ERA-NET NEURON Cofund

Symposium

‘Sensory Organ Disorders”

Wednesday, May 15th, 2019
Riga, Latvia

Report by **Anton Iftimovici**

Psychiatry Resident,
Paris Descartes University,
"Médecine-Sciences" MD-PhD programm
France

This symposium is part of the Work Package

“Call topic”

Work Package leader are Inserm and CNRS

Tables of Contents

Wellcome

Dr. Marlies Dorlöchter, DLR-PT, NEURON Coordinator, Bonn, Germany

Marlies Dorlöchter introduced the scientific symposium on “Sensory Organ Disorders” by addressing a few welcoming words to the speakers and the NEURON Scientific Advisory board. She emphasized the need of funding organizations to have such a meeting to understand what is important in the field of sensory organs for shaping future work.

Introduction

Etienne Hirsch (INSERM) and Bernard Poulain (CNRS), Paris, France

The meeting welcomed different groups of people mixed together: leading experts on the field of sensory organs, members of the scientific advisory board, whose general vision of all projects will be useful, and representatives of funding agencies, who need to be convinced that research in sensory organs is a crucial topic for funding. Importantly, representatives of patients’ organizations are also present, as there is a societal need and perspective for such research. It is therefore an ambitious brainstorming.
Experts have spoken about the state-of-the-art in vision and audition treatments and neuroprostheses, as well as research in social and health economics. The speakers were asked to give a general presentation about what is known and what still is at the stage of research, and what should be done in the future to make breakthroughs in terms of knowledge in their field.

State of the art and challenges in Vision

Serge Picaud, Vision Institute, Paris, France

Burden of sensory organ dysfunction

The importance of sensory systems was underlined by a recent study, which showed that people subjectively experience the loss of vision as having the most severe impact on daily life, even more than the loss of memory (Scott AW et al. JAMA Ophthalmol. 2016). Hearing loss is also among the top five conditions affecting daily life. There are many diseases generating visual loss, such as age-related macular degeneration, glaucoma, or cataract. Importantly, the number of these diseases is drastically increasing with ageing populations. Presently, age-related macular degeneration, due to the loss of photoreceptors, is affecting 30 million patients worldwide; diabetic retinopathy is touching 20 million of patients, while 6 million patients are suffering from glaucoma, due to the loss of ganglion cells (the neurons that send the information to the brain) – but there are also many other inherited diseases, such as retinitis pigmentosa, Leber's hereditary optic neuropathy, Stargardt’s disease, etc.

What is know about sensory organs and their pathologies?

From a conceptual perspective, it is important to consider the eye or the ear as an organ, in a comprehensive view. This point-of-view allows to better understand phenomena associated with the interaction between different parts of the organ. For instance, in glaucoma, the blockade of the exit of aqueous humor increases the intra-ocular pressure, leading to retinal ganglion cell degeneration. Hence, the organ itself can induce a sensory loss. In myopia, the lack of focus of light on the retina induces dysregulated growth mechanisms.
The retina is not the sole object of eye research as corneal pain has gained recognition as a public health concern given its prevalence, morbidity and cost implications. Indeed, cornea is one the highest innervated tissues in the body and many causes can induce corneal pain: dry eye disease, neuropathic pain, infectious keratitis, herpetic keratitis, surgery or chemical burns. Yet, there is in no current treatment for this condition, thus making it an important therapeutic challenge in ophthalmology. The development of therapeutic strategies should therefore addressfollowing steps: i) to develop pre-

clinical models of ocular pain to mimic the human pathology, ii) to screen novel analgesic compounds, iii) to improve the understanding of peripheral and central neuroimmune mechanisms that occur during ocular pain, as it seems that the immune reaction can indeed generate pain at that level.
Of course, it is important to understand normal function of the entire visual sensory system, to improve therapeutic approaches for the varous diseases affecting the visual system. There is a need to understand how the macula is connected to the brain. In the macaque model, it is possible to mark visual connections with specific stainings that one can follow to the brain. Functional studies are indeed crucial as there are more than 40 ganglion cell types but the kind of image these different cell types send to the brain, and how the processing in the retina is able to generate these different informations at the ganglion cell level, are still poorly understood. The level of network complexity increases all the more that one approaches the cortex. This is why multi-omic, coding and connectomic approaches are needed. Tackling the understanding of retinal tissue development is another challenge, for which retinal organoids or techniques such as Brainbow clonal labels could be used.

