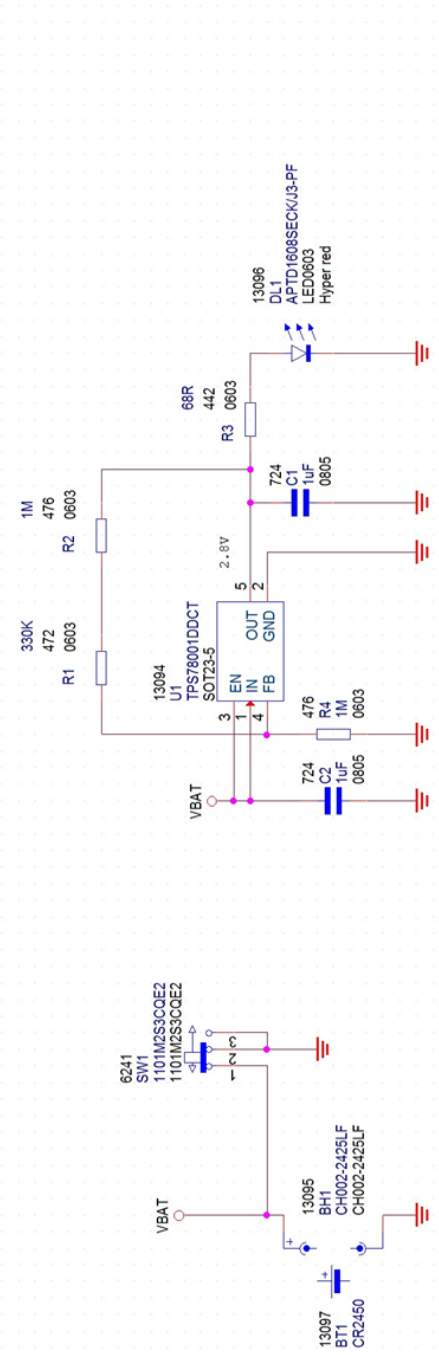

Figure 2.5 Schematic diagram for AVT device

Figure 2.4 shows a photograph of the device, both from the top and from the bottom. The system has two buttons, one to operate the LED and one to operate the buzzer both in continuous mode. The system can be installed on an index, middle or ring finger using a velcro strap that must be made pass through the tabs located at the bottom of the device. The system uses two CR1220 type batteries. Once activated, the device produces a sound tone and a red light near the end of the phalanx. The subject wearing AVT is seated in front of a 70cm x 70cm panel having black Archimedean spirals on a white background. The subject explores the panel with his finger while taking advantage of feedbacks from LED and buzzer with a sole purpose to increase visibility in the healthy parts of retina.

2.3.2 Device modes

Figure 2.6 shows a detail on the switches, in particular on the switch for the LED (L) and for the buzzer (B). At the bottom of Figure 2.6, the switch activation configuration is shown. When the switch is on facing downwards (towards the rounded edge towards the bottom of the LED) it is considered inactive (OFF). Vice versa when the switch is positioned upwards it is considered active (ON). AVT allows to select whether to activate only the LED or the LED and the buzzer together. To select the desired mode it is necessary to refer to the following table, which shows all 4 possible combinations of the switches, and the operating status of the device.

Once the rehabilitation activity has been carried out, the device is switched off by returning the two switches L and B to OFF position (both).

2.3.3 Battery replacement

AVT is equipped with a plastic case that can be opened in order to allow the exchange of the batteries. The batteries are considered exhausted when the LED light fades and the sound produced from the buzzer it decreased in intensity until the battery is completely exhausted. As shown in Figure 2.7, the battery can be easily replaced like a battery for a toy. On the back side of the device, the plastic housing can be slided to split the device into A and B (as shown in the figure). Once separated, the twin batteries can be replaced by new ones by sliding the old ones under the pin as shown in the Figure 2.7.

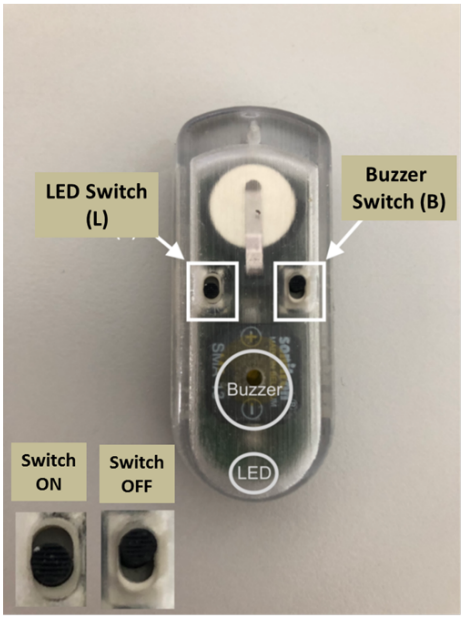

Figure 2.6 Indication of the switches, their status and positioning of the output devices, the LED and the buzzer

Table 2.1 AVT Device Modes

L	B	Device Mode
OFF	OFF	Device turned OFF Battery disconnected LED OFF, Buzzer OFF
ON	OFF	Device turned ON Battery connected LED ON, Buzzer OFF
OFF	ON	Device turned OFF Battery disconnected LED OFF, Buzzer OFF
ON	ON	Device turned ON Battery connected LED ON, Buzzer ON

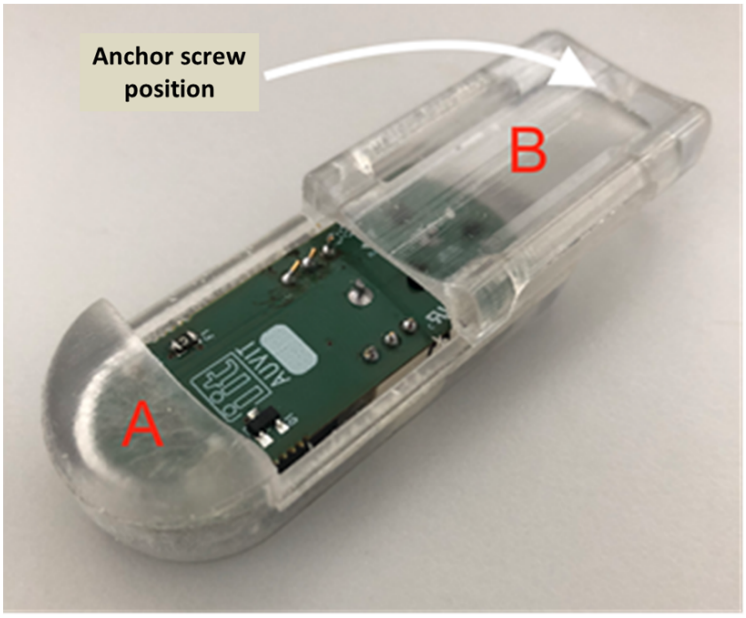

Figure 2.7 Opening the device case to allow battery change

2.3.4 Risks and Precautions

The AVT device has intrinsically low risk of harm to the user, because is made using watertight switches, is low voltage, has a case protection and consists solely of an LED, an oscillator circuit and a buzzer. Nevertheless, particular attention must be paid during use to avoid malfunction and avoid actions that may also cause a failure also serious damage to the user. An instruction manual is provided with the device and the experimenter has to take special care of risk and safety instructions. To avoid, categorically the use of AVT when:

1. The user's upper limbs are wet. The hands, upper limbs and face must be dry or at most moderately sweaty.
2. The user is in the water even with only his lower limbs immersed.
3. The ambient temperature of the place of use is above 40 ° C.
4. The ambient temperature of the place of use is below -10 ° C.

2.3.5 Applications and future of AVT

AVT is a preliminary device of its kind that is designed with an idea of providing rehabilitation training to individuals with visual impairments by integrating audio and spatial sensory

modalities. In Chapter 4, I will talk about a rehabilitation training using AVT for patients with scotoma. As the very first step, this idea can be led further to investigate the multisensory integration and rehabilitation for these patients.

There is a big room for improvements in AVT device. In terms of design, the device can be designed in a more user friendly manner and can be improved to meet the local ethical committee standards so that patients can use it at home as well. In terms of technology, though AVT is a very simple device, however it can be incorporated with a smart phone to make it more customized and user friendly. Nevertheless, AVT is a first step forward and we hope that it will open doors to new dimensions of rehabilitation for people suffering from Macular Degeneration.

2.4 Summary

Rehabilitation techniques for individuals with central scotoma, as a result of AMD, generally involves training to learn to develop a pseudo fovea in healthy part of their retina (Midena et al. (2018)). Hence, the focus of these techniques is visual modality only. We present a concept of multi-sensory integration techniques, which involves the audio modality to quantify the visual deficit (ARENA) and train it by using a multisensory training (AVT). The concept of multi-sensory integration and sensory substitution devices for blind individual's has been investigated in past, in fact there are many rehabilitative and assistive devices for blind adults (Setti et al. (2018), Nelson et al. (2018)) and children (Martolini et al. (2018), Cappagli et al. (2018)). On the other hand, this concept has never been used for the screening and rehabilitation of individuals with visual degeneration as MD. Here, we present two devices: (I): ARENA to understand the role of audio modality on space representation due to a central scotoma. ARENA is a 2-D matrix (5x5) of speakers covered with tactile sensors. The device is capable of producing sounds and recording response positions; thanks to the tactile sensors. As an application, we have elaborated an application of ARENA in details in Chapter 3 for MD individuals; (II): AVT device which is designed to improve the audio and visual localization bias in MD patients. AVT is composed of an LED and a buzzer which provides visual and auditory feedbacks respectively. AVT can be an effective device to develop PRL (Preferred Retinal Locus) or pseudo fovea in the residual healthy part of retina.

Chapter 3

Effect on audio-space representation due to Macular Degeneration

3.1 Audio-space representation and scotoma

The visual cortex of sighted individuals responds mainly to visual inputs. These individuals show a reset in visual cortex caused by an auditory phase shift. This kind of cross modal changes is extensively present in visual cortex (Mercier et al. (2013), Keil and Senkowski (2018)). Studies have shown that sighted people have multisensory interactions between sensory modalities in human primary cortices (Martuzzi et al. (2006), Romei et al. (2009)). On the other hand, for blind individuals the visual cortex processes audio and tactile signals as spatial information. This multisensory integration makes them able to navigate around and understand spatial environments, which is the basic phenomenon behind rehabilitative techniques for blind individuals (Budzynski et al. (2007), Collignon et al. (2009), Collignon et al. (2013)). This cortical reorganization in blindness is associated with the enhanced abilities of blind individuals in processing audio information such as sound localization in the azimuth location (Röder et al. (2007), Voss et al. (2004)). However, blind individuals are not always better in the audio processing than sighted individuals and in some cases they show strong impairments in audio space representation tasks such as in the spatial bisection task or in the dynamic sound localization (Gori et al. (2014), Finocchietti et al. (2015)). To date, it is not clear why some skills are enhanced and some other impaired. More in general, an open question is the start of cortical and perceptual reorganization after the beginning of the visual impairment.

These studies on blindness are limited to studying cortical representations after visual loss. We consider this as a *stable* system and it does not allow for study of the mechanisms

that subtend the progress of cross-sensory plastic changes. To fill this gap, we studied audio spatial reorganization in individuals with macular degeneration (MD). For these individuals the loss of vision due to scotoma or black spot is still an ongoing progressive process. MD is an irreversible retinal disorder that damages the retina and produces scotoma (blind spots) on the eye cutting inputs on corresponding visual cortical representations. Depending upon the pathology, scotoma can be central or peripheral, hereditary (also called juvenile macular degeneration JMD), or age-related (AMD). More in general, retinal damage increases with time and thus the scotoma size (Schuchard (2005), Hassan et al. (2002)). This condition makes MD an ideal condition to study the mechanisms that subtend audio spatial reorganization.

Our study involves 18 adults suffering from MD with central visual loss. They performed an audio-spatial task in which auditory stimuli were presented at different points of the audio-tactile device called ARENA (ARENA is discussed in detail in Chapter 2), considering central and peripheral regions (visual angles 23,73 and 47.47 degrees respectively) at a distance of 30 cm. We hypothesize that if the absence of vision has a direct and immediate effect on the cross-modal reorganization of spatial audio perception, there should be a distortion of audio processing within the scotoma zone in MD but not in sighted individuals. Results of our study support this hypothesis showing that loss of vision produces changes in the processing of spatial audio signals in MD patients. There is a strong bias in audio-spatial representation as lateral sounds are "attracted" towards the blind zones. This result suggests that audio space representation is a fast and plastic mechanism starting after visual loss.

3.2 Audio localization experiment

3.2.1 Participants

A total of 36 participants were tested divided in two groups: the experimental group composed by 18 participants with MD (*mean age*: 66.28, *standard deviation*: 21.74) and control group of 18 typical participants (*mean age*: 53.72, *standard deviation*: 19.55), *unpaired* $t-test$ ($t = 1.58$, $df = 33.55$, $p = 0.12$) performed the experiment (see details in Table 3.1).

All MD participants had a central vision loss due to scotoma caused by different diseases as reported in Table 3.1. Some of these participants were born with congenital retinal diseases (JMD, e.g., RP) leading to slow degeneration of the retina and development of central scotoma with growing age, while others were suffering from AMD; hence developing a scotoma in one or both eyes in later years of life. All these patients were recruited from

Istituto David Chiossone based in Genoa, Italy. Since all these participants were suffering from central vision loss (central scotoma). These participants were part of a rehabilitation program where they were learning to fixate with their preferred retinal locus (PRL) instead of damaged fovea using certain rehabilitation training techniques. All necessary participant's data (history, visual acuity, disease, dominant eye, PRL, fixation stability, and retinal maps) were obtained from the ophthalmologist and rehabilitators at "Istituto David Chiossone" as shown in Table 3.1.

The dominant eye of sighted participants was determined prior to the experiment using the classic dominant eye test (Heiting, 2017). This is a simple test with which a person can find his/her own dominant or preferred eye. It involves extending the arms to create a triangular opening between thumbs and forefingers. It is done by placing hand together at an angle of 45 degrees. Then, with both eyes open, the triangular opening is centered at a distant object (e.g. wall clock). In this position, each eye is closed (one at a time). Dominant eye would be the one with which the fixated object still stays in center of triangle made with hands.

Table 3.1 Characteristics of MD participants (visual acuity for P06, P16, P17, and P18 are not reported as the hospital was unable to provide a VA record for these participants), *eye , **years

ID	Age (Y**)	Disease	Duration of Disease (Y**)	Visual Acuity			Dominant Eye
				Left*	Right*	Both*	
P01	83	Glaucoma	15	1/20	1/20	1/20	Right
P02	87	AMD	03-04	1-2/10	Blind	1-2/10	Left
P03	86	Myopia + Maculopathy	02	Blind	1/15	1/15	Right
P04	85	Myopia	15	1/10	Blind	1/10	Left
P05	18	Maculopathy + RP	Congenital	1	1-2/10	1	Right
P06	62	AMD	15	-	-	-	Right
P07	77	Maculopathy + AMD	15	1/100	1/10	1/10	Right
P08	75	Maculopathy + AMD	10	1/20	1/10	1/10	Right
P09	82	Maculopathy + AMD	20	1/50	1/100	1/50	Left
P10	80	AMD	30	1/20	Blind	1/20	Left
P11	22	RP	Congenital	1/20	Blind	1/20	Right
P12	70	AMD	05	1/10	1/100	1/10	Left
P13	78	AMD	07-08	1/20	1/20	1/20	Right
P14	78	Myopia	20	1/20	Blind	1/20	Left
P15	73	AMD	10	1/50	Blind	1/50	Left
P16	42	Maculopathy	03	-	-	-	Left
P17	51	Glaucoma	26	-	-	-	Right
P18	44	JMD	08	-	-	-	Right

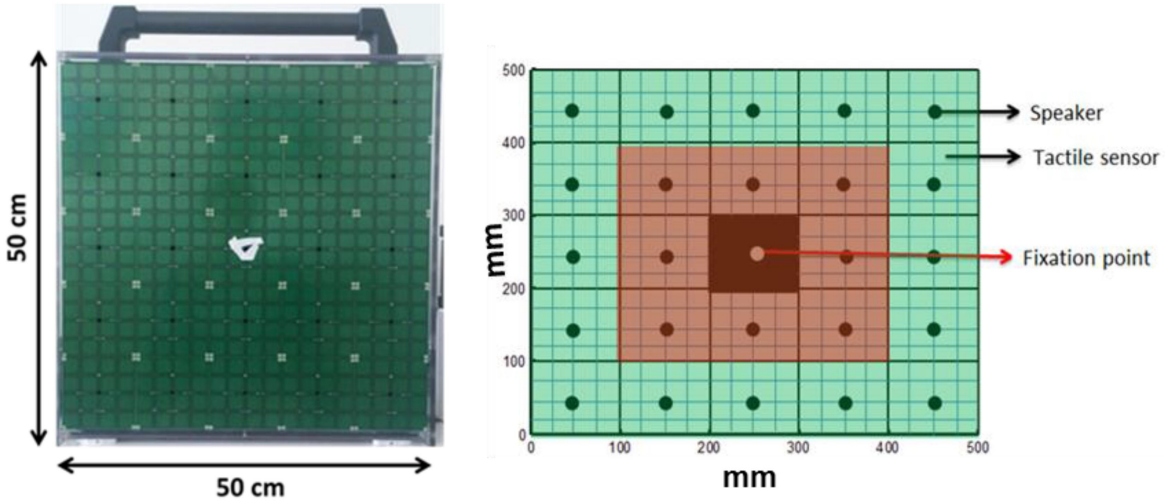

Figure 3.1 The device and simulation of device

3.2.2 Task

For the audio localization task we used ARENA device (as discussed in Chapter 2). In summary, ARENA is an audio-tactile device capable of providing spatial and auditory feedbacks. The device consists of a 5x5 matrix (dimension 50x50x10 cm) of 25 blocks (each block dimension 10x10 cm). Each block consists of a speaker in center covered by 16 haptic pads. These blocks are interconnected in cascade through USB terminals. The blocks are compact placed in the form of a vertical 2-D board. (Figure 3.1).

Before starting the experiment, fixation stability and a retinal map of each patient were obtained using the Nidek MP-1 Retinal Microperimetry (NIDEK TECHNOLOGIES SRI) with the help of a rehabilitator at Istituto David Chiossone. The retinal images provided by microperimetry covered a visual angle of ± 20 degrees (region where the central scotoma was present). Since all the MD participants had vision loss due to central scotoma, ARENA matrix was virtually divided into central and peripheral parts as shown in Figure 3.1 (right side). The red highlighted part mimics the center of the eye (covering a visual angle of ± 23.7 degrees) while the green highlighted part mimics the periphery (covering visual angle of ± 47.47 degrees) subtended from a distance of 30 cm. None of the subjects were aware of the virtual division of the matrix.

Participants sat straight at a distance of 30 cm from the ARENA with their eyes positioned in front of the fixation point in the center of matrix (see Figure 3.1). The height of ARENA was adjusted according to each participant so that fixation point remains at eye level. During the experiment, participants were instructed to always fixate (with dominant eye) at the marked fixation point in the center of the ARENA. To fix the fixation point, MD participants

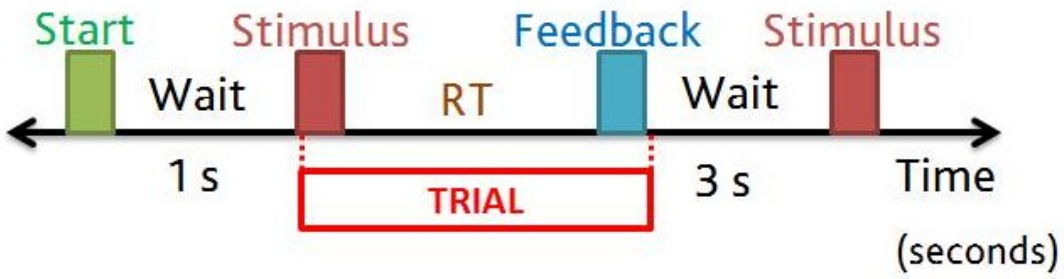

Figure 3.2 Experimental Design

were asked to use their PRL, while controls used their fovea. Participants listened to a white noise sound of the duration of 1 s. Participants were asked to touch, with the index finger of the dominant hand, the perceived position of the sound. Once pressed the tactile sensors, a feedback sound ("meow" of a cat) was reproduced from the central speaker to notify end the trial. Thus, the subject was allowed to bring his/her finger back to resting position. A pause of 3 s was inserted between trials (Figure 4.4). Each position (speaker) was repeated 3 times randomly, for a total of 72 trials (central speaker marked as fixation point only produced feedback sound). A training session was also run until subject understood the task before starting of actual experiment.

3.2.3 Participant's responses on ARENA

As mentioned earlier, ARENA was virtually divided into central and peripheral parts as shown on the right side of Figure 3.1. At a distance of 30 cm from the eye, central part (red) subtends an angle of ± 23.7 on the eye (which is the center of eye as recorded from retinal maps of microperimetry), and peripheral region (green) subtends an angle of ± 47.47 degrees (covering the periphery of the eye). To determine the scotoma position, the fixation stability of subjects and the exact visual angle subtended by the scotoma, we collected retinal maps Chen et al. (2009) for all the MD participants (see Figure 3.3 left for an example of retinal maps in two participants). Subject responses were recorded over the ARENA matrix and are shown as a function of visual angles in relation with the fixation point on the ARENA (Figure 3.3). As an example, in Figure 3.3 (central panel) are provided responses of the two

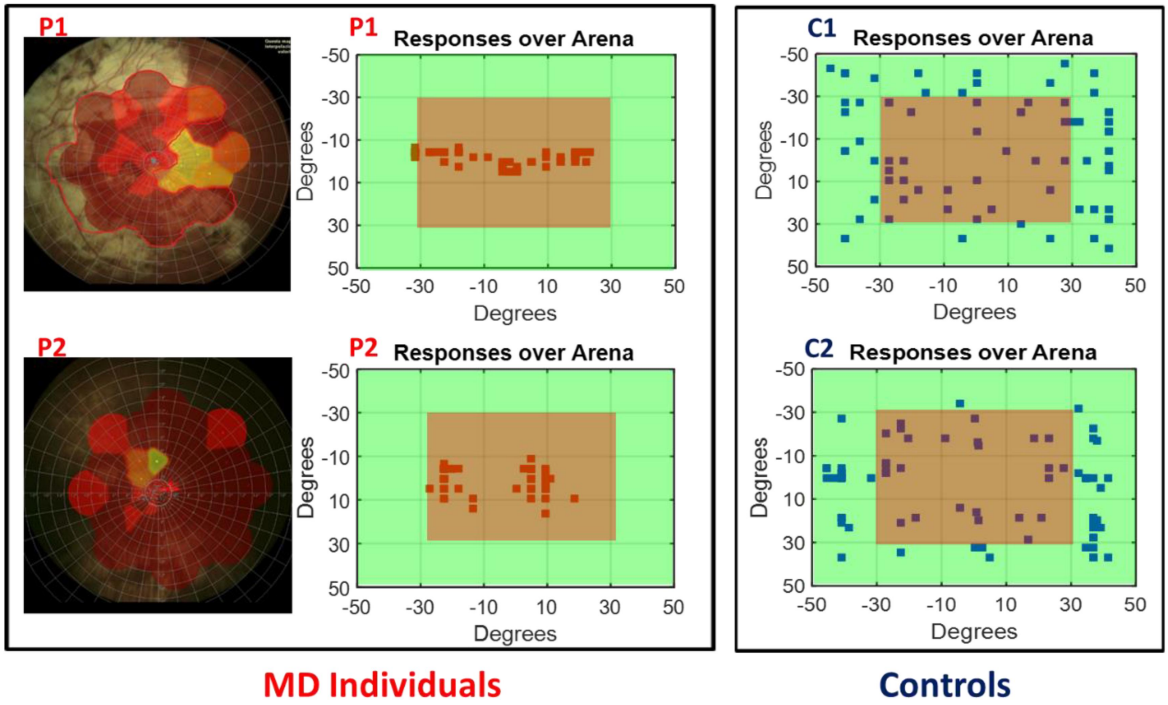

Figure 3.3 Responses of four participants recorded on ARENA. On the left the results of two participants of the MD group and on the right the results of two participants of the control group are shown

MD participants (whose retinal maps are presented on the left) and two sighted individuals. While for sighted individuals (Figure 3.3, blue dots) the responses for sound localization are equally distributed on the surface, the responses of the MD participants (Figure 3.3, red dots), were mainly localized on the central region, namely where the scotoma was present suggesting an attraction of sound toward the scotoma position.

3.3 Results

3.3.1 General Results

First, to check that responses of both groups are a result of stimulus and not just random responses over the device, we calculated distance errors. Distance error is the distance between stimulus position (speaker that produces sound) and response position (position where the participant touch to localize the sound). We found that for central stimuli i.e. when the speaker of central region produce sound (CS), the distance errors for MD and control groups are 9.86 and 9.74 cm, respectively, while for the peripheral stimuli i.e. when the

speaker of peripheral region produces sound (PS) the distance errors are 15.8 and 14 cm, respectively. As mentioned in section Audio localization experiment, and shown in Figure 3.1, the distance between two speakers on the ARENA is 10 cm. Hence, for both conditions (CS and PS) the distance error is within 15 cm showing that responses correspond to stimuli and are not random.

Next, we computed response behaviours for independent condition (MD v/s sighted) and dependent condition (CR v/s PR). To quantify the sensory precision and the bias in sound localization (i.e., the sound attraction toward the scotoma position), responses were subdivided as central responses (CR) and peripheral responses (PR), considering the central and peripheral portions of the ARENA (Figure 3.1), respectively. Then, we computed the hits and misses chart for responses in each region and lastly, we studied the correlations between responses, age and scotoma duration. These results are explained one by one below.

3.3.2 Responses in MD and Sighted groups

A significant difference between CR and PR was found in MD participants with a higher number of responses in the CR than in the PR. A mixed model *ANOVA* (2*x*2) was performed with the group as *between* factor (two levels, *sighted* and *MD*), and *position* as *within* factor (two levels, *CR* and *PR*). A significant interaction was found between *group* and *position* [$F(1,34) = 6.79$, $p = 0.02$]. Post hoc $t-tests$ revealed that MD individuals tend to touch the central speakers (CS) more compared to the sighted individuals (MD: $mean = 45.56$, $SEM = 3.18$, Controls: $mean = 34.72$, $SEM = 2.67$, un-paired $t-test$, $t = 2.58$, $df = 33.01$, $p = 0.014$), while sighted participants tend to touch the peripheral speakers more compared to the MD individuals (MD: $mean = 26.45$, $SEM = 3.18$, Controls: $mean = 37.56$, $SEM = 2.72$, un-paired $t-test$; $t = -2.65$, $df = 33.19$, $p = 0.012$). Also, MD individuals touched more the central rather than the peripheral speakers (CR: $mean = 45.56$, $SEM = 3.18$; PR: $mean = 26.45$, $SEM = 3.18$, paired $t-test$: $t = 3.01$, $df = 17$, $p = 0.008$). Sighted participants respond equally in the CR and PR (CR: $mean = 34.72$, $SEM = 2.67$; PR: $mean = 37.56$, $SEM = 2.72$, paired $t-test$: $t = -0.53$, $df = 17$, $p = 0.61$).

In order to get a detailed picture of how CR are comparable to PR, we implemented in R the methods developed by Rousselet et al. (2017). First, we extracted all the deciles and medians of distributions in each condition (CR and PR) and for each group (MD and controls) as shown in Figure 3.4 (A,B), respectively. The horizontal lines represent the nine deciles with a thicker line showing the median of each condition, the dots represent each participant.