Vision disorders and their current pathologies
Complex multifactorial diseases and the ones due to specific mutations should be included in the same framework, as they share mechanisms leading to neurodegenerative processes of sensory loss. An emphasis should be made on disease modelling and biomarkers: not only in rodents or zebrafish, but also in non-human primates as they are the only ones who have a macula and would allow to study information processing in the visual centres. For gene therapy, one would need promoters, but they are not the same between mice and primates, further justifying the need for primate models. Indeed, using human tissues from post-mortem retina samples remains difficult as ganglion cells die quickly, in less than six hours after decease.
The common therapies for restoring vision vary according to the stage of intervention:

- *Gene therapy (RPE 65, ND4) to intervene on specific mutations*

The first gene therapy in ophthalmology was recently accepted, and it targets RPE65, an enzyme essential for visual pigment regeneration, in the retinal pigment epithelium, just below the photoreceptors. The company Spark is commercializing this treatment, which costs 800 000 € / person; it is reserved to children, and allows them to recover their vision. Other gene therapies are still emerging in ophthalmology, for many various diseases. Moreover, gene therapy will be able to target foveal cone receptors by peripheral injection, thus broadening the range of disorders one could treat. However more and more mutations in genes associated to the disease are discovered, and it will be difficult and expensive to develop therapies for each of them. Notwithstanding the fact that for some diseases, the genes involved are still unknown. Therefore, a higher-level approach might be more fruitful.

- *Gene independent therapy to prevent the evolution of the disease*

The injection of a trophic factor released by cones and inducing their survival (the rod-derived cone viability factor – RdCVF) has thus proven to be an efficient treatment, prolonging vision in rodent models regardless of the causal genes. On the other hand, inflammation is an important process of age-related macular degeneration, as many macrophages invade the tissue and are toxic for photoreceptors. Therefore, new strategies consider preventing inflammation in the tissue or limiting the effect of genes which were shown to prevent the elimination of macrophages.

- *Cell therapy and transplantation to prevent the evolution of the disease*

Knowing it is possible to generate retinal organoids from iPSC, there is hope to use tissue from patients' biopsies and produce these retinal organoids, in order to grow photoreceptors, which could then be transplanted back. However, at the moment, it is very difficult to connect them back and further research is needed into the mechanisms of axonal regrowth. Presently there are many clinical trials using retinal pigmental epithelium, in the United-States, France, Japan, the United-Kingdom, or Israel, in various presentations, RPE cell suspensions or RPE cell sheets (of note, it is also possible to generate hearing cells from iPSC and auditory neurons, which can be reintroduced and reconnected to the hair-cells).

- *Prostheses to treat sensory loss*

In vision, it is possible to generate subretinal and epiretinal prostheses. Epiretinal prostheses are currently the state-of-the-art, but the resolution is not great. However, there is hope of improving it, by using smaller electrodes and materials enhancing their conductivity, as well as new flexible implants, like polymers, that are photosensitive.