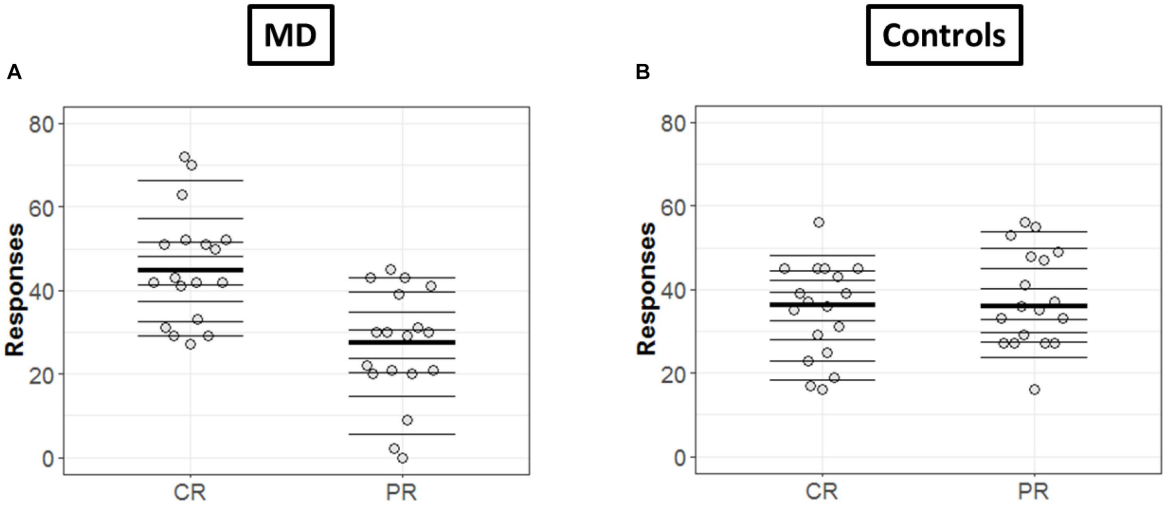

Figure 3.4 Differences in CR and PR for (A) MD and (B) control groups

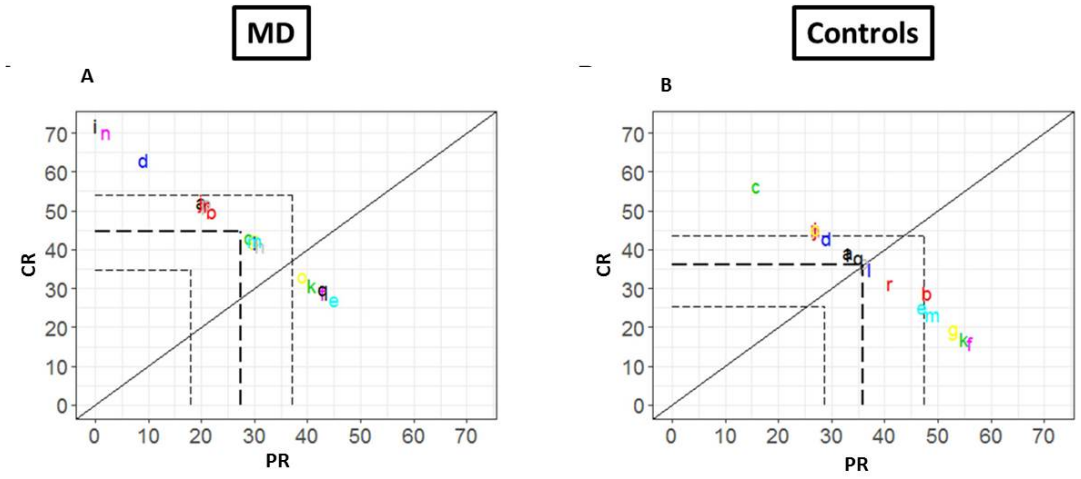

Figure 3.5 Scatter plot for differences in CR and PR (central line is a reference line CR = PR) for (A) MD have a greater percentage for CR than PR and (B) control group respond symmetrically around the reference line

Figure 3.5 (A,B) also show the link between two conditions in terms of decile differences, the thicker line represents the difference in medians for two conditions. The black diagonal shows line of no effect with slope one and intercept zero as reference line ($CR = PR$). Quartiles of two conditions are shown by the dashed lines. Here, it is important to mention that since the total number of trials is constant (i.e., 72), CR and PR are negatively related ($CR = 72 - PR$). This means that if a subject responds more in the center (CR), the value of PR automatically reduces and vice versa, hence a negative correlation between CR and PR. For the MD group, Figure 3.5A shows differences that are quite scattered from the center. Whereas for controls, Figure 3.5B shows that the differences are rather symmetrically grouped around the central line revealing that the probability of having subjects with positive or negative differences between conditions are similar.

3.3.3 Responses in Central and Peripheral positions

Figure 3.6 (A,B) show the two marginal distributions in the form of a strip chart for each condition (CR and PR), respectively. The spread of the dots for each group (MD and Control) is proportional to the local density of responses recorded for the said condition (CR or PR). The vertical lines show the deciles for each group with the thicker line showing the median of distributions. For instance, Figure 3.6A shows the distributions for two groups when the responses were recorded in the center (CR). For MD, the median of responses is 42.5 and for C median is equal to 36.5; hence the marginal difference is $+6$. As can be seen in Figure 3.6A, there is a shift between the distributions of the two groups: the deciles of MD are systematically greater compared to the Control group. The difference in deciles is positive and is represented by orange lines joining corresponding deciles for each group. Decile values for first and ninth decile are $+10.82$ and $+17.67$, respectively as shown in Figure 3.6A. Similarly, Figure 3.6B shows the marginal distributions in the similar fashion as that of Figure 3.6A but for the PR condition. It is evident from Figure 3.6B that the shift between distributions is opposite in PR condition compared to CR condition, as expected because $CR = 72 - PR$. MD group is shifted to lower values ($median = 29.5$ and controls have higher values $median = 35.5$). The difference in the medians is -6 and the corresponding deciles are joined by purple lines showing a negative shift. This means that MD participants show dominance in CR condition compared to Controls and vice versa for PR condition.

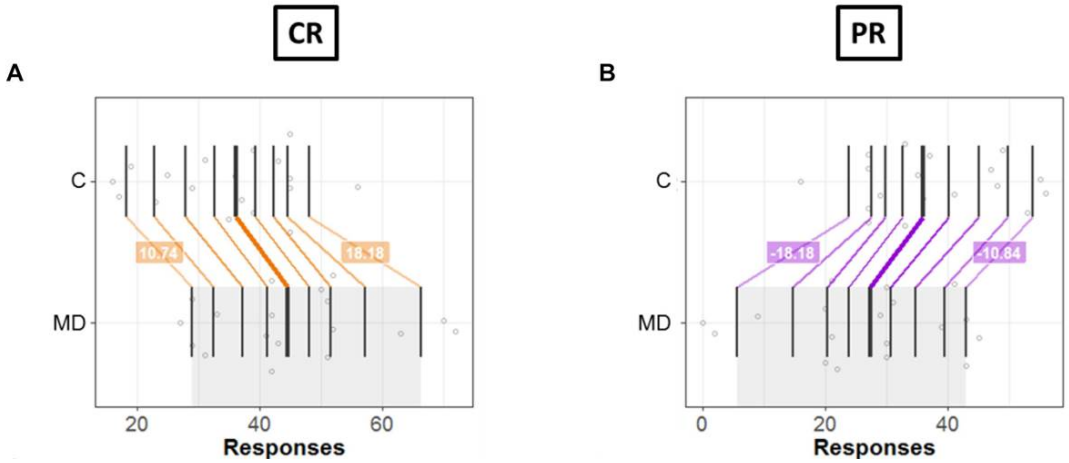

Figure 3.6 Differences between groups; MD and Controls for (A) CR and (B) PR

3.3.4 Hits and Misses chart

We also performed supplementary analysis as an evidence that subjects actually responded to the stimulus and did not make random responses on the device, a Hits and Misses matrix was computed for the two groups. Figure 3.7 shows the matrix computed to evaluate the percentage of responses. CS and PS represent the Central Stimulus and Peripheral Stimulus, respectively while CR and PR represent the CR and PR, respectively. The $2x2$ matrix show the responses against the stimuli in terms of percentage. Percentage for CS (first column) is computed as the total number of responses when the sound was produced from CS divided by the total number of trials in the center (9 speakers x 3 trials each = 24). Similarly, the percentage value for PS (second column) is computed as the total number of responses when sound was produced in the periphery divided by total number of trials in the periphery $(16x3 = 48)$. For instance, index (1,1) of the matrix shows the percentage of responses when both the stimulus and response were central, index (2,1) shows the percentage of responses when the stimulus was central but the response was peripheral, index (1,2) is the case when the stimulus was peripheral but the response was central and lastly, index (2,2) is the case when both stimulus and response were peripheral. Figure 3.7A represents that MD participants had a higher percentage to respond in center for central stimulus compared to Controls group (Figure 3.7B). The higher accuracy for the MD group can be explained as

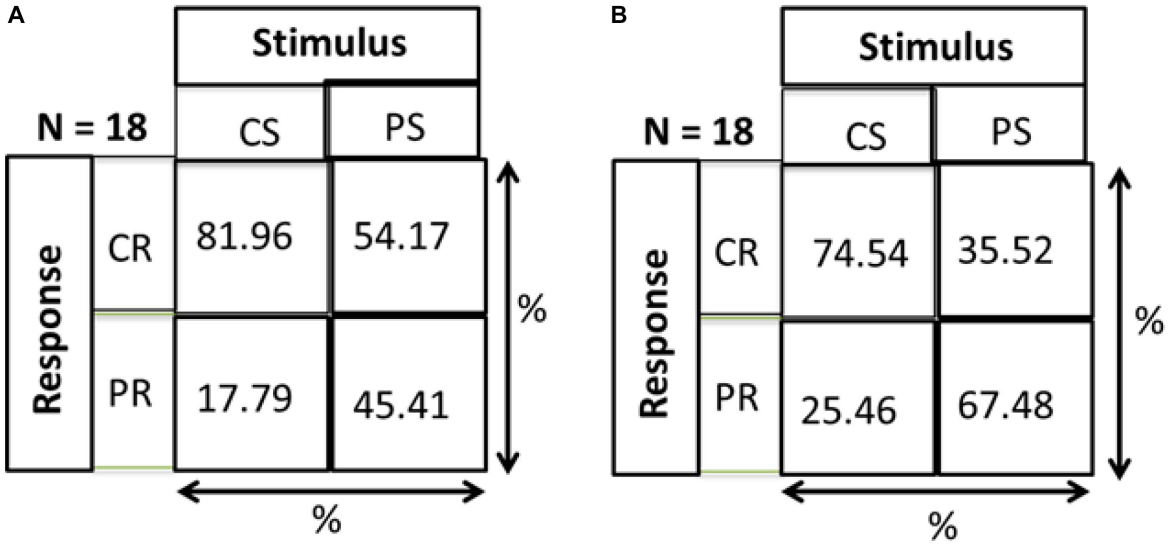

Figure 3.7 Hits and misses chart. (A) MD group. (B) Control group

since this group has a higher tendency to respond in the center, they have a higher probability to respond to central stimulus. This can also be explained in terms of peripheral stimuli. The percentage to respond correctly for peripheral stimuli is lower in MD compared to controls because MD group respond more frequently in the center. The same is true for incorrect responses as well. For the MD group, the percentage of correct responses in the center is almost double to the percentage of correct responses in periphery, which confirms the dominance to respond in the center. For controls group, the percentage of correct responses are almost equal, again as an evidence that they are not attracted toward any specific region, hence they are equally probable for correct and incorrect responses. A chi-square test of independence was performed using a 2x2 contingency table to examine the relationship between stimuli (CS, PS) and responses (CR, PR). For MD group, the relation between these variables was significant, X2 (1, N = 18) = 17.33, p = 0.0003. Responses in center are more likely than periphery to be able to for both central and peripheral stimuli.

3.3.5 Correlations

To fully take advantage of MD as a model for audio-spatial representation and to provide more information about the mechanisms of multisensory recalibration we have analyzed the correlation between scotoma duration and sound attraction. This correlation is analyzed by defining two parameters: Percentage of CR: which is calculated as $CR/72 * 100$ (where 72 is the total number of trials); and the onset of scotoma that indicates when the scotoma was diagnosed in the first instance (Table 3.1); it is equal to the difference between the age

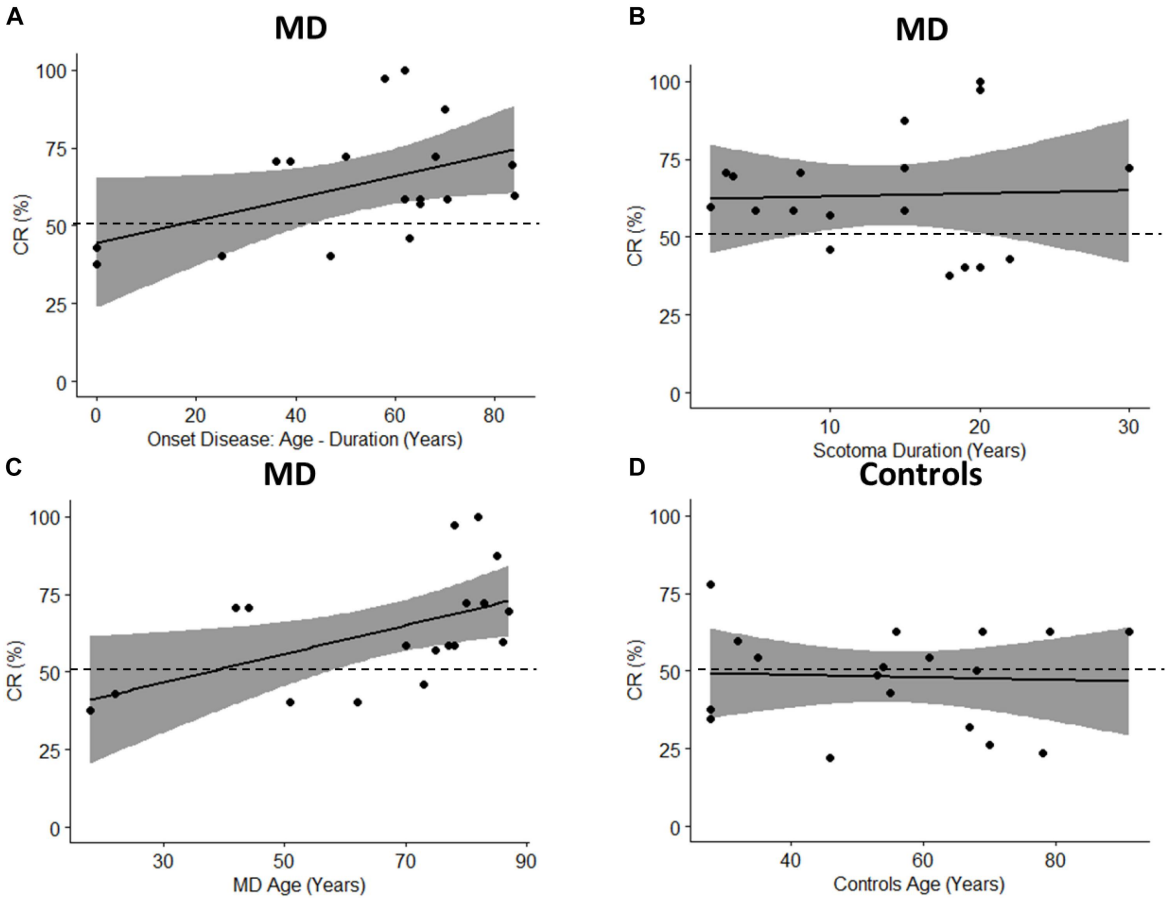

Figure 3.8 Pearson's Correlations. (A) Correlation between onset age and percentage of CR. (B) Correlation between scotoma duration and percentage of CR. (C) Correlation between age of MD group and percentage of CR. (D) Correlation between age of controls group and percentage of CR.