- *Optogenic therapy to treat sensory loss*

Using photosensitive ionic channels, expressed from photosensitive algaes, one can induce action potentials through the activation of the optogenetic protein, thus activating ganglion cell neurons. This is now in clinical trials in patients suffering from retinitis pigmentosa. However, only one of the forty types of ganglion cells are targeted with this strategy, so one would need to improve differential cell types activation, to send a more discriminate information to the brain. Another topic of research is to explore whether it is possible to regain function even after the loss of ganglion cells, by a cortex-directed stimulation (an experiment showed indeed that by stimulating cortical visual areas, patients saw phosphenes). Optogenetic therapy could also be done at the visual cortex, as it was recently shown by a Chinese team in non-human primates (Ju et al. Plos Biol. 2018)

Research priorities in the field of sensory organs

Research in sensory organs appears crucial given its impact on public health and the incidence of degenerative processes such as age-related macular degeneration. Furthermore, it appears that very frequent conditions such as age-related hearing impairment or Ménière's disease, although considered as benign, are nevertheless poorly understood and treated. It is therefore essential to characterize the various axes of research one would need to develop. Of course, there are generic directions, shared with other field of neurosciences and already mentioned above, such as the need to bridge multiple temporal and spatial scale analysis, from circuit to behavior, to be more specific in pathway-targeting, to improve disease modeling and combine it with mathematical and informatical approaches. However, there are some axes specific to research in sensory organs.

Firstly, to understand sensory organs' function one needs to improve our knowledge of receptors, circuits, connectomics of these circuits, as well as the way information is coded and understood by the brain. The developmental aspect of sensory organs is thus a major focus of research.

Secondly, one needs to take advantage of the accessibility of sensory organs, to implement, replacement strategies for sensory organs, like gene and cell replacement therapies. The challenge is now to move from pre-clinical trials to clinical trials. However, this would require decreasing the costs of treatments, which in most instances are an obstacle to larger scales therapeutic strategies. Moreover, the easy access to sensory organs allows for potential replacing of part of the nervous system with artificial biosensors and brain-machine interfaces. This is why one would need to decode the mechanisms of information processing, through a strong collaboration between physicians, neuroscientists, engineers, informaticians, applied mathematicians, etc. Interestingly, while many investments went into gene therapy in ophthalmology, hearing rather benefited from prostheses development, which benefited to a large amount of the population, regardless of the etiology of the disease.

The interpretation of the perceived sensory information remains a topic that has somewhat been left aside, as it is not covered by the call on sensory organs. Nevertheless, characterizing for instance what defines the balance between nociception and pain (e.g. between a normal nociceptive sensation during sport, and actual pain) appears as an important challenge to improve acute and chronic pain-related therapies. At a different level, expectations play an essential role in the interpretation of external stimuli (e.g. the placebo effect). Altogether, the study of the perception of sensory information might benefit from interventional approaches such as deep brain stimulation, high intensity focused ultrasound, transcranial magnetic stimulation or close loop approaches. Finally, scientific-oriented rehabilitation and training are one often overlooked and understudied efficient therapy in the field of sensory organs, which could benefit from further research.

State of the art and challenges in Audition

Brigitte Malgrange, University Liège, Belgium

The multifactorial causes of deafness

Hearing loss is an important societal problem. 360 million deaf people worldwide, ranging to 5.3 % of the total population, have a hearing loss superior to 40 decibels (dB), and 16 % of the European population has a hearing impairment, with a loss superior to 25 dB. Furthermore, this issue is aggravated by age: one in every three persons over 65 years old experiences some degree of hearing loss, while 80 % of hard of hearing people are in denial, becoming increasingly isolated, thus constituting a risk factor for accelerated cognitive decline and cognitive impairment, including Alzheimer's disease. This is the reason why the direct and indirect costs of untreated hearing loss amount to 213 billion euros in Europe.

Hearing impairments can be classified in three types, according to the anatomy of the ear: i) central deafness, which is caused by damage to the hearing centers in the brain, is quite rare; ii) conductive deafness, which results from the blockade or interference of sound at the level of the middle-ear, is easily treated by surgery; and finally iii) sensorineural hearing loss, which is the most frequent type, is due to damage to the nervous system in its auditory portion of the inner ear.

The inner ear itself is comprised of two different portions: the vestibular one, in the upper part, implicated in balance, and the cochlear one, ventrally, which is the sensory organ for hearing. The cochlea has different loops, containing the organ of Corti, fundamental for hearing, which is composed of two main cell-types: the hair-cells (inner hair-cells and three rows of outer hair-cells), and the spiral ganglion neurons. The inner hair-cells transduce directly the sound to the spiral ganglion neurons, which constitute the first relay towards the brain (Frolenkov, Nat Rev Genetic, 2004). Moreover, beneath the hair-cells are supporting cells, which might be a good ressource during treatment, as described below.

This anatomical complexity of the ear explains the diversity of damages that can occur, dependent on location and etiology. In the organ of Corti, the hair-cells can be damaged by loud noises, ototoxic drugs, ageing or genetic abnormalites, whereas the spiral ganglion neurons can degenerate from primary or secondary causes.. In addition to neurons and hair-cells, a third structure, stria vascularis, can support important damage due to ageing or ototoxic drugs, leading also to deafness. Stria vascularis seems slightly neglected in current treatment strategies.

Overall, deafness appears as the common consequence of many very different pathological mechanisms that require an equivalent variety of different therapeutic approaches. Indeed, among the causes of neurosensory deafness, half are genetic of which 30 % are syndromic and 70 % non-syndromic. Half are environmentally acquired, because of ototoxic dugs (antibiotics such as aminoglycosides, largely used in clinical practice, especially for pulmonar infection; ofcisplatinum for cancer), of presbycusis (hearing impairment during ageing), or of acoustic trauma (the fact that young people are listening more and more to loud sounds increases the occurrence of deafness).

Although this report will focus on neurosensory deafness, there are other major inner ear diseases. This includes tinnitus (persistant ringing in the ear), Ménière's disease (complex range of symptoms that includes vertigo and hearing loss, mainly due to perturbation of the ionic fluid, in the inner ear) or otitis media, which is common in children and can lead to hearing loss, if recurrent.

Challenges and therapeutic strategies to treat neurosensory deafness

The first barrier to treatment is the difficulty to access the inner ear and the cochlea, protected by the skull. Local treatments are therefore uneasy to perform and require surgery. In addition, hair-cells and spiral ganglion neurons cannot regenerate and need to be connected with each other. Therefore, there is a need to address both the problem of regeneration and connectivity. However, good therapeutic models, whose results could then be translated to humans, are missing.

Many preclinical research trials first addressed new drugs on protective strategies, as they are easiest to translate from pre-clinical to clinical models. There are examples of a new oral formulation of Ebselen (an antioxidant that induces glutathione peroxidase), of LPT99 – a blocker of apoptosis in cisplatinum induced hearing loss model, and injected transtympanically, or of ORC 13661, protecting against aminoglycoside induced hearing loss. However, although protective strategies appear easier and more attractive to develop in research, they remain difficult to generalize to all at-risk patients, unless in the very specific contexts of exposure to ototoxic drugs, for instance. Addressing regenerative strategies, to produce new hair cells, new spiral ganglion neurons, and restoring the connections between hair cells and spiral ganglion neurons are therefore crucial. Research in curative treatments range from stem cells to gene and molecular therapy, and no pharmacological drugs have been developed. Currently, only substitutive medical devices are used in clinic.

The various etiologies of deafness require a diversity of therapies.