of patient and duration of the scotoma (for how long the subject has had the scotoma). A positive trend in correlation (Pearson's coefficient $r = 0.47$, $p = 0.051$) is found between the Percentage of CR and the onset age of the scotoma (Figure 3.8A). Results suggest that there is a trend in correlation between attraction toward the scotoma (CR) and clinical onset of the scotoma, suggesting that subjects diagnosed with scotoma at an elderly age are more biased, compared to ones diagnosed at younger age. Another correlation is computed between the Percentage of CR and duration of scotoma ($r = 0.04$, $p = 0.88$). As we have no significant correlation with the duration of disease, this shows that the effect remains consistent even when the duration increases (Figure 3.8B). On one hand, these correlations show that people show a greater bias when scotoma develops at older ages, on the other hand, it also shows that time spent with scotoma does not have an effect on central bias. An explanation for this could be that people diagnosed with scotoma at younger age have a better plasticity and so they can easily adjust with new pathology while older people with more visual experience without scotoma pay more attention towards the blind zone making them biased towards the scotoma position.

The same result is confirmed by another correlation in which we considered the Percentage of CR against the age of MD individuals (Figure 3.8C) and the Percentage of CR against the age of typical participants (Figure 3.8D). A significant correlation between age and CR is evident only for MD individuals (Pearson's coefficient ($r = 0.53$, $p = 0.02$) and not for typical (Pearson's coefficient ($r = 0.05$, $p = 0.94$). The presence of an effect for the correlation of Age and CR for MD group and not for Controls group shows that MD participants are attracted more to the scotoma position with increasing age and that the correlation is present only when there is a scotoma, without scotoma (controls) we found no correlation.

3.4 Conclusions

In this work, we studied audio-spatial representation for the first time in adults suffering from central scotoma due to Macular Degeneration (MD) disease. Our results show that sounds are attracted towards the blind zones. There is a strong bias in lateral sound positions and perceived as coming from the central scotoma region. The similar precisions in central and peripheral regions between MD and sighted participants (distance errors) suggest that the bias was not due to a less reliable spatial perception in MD individuals. On the contrary, there is no attraction towards a specific area of the device in controls group. Results also support the idea that spatial reorganization of audio processing is an ongoing process that occurs

after the loss of visual input in a plastic manner. The correlation that we observed between the attraction toward the center and onset of scotoma, indicates that the older the subject is at the onset of the scotoma, the more s/he is attracted toward the center. As expected, this result suggests that this multisensory re-calibration process reflects the brain plasticity that is maximal in younger individuals and reduced at older ages (Lund (1985), Kramer and Erickson (2007)). The correlation effect between age and percentage of responses in the center was found only in the MD group and not in the control group. This suggests that central blind region has a minimal effect on audio-spatial reorganization of younger MD individuals, thanks to their cortical plasticity, and this effect due to scotoma increases in elderly population as cortical plasticity reduces with age (Erickson et al. (2007), Kramer and Erickson (2007)).

We can speculate from our findings that the bias towards blind zones could be the result of ongoing audio cortical reorganization due to the lack of visual input. This cortical reorganization is a fast process that starts immediately when the visual input is loss such as in MD individuals. The recruitment of the visual cortex from the auditory modality could produce the misperception of sound localization that we observed because audio and visual spatial maps require some time to realign. On the other hand, it is not clear which is the short term benefit of this audio reorganization. Indeed on one side, the attraction of sound is not useful to enhance audio spatial precision as it happens in blind individuals. On the other side, it produces a strong misperception of sound, which is perceived as more central than the real position and this can be problematic for MD individuals.

Chapter 4

Intelligent Audio Visual Thumble Training (IVATT)

Several studies have shown how the absence of a sensory modality can induce perceptual deficits in tasks involving the remaining sensory modalities. For example, people with Macular Degeneration (MD) with central scotoma show biased auditory localization abilities toward the scotoma area of the visual field, indicating a spatial specific reorganization of cross modal processing. In the present study, we wanted to evaluate whether a multisensory training can modify this bias. We tested two groups of MD patients in an auditory and visual localization task. The training group was tested before and after a multisensory training (training group), called Intelligent Audio Visual Thumble Training (IVATT), while the control group performed the two task twice after ten minutes of break. IVATT is an audio-spatial motor training that can provide spatially and temporally congruent audio, visual and proprioceptive feedbacks with a goal to improve audio and visual localization skills in space for MD individuals. Our findings show an improvement in audio localization and visual precision for MD individuals in the training group and not for control group. The idea of integrating different sensory modalities can potentially ignite further research and applications for people with central scotoma for whom rehabilitation is classically focused on training visual modality only.

4.1 Macular Degeneration

Macular Degeneration (MD) is an irreversible, chronic and progressive disease significantly effecting patient's life quality, psychological well-being and the ability to perform ordinary daily life tasks like walking, reading, social interactions and so on (Lim, Mitchell, Seddon,

Holz, & Wong, 2012). It is among the leading causes for blindness worldwide. A study conducted in 2016 shows that around 6.2 million people were globally effected by the disease (Vos et al., 2017). MD was ranked fourth among causes for blindness in a survey conducted in 2015; first three being Cataracts, pre-term birth and Glaucoma (Vos et al., 2016). Macular Degeneration can either be Age-related Macular Degeneration (AMD) cause with aging after around 60 years of age, or it can be hereditary or genetic called Juvenile Macular Degeneration (JMD). The number of population effected by AMD is expected to increase even more because of longer life expectancy. During the early stages of Macular Degeneration, a person may not experience any visual loss. With advancement of disease, visual inputs are lost at damaged retinal positions and blind spots or scotoma appears in visual fields. These scotoma appear due to permanent loss of retinal pigment epithelium and photoreceptors (Curcio, Medeiros, & Millican, 1996). Unfortunately, to-date there is no effective clinical treatment available to stop this continuous damage except for some drugs that can slow down the retinal degeneration process (Senra et al., 2019).

4.2 Low vision and plasticity in adulthood

Our brain is capable of adapting to changes in environment, thanks to the plastic nature of our brain. The term “critical period” for vision refers to the developmental period of humans when the cortical organization for visual pathways develop depending on visual experience, either normal or impaired. After critical period, the cortical organization and neural pathways matures and become stable and becomes harder to adapt any changes in sensory inputs (Fagiolini & Hensch, 2000; Wandell & Winawer, 2015). This is the reason why adults who suffer from visual deprivation at a later stage in life (such as cataract or age-related macular degeneration) are expected to show less plasticity to ongoing changes in sensory inputs. However, evidence are still present showing plasticity to some extent in adults (sighted or low vision) even after critical period. Studies show that visual experience of a person can be altered at adult age through perceptual learning or training techniques over a certain period of time (few hours to weeks) by repeatedly showing similar stimuli. For example, position judgment (Li, Levi, & Klein, 2004), face identification (Trauzettel-Klosinski & Dietz, 2012), orientation discrimination (Chen & Fang, 2011), texture identification (Palmer, Logan, Nabili, & Dutton, 2010) and letter recognition (Seiple, Grant, & Szlyk, 2011). Similarly, for cataracts, it is possible to regain the visual functions like acuity and contrast sensitivity after surgery, even if the surgical procedure is performed years after the cataract occurred showing plastic behavior of learning (Fine, Smallman, Doyle, & MacLeod, 2002; Williamson &

Seewoodhary, 2013). Similarly, It has been shown that reading abilities are badly effected as a result of central visual loss in macular degeneration, and certain perceptual trainings have proved to be effective in improving reading skills by learning to use healthy retinal regions (Coco-Martín et al., 2013; Seiple, Szlyk, McMahon, Pulido, & Fishman, 2005; Tarita-Nistor, González, Markowitz, & Steinbach, 2009). The topic is of critical importance because it has direct implications of rehabilitation. For example, consider if there plasticity is totally absent in adult age, the person deprived of vision will not be able to adapt to changes in visual inputs and hence there will be no impact of any rehabilitation. In this case, the only possibility will be a cure that can restore vision to its normal state, which is practically impossible to-date especially for retinal diseases

As a result of MD, fovea (responsible for fixation stability and focus) is lost. Naturally, to fulfil this damage, an adaptive strategy is built by the brain, thanks to its plastic nature, by trying to see through the residual vision in periphery. Eccentric fixations in MD individuals has been described for more than fifty years (Hassan, Ross, Massof, & Stelmack, 2019). MD patients learn to use eccentric retina at a discrete area called the Preferred Retinal Locus (PRL) (Crossland, Culham, Kabanarou, & Rubin, 2005). It can also be described as a distinct area of retina that contains the central target of an image for greater than 20% of fixation interval (Whittaker, Budd, & Cummings, 1988). Indeed, perceptual learning by using PRL are encouraging for rehabilitation techniques showing that it is possible to make use of residual vision for macular degeneration individuals.

4.3 Multisensory reorganization for a sensory deficit

In addition to the problems with visual inputs, we showed in another study on MD, that they have problems also for audio-spatial processing (Ahmad, Setti, Campus, et al., 2019). The findings of this study show that MD individuals are biased (attracted) towards their blind zones, meaning that lateral sounds are attracted towards the scotoma positions. This study was conducted on 36 participants (18 with MD and 18 sighted) using a sound localization task. Sounds were produced using the ARENA device (Ahmad, Setti, Maviglia, et al., 2019). Results show that MD participants are biased towards the central part of ARENA (within $\pm$20 degrees) in localizing the sounds while sighted participants could fairly localize the sounds produced from the device. This interesting result led to a speculation that due to partial loss of vision in the central visual field, patients are more attentive towards the blind zones and leads to an increased attention for audio-space representation in this region. This

suggest that the visual impairment due to central visual loss can have a multisensory influence by effecting not only the visual perception but also the audio-space perception.

It is a well-known fact that the integration of different sensory modalities is an efficient and plastic process that helps optimizing human performance in different contexts. More in particular, in presence of an important deficit for one sensory modality, previous works have shown that other sensory modalities can, under specific conditions, reveal an impairment (e.g. auditory spatial perception for blind individuals) (Finocchietti, Cappagli, & Gori, 2015; Gori, Sandini, Martinoli, & Burr, 2014). On the other hand, there are also some studies showing that in the absence of vision, the visual cortex of blind individuals process tactile and auditory inputs (Collignon, Voss, Lassonde, & Lepore, 2009; Röder et al., 1999; Voss et al., 2004). The study from Alais and Burr (2004) is an example of the hierarchy of how audio and visual sensory inputs are ordered by our brain. They have provided an evidence that when visual and auditory information are presented at the same time, the visual modality dominates over audition in the spatial domain. However, in the absence of vision, the high weightage of visual inputs (which is impaired for blind individuals) is shifted towards the auditory cortex and the visual cortex is recruited by auditory to form a multisensory integration (Alais & Burr, 2004).

4.4 Rehabilitation for Macular Degeneration

Low-vision rehabilitation options have always been a focus for MD individuals since the medication and surgery have not shown any worth mentioning improvements. Among the typical rehabilitation techniques used for MD is the assessment of residual functional retina and vision, identifying preferred retinal locus (PRL) and training for its active use as a pseudo fovea (Deruaz, Whatham, Mermoud, & Safran, 2002; Radner et al., 2002; Seiple et al., 2011). Certain other rehabilitation programs offered at specialized centers are meant for specific skills like driving or education (Hooper, Jutai, Strong, & Russell-Minda, 2008; Radvay, Duhoux, Koenig-Supiot, & Vital-Durand, 2007). These examples are just a few from the massive research already in progress for this disease. These techniques have proven to bring a small change in life of these patients especially in terms of learning to use their residual vision that has improved their reading and orientation skills and learning to move their eyes to an extent where they can see the missing information due to scotoma. However, the focus of these rehabilitation techniques is mainly on visual modality only i.e. learning to use residual vision by means of visual aids and visual search techniques.

An appropriate training based on the active use of one (or more) different sensory modality can help reducing the original deficits. For example, it has been shown that audio-motor integration is associated with spatial representation development (Bremner, Mareschal, Lloyd-Fox, & Spence, 2008). Audio-motor training can also improve spatial processing. For example, "ABBI", which is an Audio Bracelet for Blind Interaction. It can be wore on hand as bracelet and provides audio feedback enabling blind children to explore their body dimensions in space (Cappagli et al., 2019). Similarly, it has been shown that in blind people, spatial and temporal coincidence of audio-visual stimuli can improve visual perception with enhanced orientation skills (Frassinetti, Bolognini, Bottari, Bonora, & Làdavas, 2005). Long lasting improvements in visual field deficits for low vision individuals were found by using audio and visual stimulation of the visual field (Bolognini, Frassinetti, Serino, & Làdavas, 2005).