1) ***Genetic therapy.*** Genetic hearing loss can involve more than 700-1000 genes and currently only 100 have been identified, most of them expressed in hair cells. To treat it, viral (adeno-associated virus – AAV, for instance) and non-viral (lipidic agents) vectors are promising treatments to complement or augment cells with the missing or dysfunctioning gene. For instance, a gene therapy recently performed at the Pasteur institute using AAV vectors durably reversed congenital deafness in mice, and a startup is presently on the way to translate this experiment to the clinical level. However, AAV vectors have a limited packaging capacity, up to 4.7 kb. Therefore, the gene of interest should be quite short. For genes with longer coding regions of interest, dual AAV strategy have been tested, where each AAV vector contains one part of interest. Furthermore, this requires a single intracochlear (or intralabyrinthine in some trials) injection, as it is not possible to use the systemic fluid. Overall, the few clinical trials for gene therapy are all addressing safety issues, and not efficacy (for instance Atoh1 gene therapy for vestibular function; or Genvec/Intrexon therapy using next generation adenoviral delivery with higher capacity, up to 30Kb). Overall, gene replacement faces important challenges. First, most trials performed in mice have been done very early in development, neonatally, before hearing. So translating it in human, knowing that hearing develops around week 26 would require in utero gene therapy, which seems complicated. Secondly, it is important to characterise the long-term expression and outcomes of gene therapy; and while gene therapy has indeed been performed in mice, there is no information about long-term expression of the vectors.

2) ***Inducing hair-cell regeneration.*** Changing the fate of endogenous cells can only be achieved when knowing which factors induce differentiation and which cell type retained the capacity to transdifferentiate into hair cells inside the organ of Corti. Nevertheless, it is possible to imagine grafting exogenous hair cells or exogeneous progenitors that can in situ differentiate into hair cells. Other therapies are based on the idea that it is possible to induce differentiation of supporting cells into hair cells. For instance, the Regain European consortium tested a Notch inhibitor, LY3056480 for tolerability and safety in patients with mild to moderate hearing loss (mild to moderate) and showed that intratympanic delivery of 3 administration of 250 µg, one week apart, was safe. Nevertheless, all current studies are safety trials only; it shows however that the field is moving fast forward, as none of this progress was imaginable ten years ago. In addition, these studies address regeneration of hair cells, and there is still research to be done on regeneration of spiral ganglion neurones and ribbon synapses between hair cells and neurons. Furthermore, all the regenerative mechanisms discovered are on non-primate species, and it is not clear whether these preclinical models are transferable and whether the same mechanisms apply in humans. The recent discovery of induced pluripotent stem cells (iPSC) might therefore help overcome this problem by providing information on what is happening during human development. Brigitte Malgrange's lab demonstrated that using human iPSC and 3D reconstruction, it was possible to obtain organoids that presented specific markers of the organ of Corti after 60 days of culture. This allows them to look for new factors that induce differentiation in hair cells, neurons, or increase synaptic connection.

3) ***Anti-inflammatory treatments.*** Acute hearing loss, also called sudden sensorineural hearing loss, seems to be idiopathic, and is defined by a hearing loss of 30 dB or more that develops over 72

hours or less in relatively young adults (40-50). There are 160 cases / 100 000 people / year, but it is largely underdiagnosed and it has been increasing over the last years. It does not have any equivalent animal model, and currently only anti-inflammatory drugs are tried, with variable success. Nevertheless, it presents an interesting advantage for clinical trials, as patients with this disorder constitute a more homogenous population, and clinical trials can be short with short-term outcomes and treatment, after which audition can be recorded. Currently, one drug is entering phase 3 with some success: a JNK inhibitor (inhibiting autophagy processes) showed good results after a single dose of 0.4 mg/ml intratympanic otic gel injection, but only for patients with profound hearing loss; they manifested a hearing recovery at day 28 of 42.7 dB vs. 26.8 dB initially.

4) ***Therapies that prevent or reduce hearing loss resulting from striatal degeneration*** in presbyacusis. Presbycusis typically presents itself as a progressive bilateral hearing loss (and mainly a loss of hearing sensitivity). It can be a combination of injuries at different levels: hair cells, spiral ganglion neurons, synapses and stria vascularis, due to metabolic changes. Therefore, the treatment strategies could include gene therapy to up-regulate expression of tight junction proteins to repair a leaky stria vascularis, delivery of angiogenesis-inducing growth factors, or antioxidant treatments to ameliorate the effects of inflammation on barrier leakiness.

Another critical challenge is the delivery modality, which faces, for local delivery, the problem of accessibility of the inner ear, and for general systemic delivery, the blood labyrinthine barrier (BLB), between the vasculature and the inner ear fluids, either endolymph or perilymph. This barrier is critical for the maintenance of the inner ear fluid ionic homeostasis and for the prevention of the entry of deleterious substances into the inner ear. It is therefore important to understand the dynamics of the barrier to develop therapeutic drug delivery systems to the inner ear to block or enhance the BLB inflammatory response. Regarding, local delivery, there are mainly two methods: i) intratympanic direct delivery at the level of the round window into the cochlea through the perilymph, but there is a huge inter-subject variability and it is difficult to reach the more apical cell types; ii) delivery to the endolymph, but then one needs to go through the cochlea so there is a risk of damage during injection. Another delivery possibility, going through the semi-circular canal, has shown an efficiency of the drug when delivered in the vestibular system, but the percentage of the drug actually going through the cochlea remains unknown. Ameliorations of the delivery mode are therefore considered, using microcapsule formulations for bethamethasone delivery in Ménière's disease for instance, or incorporating hydrogels, nanoparticles, and supraparticles, to have controlled and sustained release systems.

Gaps in research on deafness and proposed topics to be funded

The main issues are:

i) the administration pathways and how to overcome the blood labyrinth barrier;

ii) how to improve diseases' models, with models closer to humans – although it doesn't seem one can avoid in vivo research on primate cells, humans iPSCs appear to be promising;

iii) the need to isolate human cells, and the generation of protocols controlling their differentiation into sensory lineages;

iv) identification of genes involved in deafness – currently, around 100 genes are identified, while around 1000 are expected to be implicated in the disease.

The topics to be funded are, therefore:

- the acquired synaptopathy and hidden hearing loss
- the human models to mimic deafness
- the hair-cell regeneration therapies
- new drug delivery methods (biomaterials or cell-based therapies)
- gene therapy
- amelioration of electronic devices (cochlear implants ameliorated with spiral ganglion neurone peripheral fibre regeneration and reduction in inflammation)

State of the art and challenges in other sensory organs

Andrew J Bremner, University of London, UK

A multisensory perception of the world

The idea of a strict separation between the senses has persisted in common culture since Artistotle's classification of the five senses – touch, taste, smell, sight and hearing, corresponding to the five basic elements – earth, air, fire, water and aether. However, none of these senses is a unitary channel of information, all are processing very different kind of inputs, and most perceptions are combinations of these senses. For instance, taste is subdivided according to different receptors for sourness, sweetness or bitterness.

While most sensory research tends to focus on just one sense modality of input, the perceptual ecology is indeed multisensory, not relying just on vision or hearing, for instance (babies learn about face perception or humans through the sounds of people's voices, through tactile interactions, smells, etc). Moreover, the brain and the sensory pathways are cross modal, combining inputs and outputs from all sensory modalities, and a disorder in one sense channel will influence how the other sense channels respond, through neuroplasticity in the brain or adapting behaviour. This multisensory integration yields therefore both benefits and costs to perception, leading to a better understanding but requiring a costly integration that might be at the heart of sensory processes disorders.