Can an audio-motor training improve audio and visual spatial processing in MD patients? To test this hypothesis, we measured audio and visual spatial processing before and after an audio-visual-motor training called Intelligent Audio Visual Thumble Training (IVATT). IVATT technique is capable of providing audio, visual and proprioceptive feedbacks so that visual targets outside or at the edge of scotoma can be identified. Using the two secondary feedbacks (audio and proprioceptive) for finding visual stimulus, MD individuals are able to focus on scotoma region using their residual vision. IVATT makes use of a simple device called Audio Visual Thumble (AVT). Using IVATT protocol, we expect an improvement in audio and visual spatial representations for MD individuals.

4.5 IVATT equipments

IVATT is a simple, easy to adapt training technique which uses two very simple devices (low-technology and user-friendly); the Audio Visual Thumble (AVT) and Archimedean spiral board as discussed below.

4.5.1 Audio Visual Thumble (AVT)

Audio Visual Thumble or AVT device is already described in detail in Chapter 2 (Section 2.3). To summarize here, (AVT) is a device that incorporates auditory and visual feedbacks, by means of a high integration buzzer and a high brightness red LED, respectively. The device can be worn on index finger and provides multisensory feedback that allow integrating auditory, visual and proprioceptive (motion) information together. AVT can be operated in

Table 4.1 Switch Modes

L	B	Device Mode
OFF	OFF	Device turned OFF Battery disconnected LED OFF, Buzzer OFF
ON	OFF	Device turned ON Battery connected LED ON, Buzzer OFF
OFF	ON	Device turned OFF Battery disconnected LED OFF, Buzzer OFF
ON	ON	Device turned ON Battery connected LED ON, Buzzer ON

either uni-mode (visual only) or dual-mode (visual + auditory) with the help of two on/off switches called L (for LED) and B (for buzzer) respectively, as shown in Table 4.1. Two replaceable batteries are used to provide power to LED and buzzer. The PCB is enclosed in a biomaterial casing with a slot to pass a velcro-strip from the back side that can help wear device on index finger. Battery can be easily replaced (like battery of a toy) by sliding section of the casing from back side. Figure 2.4 A, B and C shows the front side, back side and components of the device respectively.

4.5.2 Archimedean Spiral board

The second equipment used for IVATT training is a simple 70x70 cm board. The board has a white background with black Archimedean spirals on it. The spiral starts at the central point of the board (x=35, y=35 cm) and ends at the edge making 14 spiral rings. Radius of smallest and biggest spirals are 2 cm and 28 cm respectively with increasing steps of 2 in between spirals. Hence the diameter of smallest and biggest circles are 4 cm and 56 cm respectively. At a distance of 30 cm between the central point on spiral board and the eye, each 1 cm corresponds to 1 degree of visual angle, therefore the spiral path at its maximum diameter covers $\pm$56 degrees of visual angle. The idea of presenting visual and auditory stimuli at peripheral vision has been reported in literature as well. For example, Martens and Van Winsum (2000) reports a peripheral detection training task in which stimuli were presented between $\pm$11 and $\pm$23 degrees of visual field while driving on a driving simulator.

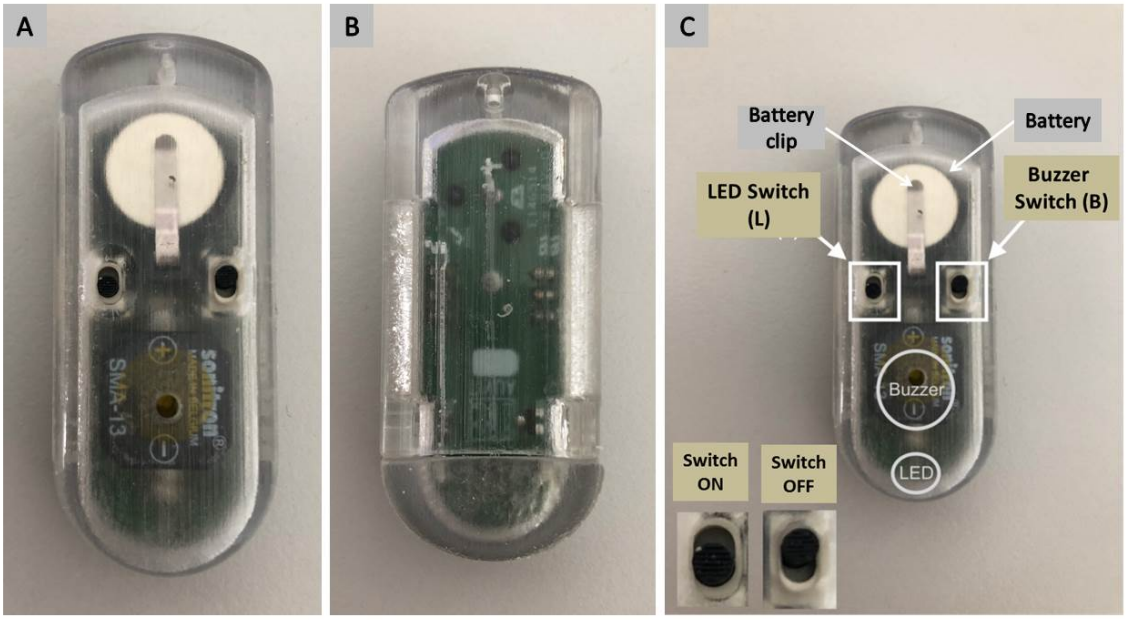

Figure 4.1 AVT Device. A. Front side, B. Back side, C. Device components

Similarly, Webster and Haslerud (1964) have presented multi-modal stimuli on a ± 60 degree arc perimeter with a radius of 76.2 cm.

The spiral pattern was first printed on the board and then was made protuberant with the help of black hot glue. This protuberant lining over Archimedean spiral makes it very easy to follow with finger thus providing proprioceptive feedback. The pattern of Archimedean spiral is shown in Figure 4.2. The central point of the spiral (marked red in figure) is called the fixation point. This fixation mark is covered by a simple circuit with a red LED, switch and battery. This PCB is pasted on the central red fixation point on the board. When the LED is turned ON via switch, it makes the fixation point prominent for users.

4.6 IVATT protocol

The IVATT protocol is performed in three short phases; Pre-training tests, Training and Post-training tests (Figure 4.3). I will explain first the pre and post training tests and then the training. Two tests; Audio localization test and Visual localization test are performed both before and after the training in order to see if there is any improvement in spatial representation of audio and visual modality due to training. The spatial representation in audio and visual modality is evaluated in order to see if the training can improve the audio-

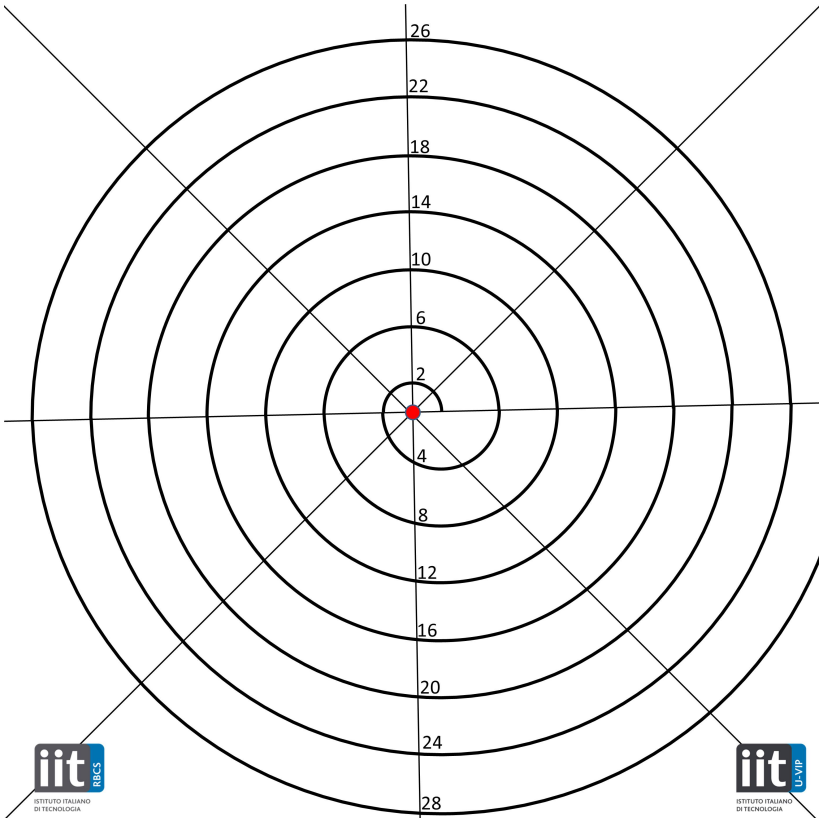

Figure 4.2 Archimedean Spiral Board

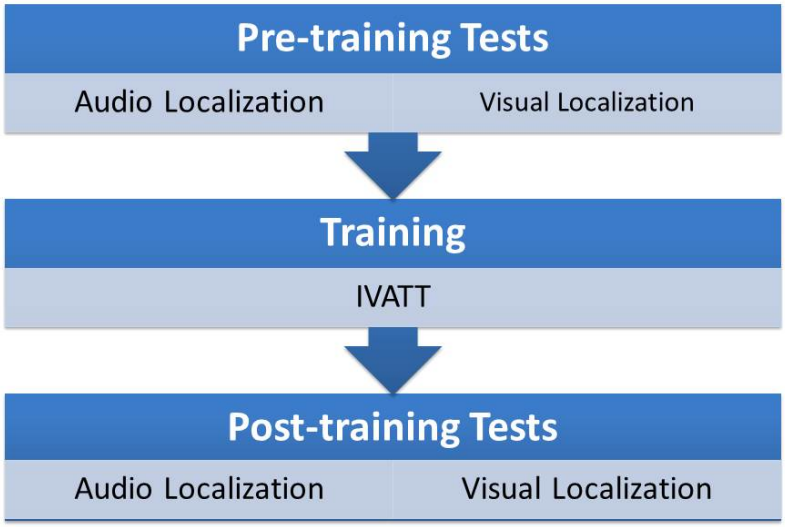

Figure 4.3 IVATT protocol

spatial bias towards scotoma positions (as shown by Ahmad et al. (2019)) and and if it can bring change in visual localization using residual vision.

4.6.1 Audio localization test

The first test that is used as evaluation criterion to see the effectiveness of IVATT is Audio localization test. The test performed is similar to the audio-spatial task explained in Chapter 3. We chose this test as a quantification measure based on our results in a previous study (Ahmad et al. (2019)). Based on the results of this work, we know that there is a bias towards blind zones while localizing sounds in MD patients. This bias leads towards mislocalization of sounds towards the damaged retinal regions. The same task is used again here to see if there is an improvement in bias after performing IVATT training. To recall the task in summary, subjects were asked to point out the position of sounds (white noise, duration 1 second) produced by one of the speakers of the ARENA (Chapter 2, section 2.2). Thanks to the tactile sensors covering the whole ARENA, the subject's response was automatically recorded, allowing to calculate the exact position indicated. Each position corresponding to a speaker has been repeated 3 times, except for the central speaker, for a total of 72 trials. A gap of 3 seconds was inserted between trials, with a trial ending immediately after subject

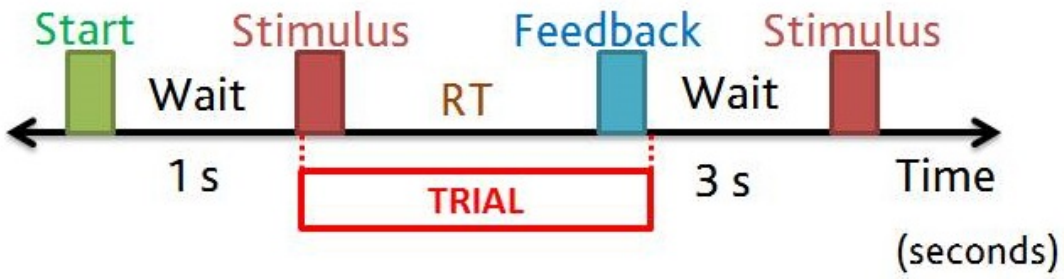

Figure 4.4 Experimental Design for Audio Localization Test

response is recorded by tactile sensors (Figure 4.4). A feedback sound is produced at the end of each trial (as soon as the subject responds on ARENA).

4.6.2 Visual localization test

The second test used as an evaluation criterion is Visual localization test. This test is designed on similar concepts as audio localization test. Therefore, it involves localizing white light flashes on a tactile monitor. For this purpose, a tactile screen of dimensions 48x28 cm (width x height) and resolution 1920x1080 pixels (21 pixels per degree) was used. Using the MATLAB Psychophysics toolbox, white flashes (luminance = 180 cd/m2, [R G B]=[1 1 1], size = 21 pixels) were displayed on black background. 25 flash positions were used on the screen to show the stimuli (one at a time). 75 total trials were used, three random flashes at each position. At the start of each trial, a fixation point (circular grid) was shown in the center of screen for a random time between 2 to 3 seconds. After the fixation point disappeared, a flash was shown at any random position out of 25 positions for a duration of 1 second. Subjects were able to localize the position of this flash only once the flash was gone and a clear black screen was shown where subjects had to touch where they perceived flash was blinked earlier. Also, in this case the response of the participant was recorded by recording the touch of the screen thanks to MATLAB psych toolbox Subjects had a time window of 5 seconds to respond. If the response was recorded within this time window, a "tick" sign was shown as a feedback of response and the trial ends, with a beginning of next trial displaying the fixation window again. Figure 4.5 shows the experimental design of this

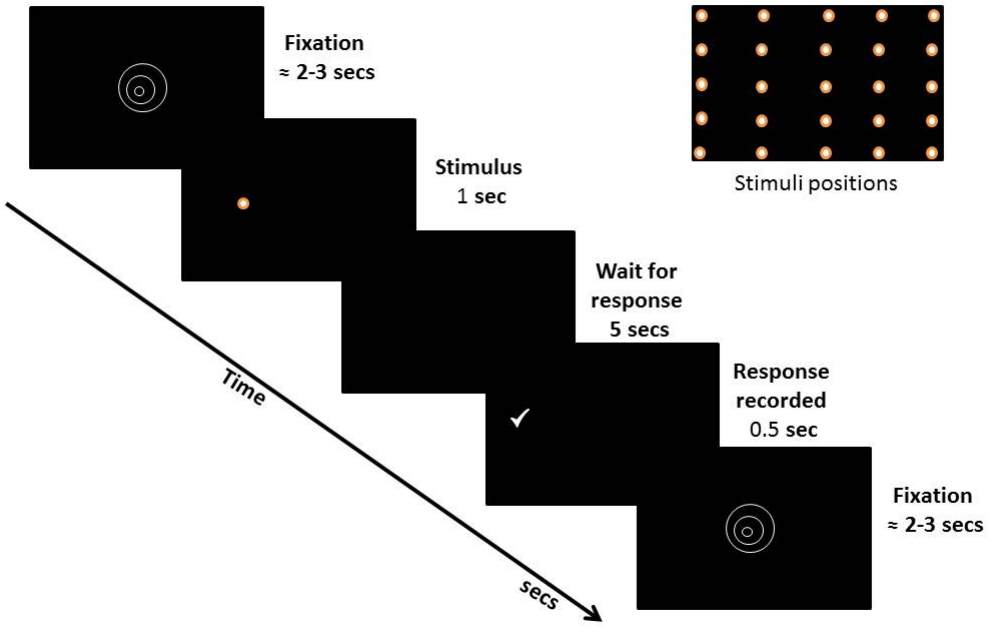

Figure 4.5 Experimental Design for Visual Localization Test

task. If the subjects could not respond with in time window of 5 seconds, next trial started automatically.. In case subjects were unable to see the flash, experimenter manually pressed right mouse button. During the experiment, subjects were seated straight at a distance of approximately 30 cm from the screen. This task was performed in a dark room.

4.6.3 Training

During the training phase of IVATT, subjects were seated straight at arm distance from the Archimedean spiral board. The fixation LED at the center was turned ON. Subjects were asked to wear the AVT on index finger of their dominant hand with both switches (L and B) turned ON, hence providing both auditory and visual feedbacks. The training was performed in a dark room so both LED's were visible easily as shown in Figure 4.6. With this set-up, the subject was asked to fixate on central LED of Archimedean spiral board and put the finger with AVT on starting position of spiral. Thanks to the raised shape of the spiral, the subject was able to follow the spiral even in dark conditions. Each subject was asked to start following the spiral from inward to outward direction while fixating in the center of spiral board.

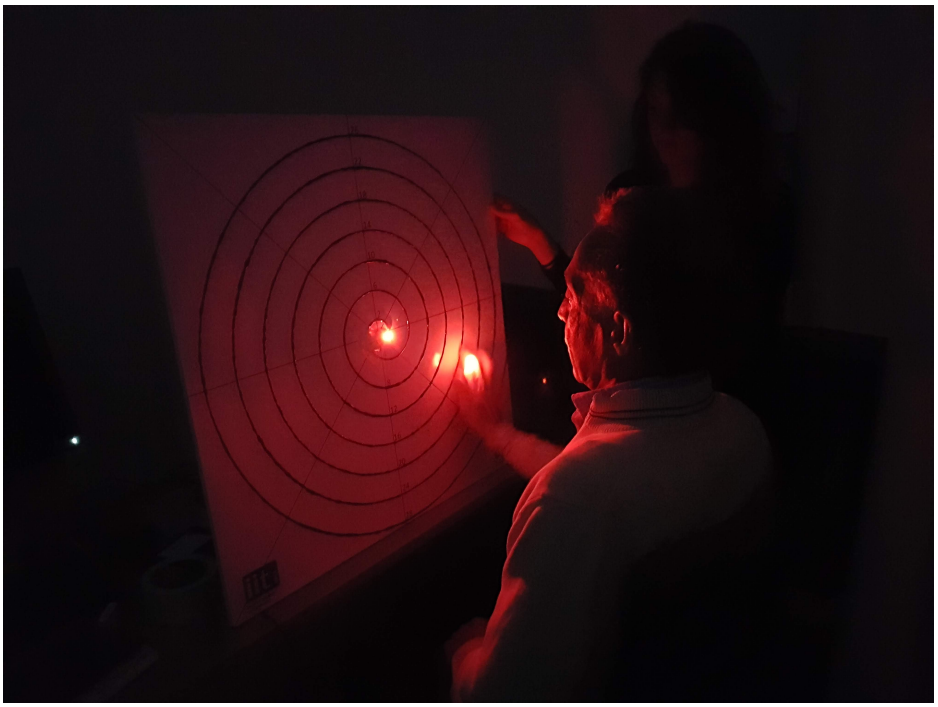

Figure 4.6 Subject performing IVATT

While following the spiral path, experimenter asked the subjects to keep following the LED of AVT on their finger using their residual vision and keep responding "yes, i can see the light on my finger". Since subjects were suffering from scotoma condition, they reached a point on spiral path where they were no longer able to see the LED of AVT along the spiral path. At this point, they responded to experimenter "no, I can not see the light here". Thanks to the multisensory feedbacks of IVATT, the subject was asked to switch the attention from the LED to the sound from buzzer, trying to localize it. Moreover, the sound localization was supported by proprioceptive feedback from their finger. With these feedbacks, the subject was asked to find the LED of peripheral visual field while fixating in the center, thanks to the high reliability of proprioceptive feedback.

Following these instructions, 6 clockwise and 6 anti-clockwise rotations over Arechimedean spiral board were performed by the subjects. Subjects were not given any time constraint, simply for the reason that they can take their time and not panic or fatigue themselves. Subjects were free to take pauses during training session.

Table 4.2 Training group data

ID	Age	Gender	Disease	Duration (years)	Visual Acuity	Dominant eye
T01	77	F	AMD	2	1/10	Left
T02	83	F	AMD	20	1/10	Left
T03	85	F	AMD	15	1/20	Right
T04	69	F	RD (diabetic)	2	1/10	Right
T05	71	F	AMD	10	1/10	Left
T06	79	M	AMD	2	2/10	Right
T07	58	M	Myopia + Glaucoma	15	1/10	Right
T08	81	M	AMD + Glaucoma	2	1/10	Right
T09	62	F	Optic neuritis	2	1/10	Left
T10	43	F	Cone rod dystrophy	congenital	1/20	Right
T11	32	M	Stargardt	2	1/10	Right

4.6.4 Participants

A total of 22 participants having central scotoma due to MD, were tested divided in two groups: the training group (those who performed training) composed by 11 participants (*mean age*: 67.27 years, *standard deviation*: 17.16 years) and control group (those who did not performed training) of 11 MD participants (*mean age*: 68 years, *standard deviation*: 19.93 years), *unpaired* $t-test$ ($t(df) = -0.092$, $p = 0.93$, $d = 0.04$) performed the experiment (see details for training group in Table 4.2 and for controls group in Table 4.3). Training group performed all three phases of IVATT protocol i.e. pre-tests, training and post-tests, while controls group only performed pre-tests and post-tests but did not performed the training. We used this set of control group who were MD patients as well, in order to see whether the results we get for training group are due to learning effect (since they are performing same tests with a short training in between) or the training is actually beneficial in improving their performance. Visual acuity of these participants was measured using the ETDRS acuity test (Rosser, Cousens, Murdoch, Fitzke, & Laidlaw, 2003).

All MD participants had vision loss due to scotoma caused by different diseases as reported in Table 4.2 and Table 4.3. Some of these participants were born with congenital retinal diseases (JMD, e.g., RP) leading to slow degeneration of the retina and development of scotoma with growing age, while others were suffering from AMD; hence developing a scotoma in one or both eyes in later years of life. Visual acuity of these participants was measured using the ETDRS acuity test (Rosser, Cousens, Murdoch, Fitzke, & Laidlaw, 2003). All these patients were recruited from Istituto David Chiossone based in Genoa, Italy. These participants were part of a rehabilitation program at this institute where they were learning

Table 4.3 Control group data

ID	Age	Gender	Disease	Visual Acuity	Dominant eye
C01	24	F	optic nerve atrophy	1/50	Right
C02	87	F	diabetic retinopathy	1/10	Left
C03	51	F	RP	1/10	Right
C04	85	F	AMD	1/20	Right
C05	81	F	AMD	1/10	Left
C06	80	M	AMD	2/20	Right
C07	78	M	AMD	1/20	Left
C08	73	M	AMD	1/20	Left
C09	47	F	RP	3/10	Right
C10	81	F	AMD	1/10	Left
C11	61	M	myopia + glaucoma	1/10	Right

to fixate with their preferred retinal locus (PRL) instead of damaged fovea using certain rehabilitation training techniques. All necessary participant's data (history, visual acuity, disease, dominant eye, PRL, fixation stability, and retinal maps) were obtained from the ophthalmologist and rehabilitators at "Istituto David Chiossone".

4.7 Results

4.7.1 Audio localization test

Response behaviours as recorded on ARENA device for audio localization test (pre and post) were compared for training groups and controls group. To quantify the sensory precision and the bias in sound localization (i.e., the sound attraction toward the scotoma position), responses were subdivided as central responses (CR) for central stimuli (CS) and peripheral responses (PR) for peripheral stimuli (PS), considering the central and peripheral portions of the ARENA as discussed in Chapter 3 (Figure 3.1), respectively. CR and PR are inversely proportional to each other, i.e. $CR = 72 - PR$, where 72 is the total number of trials. Out of total trials, CS are 33.33% while PS are 66.67%. Hence, there are more stimuli in periphery compared to center and therefore, greater number of responses are expected in periphery then in the center. Figure 4.7 show the difference between two positions (CR and PR) i.e. $CR = 72 - PR$ in terms of scatter plot and decile differences, the thicker line represents the difference in medians for two positions. The black diagonal shows line of no effect with slope one and intercept zero as reference line (CR = PR). Quartiles of two conditions are

shown by the dashed lines. Figure 4.7 (A,B) shows differences in positions for training group. Before performing IVATT training, responses of training group are quite scattered from reference line, whereas after training, differences are symmetrically grouped revealing that the probability of having subjects with positive or negative differences between conditions are similar. On the other hand, differences in CR and PR does not show an evident symmetrical grouping in pre and post tests or in other words the effect is not significant for controls group (Figure 4.7 (C,D)).

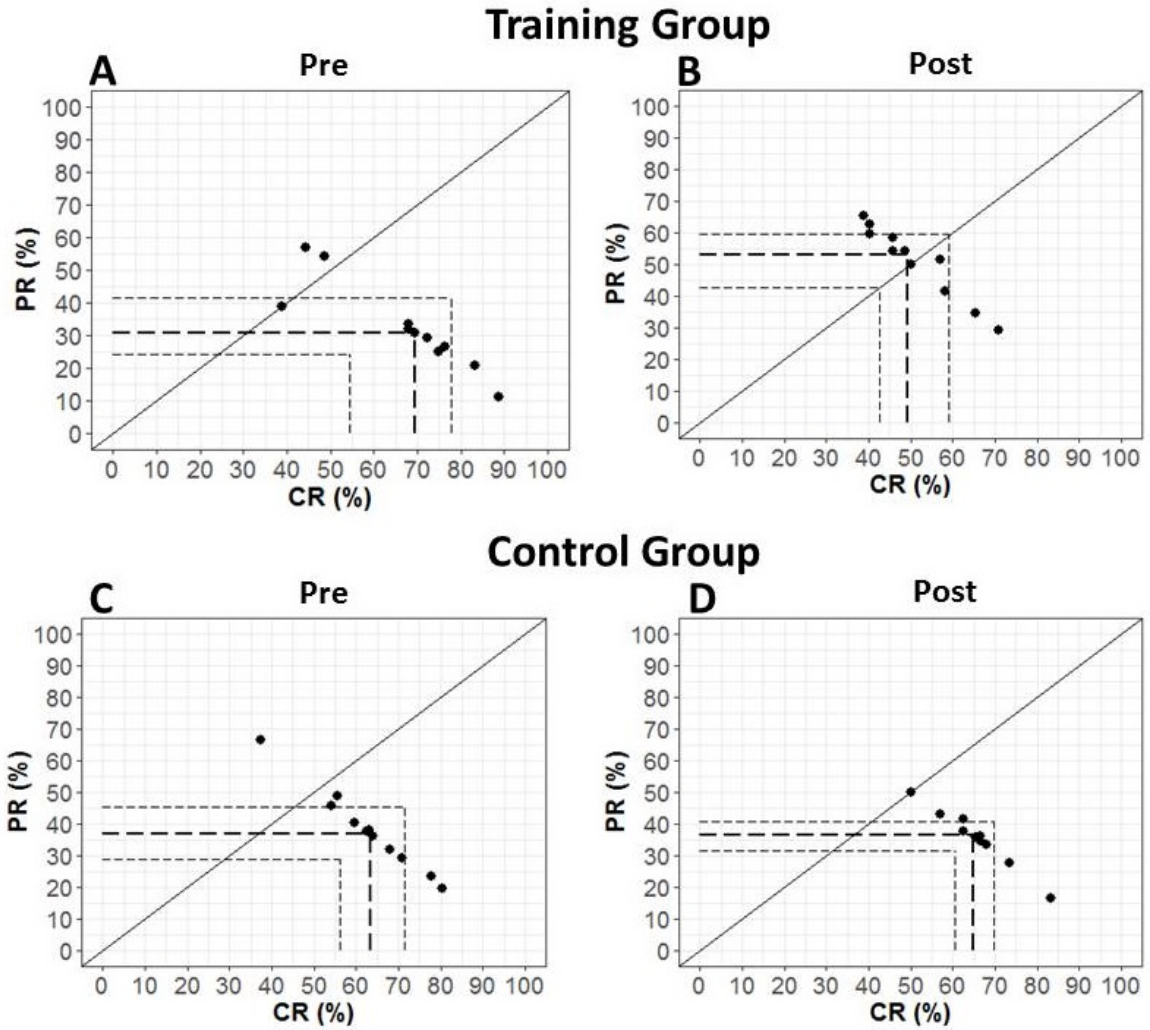

Figure 4.7 Differences in CR and PR for pre and post phases. A. Training group in Pre phase, B. Training group in post phase, C. Control group in pre phase, D. Control group in post phase

For training group, a significant difference between CR and PR was found in pre-training phase with a higher number of responses in the CR (66.67%) than in the PR (32.57%). In post-training phase, the percentage of responses reduced to 50.01% for CR and PR improved to 51.09% respectively. On the other hand, for control group, a significant difference between CR and PR was found in pre-training phase with a higher number of responses in the CR (63.06%) than in the PR (37.92%). In post-training phase, the significant difference was still present with percentage of responses for CR being 65.28% and PR 35.83% respectively. A mixed model *ANOVA* (2*x*2*x*2) was performed with the group as *between* factor (two levels, *Training* and *Controls*), and *position* (two levels, *CR* and *PR*). and *phase* (two levels, *Pre* and *Post*). as *within* factor. We found a main effect of *position (F(1,20) = 32.02, p = 0.0001, ges = 0.04)* and significant interaction between *position* and *phase (F(1,20) = 5.69, p = 0.027, ges = 0.009)* and *group, position* and *phase (F(1,20) = 9.45, p = 0.005, ges = 0.01)*. Post-hoc analysis revealed a significant difference between *phase* reproduced from *Training* and *Control* groups for both *position (CR: un-paired t-test, t = 2.70, df = 17.33, p = 0.01, and PR: un-paired t-test,t = -3.46, df = 19.51, p < 0.01)* only in the *Training* group. No significant difference was found for *position* or *phase* for *Control* group. These results show that IVATT training significantly decrease the bias of attraction towards the center in the group that performed the training while the bias still remains there for pre and post tests for controls group. Figure 4.8 shows these results as bar plots.

As another type of analysis, precisions were studied for both groups in pre and post phases. Precisions were calculated using the *distance error formula* i.e.

$$P.error(i) = \sqrt{(x_r(i) - x_s(i))^2 + (y_r(i) - y_s(i))^2}$$

where $(x_r(i), y_r(i))$ are the x and y co-ordinates of the response made as a result of stimulus produced at co-ordinate $(x_s(i), y_s(i))$ for an i^{th} trial. Distance between two consecutive speakers on ARENA is 10 cm (Chapter 2, Section 2.2). For the training group, we found an average distance error in pre phase for CR and PR as 10.8 cm and 15.6 cm respectively, while for post phase the average error for CR and PR was 11.1 cm and 16.1 cm respectively. For the control group, we found an average distance error in pre phase for CR and PR as 9.5 cm and 15.1 cm respectively, while for post phase the average error for CR and PR was 10 cm and 15.1 cm respectively. The precisions for both groups are similar in both phases and are less then 16 cm which means that both groups responded to the stimulus with similar precisions and that the responses were not made randomly on the ARENA.

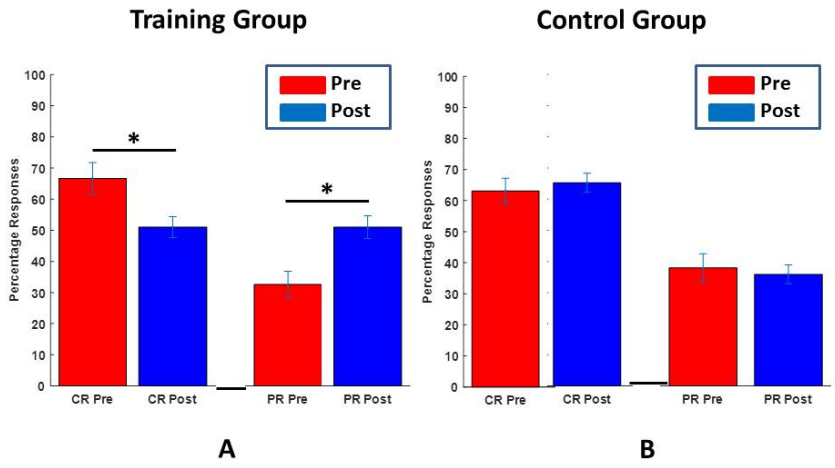

Figure 4.8 Percentage responses for Audio localization test in pre and post phases. A. Training group, B. Controls group

4.7.2 Visual localization test

Responses as recorded on tactile screen for visual localization test (pre and post) were compared for training groups and controls group. Analysis criterion for this test was kept similar to the audio localization test i.e. dividing the total area of the screen into central responses (CR) for central stimuli (CS) and peripheral responses (PR) for peripheral stimuli (PS) respectively. The resolution of the tactile screen used was 1920 x 1080 pixels with a size of 46 cm x 26 cm and pixels per inch ratio of 105 ppi (pixels per inch). Hence, CR and PR are the response positions (in cm) made as a result of CS and PS respectively (co-ordinates of CS and PS are fixed at 25 positions). Similar to audio localization test, 33.33% of total trials are in center and 66.67% are in periphery. However, since vision is much more precise sensory modality then auditory for spatial localization, analysis for visual localization test are not done by just considering the response positions. Instead, in this case percentage of hit (seen) trials in center and periphery are compared respectively. We found no significant change in the difference between percentage of hit trials in center and periphery in pre and post phase for both groups or in other words, the difference asymmetry function remains unchanged.

For training group, percentage of seen trials in center and periphery during pre phase was 96.3% and 90.7% respectively, while for post phase the central seen responses remained

similar i.e. 96.9% and for peripheral seen trials improved a little to 94.7%. A mixed model *ANOVA* (2*x*2*x*2) was performed with the group as *between* factor (two levels, *Training* and *Controls*), and *position* (two levels, *CR* and *PR*). and *phase* (two levels, *Pre* and *Post*). as *within* factor. We found a main effect of *position (F(1,20) = 7.15, p = 0.001, ges = 0.04)* and *phase (F(1,20) = 26.71, p = 0.004, ges = 0.05)*. A significant interaction was found between *group* and *phase (F(1,20) = 6.68, p = 0.01, ges = 0.01)*. Post-hoc analysis was performed by collapsing *position* into CR and PR and *phase* into *pre* and *post*. *T-tests* shows a trend between CR and PR *(t = 1.98, df = 78.53, p = 0.05)* while no significant interaction was found for other parameters. These results show that in terms of percentage hit trials, there is no significant improvement for training group, however, participants of both groups show a trend with better performance in center compared to peripheral position.

Precision was studied for visual localization tests as well, as discussed for audio localization test i.e. distance errors between stimulus and response positions in center and periphery by using distance formula. Distance errors were analysed by converting ppi (pixels per inch) of the screen to mm (millimeters). *3-way mixed model ANOVA (2x2x2)* was performed with the group as *between* factor (two levels, *Training* and *Controls*), and *position* (two levels, *CR* and *PR*). and *phase* (two levels, *Pre* and *Post*). as *within* factor. We found a main effect of *position (F(1,20) = 5.44, p = 0.03)* and a significant interaction between *group, position and phase (F(1,20) = 6.68, p < 0.02)*. Post-hoc *t-tests* were performed and a trend of improvement was observed only for PR position between pre and post phase for training group *(t = 2.07, df = 15.79, p = 0.05)*. No significant interactions were observed for other parameters (Figure 4.9). These results show that though not very significant, IVATT training can help in improving precisions for visual localization in peripheral visual field.

4.7.3 Overall performance of IVATT

Table 4.4 summarizes the performance for IVATT comparing the results for training and control groups. From the table, we can see that IVATT has an effective performance in improving audio localization bias and precision for visual localization test in peripheral region in the training group. However, the precision of training group in audio localization test remains unchanged after the training, although there is an improvement in localizing the stimuli. Similarly, for visual localization test, number of seen trials does not improve after training however, an improvement is seen in precision of localizing the stimulus position in peripheral region after the training. Controls group has no effects on performance for both audio and visual localization tests. These results are partially in line with our original

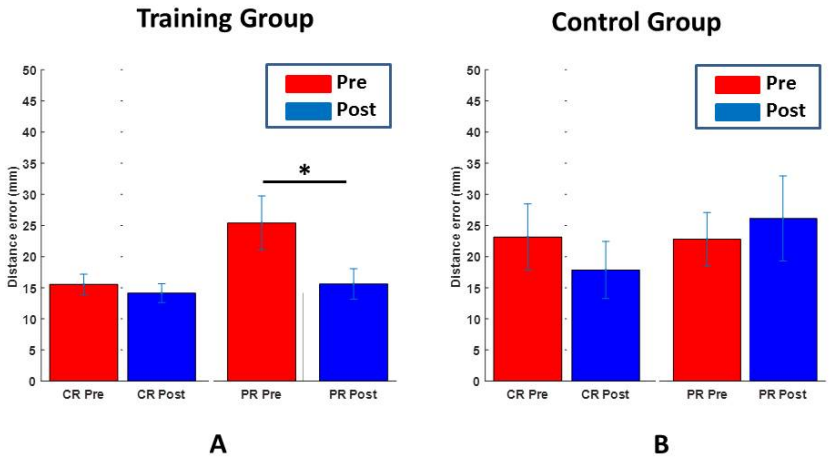

Figure 4.9 Distance errors for Visual localization test in pre and post phases. A. Training group, B. Controls group

hypothesis that an audio-motor visual training can improve the audio and visual spatial localization skills.

Table 4.4 Overall performance of IVATT

Group	Test	Parameter tested	Position	Performance Improvement
Training	Audio localization	1. Percentage responses	Center	YES
			Periphery	YES
		2. Precision	Center	NO
			Periphery	NO
Control	Audio localization	1. Percentage responses	Center	NO
			Periphery	NO
		2. Precision	Center	NO
			Periphery	NO
Training	Visual localization	1. Percentage Hit-trials	Center	NO
			Periphery	NO
		2. Precision	Center	NO
			Periphery	YES
Control	Visual localization	1. Percentage Hit-trials	Center	NO
			Periphery	NO
		2. Precision	Center	NO
			Periphery	NO

4.8 Conclusions

To test our hypothesis that if an audio-motor training can improve audio and visual spatial processing in MD patients, we measured audio and visual spatial processing before and after an audio-visual-motor training called Intelligent Audio Visual Thumble Training (IVATT). IVATT involves auditory and visual sensory modalities, and hence performance of the training was measured by analyzing the audio and visual localization before and after the training. Our results confirm our hypothesis showing a significant improvement in audio localization bias and partial improvement in visual localization.

An audio spatial localization bias was observed in our previous study on audio spatial representation in MD patients (Ahmad, Setti, Campus, et al., 2019) showing a bias in localizing the sound positions for patients with scotoma and we found that sounds are attracted towards the scotoma regions. Taking in to account this study, our new training group and control group (both suffering from MD) showed similar kind of behavior i.e. a bias towards the scotoma positions in localizing the auditory stimuli as evident from the baseline condition before training for each group. IVATT show a prominent improvement in localization for training groups and even after a short audio motor training session, participants are able to better localize the sounds. On the other hand, controls group are still biased towards the scotoma regions in post training phase.

A possible explanation of our audio spatial test results could be in terms of miss-localization due to attention. Since auditory inputs are absent at certain locations (Kong et al., 2014; Romei, Murray, Cappe, & Thut, 2009), it could be that the MD participant give more attention to scotoma regions, knowing that visual inputs are not reliable in this region. While performing IVATT, their attention is directed towards the audio stimulus and attention is directed back to true spatial locations. This has already been shown that audio-motor training can improve spatial processing in sighted (Aggius-Vella, Campus, Finocchietti, & Gori, 2017) and in blind individuals (Finocchietti, Cappagli, & Gori, 2017). This training, therefore trains the patient to keep their attention to sound positions with proprioceptive feedbacks. Our results also show that the precision in sound localization test (distance errors) remains same before and after the training. On one side, this suggests that IVATT training is not beneficial for improving spatial precisions for auditory stimuli, on the other side similar precisions show that the bias was not due to random responses on ARENA device. In fact, this shows that the responses we analyzed in this study, were actually made as a response to auditory stimuli.

Our results for visual localization test show that this training can improve the precisions of MD patients in peripheral region of visual field, however, precision in the central region remains unchanged. This improvement in spatial localization for visual modality through an audio-visual motor training can be explained in terms of behavioral and neurophysiological studies that show an improvement in visual perception when cross-modal audio and visual stimuli are congruent in space and time. For instance, Targher et al. (2012) conducted a study on low-vision adults for an audio visual integration task where subjects were asked to localize visual stimuli and ignore auditory stimulations. Their findings provides an evident proof for effect of synchronous and spatially congruent sounds for visual spatial orientation (Targher, Occelli, & Zampini, 2012). Similarly, an improvement in some visual functions for individuals with hemianopia was reported after performing an audio-visual training task (Hairston et al., 2003). This study also reports that central visual stimuli have a significantly greater biasing consequence on auditory target localization than did more peripheral visual stimuli which shows why people with central scotoma show a bias for audio spatial localization and an audio-motor training can influence the spatial localization in peripheral regions only.

In particular, evidences show that the spatial and temporal coincidence of audio and visual stimulus can help visual perception and enhance orientation in the blind zone of hemianopia patients (Frassinetti et al., 2005). Following the same concept, improvement in precisions for visual localization due to audio-motor training of IVATT can be explained as MD patients have a blind zone in center of visual field, while hemianopia patients have a blind zone to the left or right side of visual field. We analyzed the results in terms of percentage of seen trials in central and peripheral visual fields as well, but results show no effective improvement with training. This can be explained as the percentage of seen trials in both visual fields was already high (greater than 85%), hence our MD participants were already very good in seeing the visual stimulus since vision is a reliable modality and always gets a higher weightage over other sensory modalities (Alais & Burr, 2004).

Our results essentially nullifies the fact that improvement we observed for training group in both audio and visual spatial localization could simply be a result of repeated task in short period of time and involves memory factor. Because if later was the case, controls group would have also shown the same improvement effect after repeating the same task twice. These results also support the plastic nature of our brain at adult age as it has already been shown that our sensory modalities are capable to adapt to any changes in sensory inputs even after the critical period (Dionne-Dostie, Paquette, Lassonde, & Gallagher, 2015). This plastic behavior is the key for rehabilitation research in low vision and particularly MD patients.

Infact, in the absence of ability to adapt to changes in sensory inputs, rehabilitation for adult population would be out of question and the only cure left would be surgery or medication.

Chapter 5

Conclusions

The main aim of this this dissertation is present the work related to: 1) developing and testing devices that can provide multisensory feedback for visually impaired people. To achieve this point we presented two devices, first device is ARENA which is an audio-tactile matrix of speakers and can be used to understand audio-spatial representation in Macular Degeneration (MD) participants, the second device is Audio Visual Thumble (AVT), which is a small device capable of providing audio, visual and proprioceptive feedbacks that has been used in a rehabilitation protocol design for MD participants. 2) Understanding how audio-spatial representation is altered for individuals suffering from MD. For this purpose we have used an audio localization task with the ARENA device. Results reveal that MD individuals show a miss localization of sound and perceive them coming from scotoma positions. 3) Developing a rehabilitation protocol called Intelligent Audio Visual Thumble Training (IVATT) to make MD individuals more aware of their own spatial representation and overcome limitations due to their visual pathology. This training use AVT device and an Archimedean spiral board. Audio and visual localization tests are used to evaluate results of this training. Results of IVATT show an improvement in audio localization skills and precision in visual localization skills of MD patients.

5.1 Seeing, Hearing and feeling scotoma through technology

Macular Degeneration causes an irreversible and permanent damage to the retina and unfortunately to-date there is no breakthrough to stop this damage through medicines or surgery. Therefore, rehabilitation techniques for individuals with scotoma as a result of MD is a wide research topic. However, these rehabilitation methods generally involves training to learn to develop a pseudo fovea in healthy part of their retina (Midena et al. (2018)) by utilizing the residual vision. The concept of rehabilitation through multi-sensory integration and sensory substitution devices for blind individuals has been investigated widely in past, in fact there are many rehabilitative and assistive devices for blind adults (Setti et al. (2018), Nelson et al. (2018)) and children (Martolini et al. (2018), Cappagli et al. (2018)). On the other hand, this concept has never been used for the screening and rehabilitation of individuals with visual degenerative diseases as in MD. The focus of rehabilitation techniques for MD is visual modality only. Here, we presented a concept of multisensory integration rehabilitation. In this method we used the audio and spatial representations to quantify the visual deficit and train the audio, visual and spatial representations by using a multisensory device. Two devices are presented in this regard: (I): ARENA to understand the role of audio modality on space representation due to a central scotoma. ARENA is a 2-D matrix (5x5) of speakers covered with tactile sensors. The device is capable of producing sounds and recording response positions; thanks to the tactile sensors. As an application, we have elaborated an behavioural experiment using ARENA in detail in Chapter 3 for MD individuals, (II): AVT device which is designed to improve the audio and visual localization bias in MD patients. AVT is composed of an LED and a buzzer which provides visual and auditory feedbacks respectively. AVT can be an effective device to develop PRL (Preferred Retinal Locus) or pseudo fovea in the residual healthy part of retina. We have used these devices for a single application in this dissertation, but using the concept, i.e. multisensory integration for MD individuals, they can open doors to new research paradigms. These devices are first of their kind, therefore they have limitations and of course, there is a big room for improvement in design and technology in future.

5.2 Effect on audio-space representation due to Macular Degeneration

In this work, we studied audio-space representation in adults suffering from Macular Degeneration and having a scotoma in central visual field due to this disease. Our findings show that there is a robust attraction of auditory stimuli towards the scotoma position in MD individuals. Sound positions from periphery regions were strongly biased and they perceived them as they were produced in central scotoma regions. We found that there is no difference between precision of MD and sighted groups calculated in terms of distance errors. This similarity suggests that bias we observed was not due to less precise spatial perception of MD group. On the other hand, we found that sound localization of controls group was equally scattered on device and there was no bias towards a specific region of the device. Our results also supports the concept that reorganization of spatial representation of sound processing is a continuous process that starts after the visual input loss in a plastic way. We also observed a correlation between the audio bias towards scotoma positions and onset of the disease. Younger the participant is at the onset of disease, lower is the bias and older the participant is at onset of disease, higher is the bias towards the center. This effect is as expected i.e. audio-spatial recaliberation mechanism reflects the plasticity of brain which is maximum at younger age and reduces with growing age (Lund (1985), Kramer and Erickson (2007)). Interestingly, out of 18 MD participants we tested, tge age of 12 participants was greater then 70 years and the correlation we observed between age and percentage responses in central region was significant for MD group and not for sighted participants. This means that central scotoma has minimum effect on audio-spatial perception in younger MD participants because of their cortical plasticity at young age. With growing age, this effect due to scotoma increases because the cortical plasticity decreases with growing age (Erickson et al. (2007), Kramer and Erickson (2007)).

The capability to perceive the spatial coordinates related with neural signals from different sensory modalities is essential for a rational perception. The famous findings from Alais and Burr (Alais and Burr (2004)) proves that visual modality is more precise compared to other sensory modalities for spatial representation.

One possible explanation of the bias we observed could be that this bias is due to continual cortical reorganization of auditory cortex caused by missing visual inputs. This reorganization of cortex is a rapid process that begins soon after the loss of visual inputs as in case of MD individuals who are continually losing visual inputs due to scotoma development. The recruitment of the visual cortex from the auditory modality could produce the misperception

of sound localization that we observed because audio and visual spatial maps require some time to realign. However, the short term advantages of this auditory reorganization are still unclear. In fact, we have seen in our results that the attraction of sound towards scotoma is not beneficial in enhancing the audio space precision since we observed similar precision between MD and sighted groups, which is very evident for blind people (Lessard et al. (1998)). This audio space reorganization also produces a strong miss-perception of sound, making the perception attracted towards the center then the actual sound positions. This miss-perception indeed can produce problems for MD patients.

Considering the possible aspects discussed above, a second speculation we can make is that the observed bias could be due to multisensory integration process. In sighted people, audio, visual and spatial information integrate to give a complete perception of surrounding environment. When the visual inputs are present perfectly, a high reliability is given to visual information in space. Vision gets a higher dominance in this case as proved for ventriloquist effect for a Bayesian model prediction (Alais and Burr (2004)). Taking in to account these findings, we can relate our results to multisensory integration mechanisms as well. With the growing age, scotoma also develops and hence decreasing the higher reliability of vision in space. In this situation, the residual visual areas gets more weightage then normal. This wrong prediction of weightage can affect the processing of spatial information for a multisensory process and hence captures the sound which produces an *inversi ventriloquist* effect. Depending upon the size of scotoma and age of MD individual, this effect may be stronger in elder people compared to younger individuals because plasticity and multisensory integration skills reduces with growing age (Lund (1985), Kramer and Erickson (2007)), which is in line with our findings for correlations with age.

We explain our results in terms of attention as well. Attention may have a role on the aidio-spatial bias we observed. A study by Santangelo and Macaluso (2012) have discussed several behavioral and fMRI studies presenting that attention has an affect on how audio-spatial and visual-spatial inputs interact with each other (Santangelo and Macaluso, 2012; Stein, 2012). Therefore we can say that scotoma is indeed a “black hole” and with potential risks coming, attention can act as anchor by attracting audio signals in the regions without visual inputs to increase the quantity of information, hence drawing attention of audio modality toward the non-visual zone.

Two comparative hypotheses to explain the neural mechanisms of multisensory activation after vision loss have been presented (Amedi et al. (2007), Striem-Amit et al. (2012), Ortiz-Terán et al. (2017), Chebat et al. (2018)). First is the “rewiring hypothesis” showing that cross-modal cortical responses are intervened by the formation of contemporary pathways

in the regions pf sensory deprived brain. Second hypothesis is “unmasking hypothesis” suggesting that the deprivation of sensory input activates unmasking and/or enhancement of the current neural pathways. The findings of our study brace the unmasking hypothesis proposing that cortical reorganization is a rapid process that reinforces the changes of audio and space perception after a short period of visual input loss. To disentangle which one of the above mentioned explanations is the correct, further investigations will be necessary considering cortical analysis, top down processing and multisensory modeling. These results may have a strong impact for rehabilitation purposes by using the audio input to improve spatial representation and to stimulate residual visual regions of patients having central scotoma due to Macular Degeneration.

5.3 Intelligent Aduio Visual Thumble Training (IVATT)

Macular Degeneration (MD) is a retinal disorder that causes an irreversible damage to retina and produces blind spots called scotoma at damaged retinal parts. Unfortunately, there is no cure yet available to stop this retinal damage either by drugs or through surgery. Therefore, a lot of research is conducted in developing rehabilitation techniques and devices. Generally, we found that the focus of these rehabilitation techniques is learning to develop a pseudo fovea to take advantage of residual vision through tasks that involve visual modality only. In this work, we have presented an idea of multisensory rehabilitation protocol for individuals suffering from MD to make them aware of their own scotoma and develop an effective PRL (Nelson et al. (2018), Daibert-Nido et al. (2019), Midena et al. (2018)).

In this dissertation, we presented an idea based on developing a rehabilitation protocol called Intelligent Audio Visual Thumble Training (IVATT) for individuals suffering from Macular Degeneration in adults age and has developed a scotoma or a blind spot. IVATT involved auditory, visual and tactile sensory modalities. To evaluate the efficiency of the training, we assessed the localization skills of each participant in an auditory and visual task before and after the training. After the training we obtain two main results: (1) a significant improvement in audio localization bias, and (2) an improvement in precision for the visual localization task. About the auditory localization task, in a previous study (Chapter 3), we found a bias in localizing the sound positions for patients with scotoma and we found that sounds are attracted towards the scotoma regions. Taking into account this study, our new training group and control group (both suffering from MD) showed similar kind of behaviour in the pre-training phase i.e. a bias towards the scotoma positions in localizing the auditory stimuli. However, IVATT training show a prominent improvement in localization for trained

group, even after a short period of training, participants are able to better localize the sounds. On the other hand, controls group are still biased towards the scotoma regions in the post phase. This result essentially nullifies the fact that improvement in sound localization for training group could simply be a result of repeated task in short period of time because if later was the case, controls group would have also shown the same improvement effect after just repeating the same task twice. Our results also show that the precision in sound localization test (distance errors) remains same before and after the training in both groups. On one side, this suggests that IVATT training is not beneficial for improving spatial precisions for auditory stimuli, on the other side similar precisions show that the bias was not due to random responses on ARENA device. In fact, this shows that the responses we analyzed in this study, were actually made as a response to auditory stimuli. We speculate that this bias towards the scotoma position could be a result of attention i.e. MD patients are aware of their visual impairment and hence unconsciously they are giving more weightage to auditory stimuli then normal which is explained in previous section as an inverse ventriloquist effect. Performing the IVATT with auditory feedback from one's own motion could possibly re-caliberate the audio bias by integrating the auditory stimuli position with proprioceptry feedback from finger on spiral board. Thus, this multisensory integration can reduce the audio-spatial representation bias and learning to use pseudo fovea can be an effective training to reduce the audio bias.

About the visual localization test, results show that this training can improve the precision of MD patients in peripheral region of visual field. We speculate that training with AVT device having audio, visual and proprioceptive feedback can effectively force the subject to see visual stimulus through residual vision, since there are other two modalities i.e. audio and tactile to draw attention towards the visual stimulus. While fixating on the central fixation visual stimulus, MD individual is not able to see visual stimulus of periphery due to potential blind spot but then audio and tactile modality gains more weightage forcing eye movement to an extent that subject start seeing the stimulus through residual vision. Precision in the center was already better then in periphery for both groups even in pre phase, showing that these patients had already developed some sort of pseudo fovea naturally. Considering the fact that most patients had scotoma in center of their visual fields, learning to improve precision in localization of visual stimuli can eventually lead to development of an effective pseudo fovea. We analyzed the results in terms of percentage of seen trials in central and peripheral visual fields as well, but results show no effective improvement with training. This can be explained as the percentage of seen trials in both visual fields was already high (greater than 85%), hence our MD participants were already very good in seeing the visual stimulus

since vision is a reliable modality and always gets a higher weightage over other sensory modalities (Alais and Burr (2004). Contrary to training group, control group showed same results for both parameters (seen trials and precision) for both phases (pre and post). This can also be explained as discussed above for audio localization task i.e. the effect seen in training group in improving peripheral precision is an effect of IVATT training and not just cause of repetition of same task.

In summary, IVATT is an initial concept for rehabilitation of MD patients by introducing other sensory modalities. However, we have a prominent result in improving the sound localization with training, we can modify the training and bring more complex visual techniques to improve the visual modality factor as well. This is just an initial idea, but we are confident that we can take this concept to further levels where it will be possible to take advantage of the residual vision of Macular Degeneration patients and at the same time improve their audio spatial representations in order to bring a positive and healthy change in their lives.

5.4 General conclusion

There are many studies about how sensory modalities react to loss of inputs for visual modality in blindness, and how intact senses can be utilized for designing rehabilitation techniques and devices for blind individuals. On one side, studies report how loss of one sensory modality decreases the reliability of other sensory modalities (for example, audio spatial representation is effected due to vision loss), on the other hand, it has also been shown that a proper training can reorganize working modalities to compensate for lost sensory modality (for example, audio motor training can improve spatial localization in blind individuals). However, the question of multisensory integration mechanism works for partial visual input loss is less known and therefore, the focus of rehabilitation for such individuals is only limited to use of residual visual inputs. Our dissertation focused on how sensory modalities of individuals suffering from Macular Degeneration, for whom loss of vision due to scotoma is still an ongoing progressive process, reacts to gradual loss of visual inputs. We found a bias towards lost visual input regions in audio-spatial representation of these individuals. We developed a multisensory rehabilitation technique (audio-visual motor training) to re calibrate this auditory bias and to help MD individuals understand their own audio and visual representation in space. We found an improvement in audio-spatial bias and better precision in peripheral visual field as a result of this training. Two devices are presented in this dissertation. One is ARENA which is an audio-tactile matrix of speakers and used to study audio localization in MD individuals. Second device is Audio Visual Thumble (AVT) which is capable of providing multisensory feedback i.e. spatially and temporally coherent audio and visual feedbacks, and is used in the rehabilitation protocol we developed. We conclude from this dissertation that partial loss of visual inputs have a multisensory influence. It effect the spatial representation of audio and visual signals and hence focus of rehabilitation techniques can be extended to bring-in multisensory modalities in order to reduce the spatial bias and utilize residual vision of MD individuals.

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