Somatosensation is one of humans' most important senses. The tactile receptor sheet, the skin, occupies 15% of our body mass, which is more than all other sense organs combined, and the broader definition of touch includes receptors throughout the body: skin (cutaneous sensation), muscles, tendons, joints (proprioception, kinaesthesis), vestibular system (balance, kinaesthesis), internal organs (interoception). Within somatosensation and touch, there is a diverse physiology, with a range of receptors: stroking, vibration, stretch, pressure, texture, pain and temperature, integrated for a range of different functions. Detecting wetness, for instance, requires a combination across sense channels – pressure and temperature, as there are no specific receptors for wetness itself. Therefore, thinking of touch as one sense might not be relevant, although its different modalities can share common pathways in the brain. However, at the level of function itself, somatosensation and touch serve a wide range of roles based on the integration of tactile sensors with other somatosensory inputs and sensory channels. In particular, vision and hearing are important in the way touch is used and the body is perceived. Touch is not just about passively perceiving the information presented to the skin but it's also actively exploring the external world (in the sense of haptics). It can also be used to cue emotional responses to the environment, including social touch and pain. It was shown indeed that skin-to-skin touch reduced crying and grimacing in babies during the heel lance procedure. Moreover, the social touch channel, the C tactile afferent fibers in the hairy skin seem to specifically code stroking movements (as when caressing) and are therefore important social channels for touch. Therefore, a disorder in that channel might be a potential precursor to autism spectrum disorder (ASD). Touch also plays an important role in self-perception, as touching an object gives an information on the place of the body where this object was touched and thus increases our sense of self. Finally, touch and body perceptions strongly and robustly interact with the other senses, in particular vision, to modify the tactile experience. The rubber hand illusion is a good illustration of it: seeing a fake hand being stroke at the same time as the real hidden out-of-sight hand, gives a sense that the hand being stroke is actually one's own hand and that one has ownership over that limb.

Touch is understudied, but the loss of touch has dramatic consequences. Deafferent patients cannot feel their body, have a sensation of floating in space, with huge difficulties eating or moving, having to relearn the movements over long periods of time. Deafferentation, neuropathic pain is precipitated by central and peripheral lesions, while phantom limb disorder, where an absent limb is sensed as present, can also lead to neuropathic pain.

The senses of taste, olfaction and interoceptive chemoreception present the same multisensory and cross-modal characteristics. Papillae on the surface of the tongue and mouth contain taste buds, which react with certain chemicals to signal their presence. There are known taste receptors for sweetness (triggered by sugars and some proteins), saltiness (triggered by alkali metal ions, Na+, K+ etc.), sourness (triggered by H+ ions), bitterness (triggered by a range of chemicals, many noxious), savouriness "umami" (triggered by glutamate). During olfaction, molecules pass over the olfactory epithelium, and diffuse into the mucus covering it. Olfaction is important, phylogenetically, for detecting hazards, pheromones, tasting and flavour (through retronasal olfaction, from the mouth, or orthonasal olfaction through the nose, and the same chemicals give very different information when they are distributed retronasally or orthonasally. Interoception is the combination of somatosensory and chemosensory inputs signalling internal events and states. Its links with interoceptive awareness plays an important role in self-perception and emotional regulation. It was recently proposed that aberrant interoceptive development could play a central role in ASD, via difficulties in self-perception and regulation (Quattrocki and Friston, 2014).

A developmental approach to multi-sensory perception

Developmental processes are products of complex epigenetic interactions, between the genomic inheritance and the environment, which are all constrained by a biological, sensorimotor substrate. Thus, sensory disorders result from interactions between the developing physiology and the multimodal sensory experience, so their consequences are equally crossmodal across development: disability in one unisensory system will affect all other sensory channels, and vice versa. It is therefore important to understand normal development and its pathology.

Touch and chemosensation might be the first to develop. The foetus already responds to trigeminal stimulation, which is mature at about 7 weeks of gestation. Broadly speaking, the cutaneous touch anatomy and the cuteanous tactile function, as well as the olfactory system anatomy and its function appear to be developing early on during gestation, prior to the auditory and visual systems. This precedence of touch is also noticed at the connectivity level (Kostovic and Rakic, 1990): thalamic connections to the transient foetal "subplate" zone occur earlier below the somatosensory than the visual cortex, meaning that somatosensory inputs are there first, even at the level of the cortex. Furthermore, neonatal studies showed that responses to pain are very mature early on in life so regions encoding affective and sensory components of pain are already well activated in newborn babies.

The significance of touch throughout development has been demonstrated by a variety of studies. For instance, it was shown that maternally deprived macaque infants retain preferential proximity to a cloth looking like a mother they can touch, rather than to a wire than can give food (Harlow and Zimmerman, 1959). More recently, Field et al. (2000) showed that grooming and massage was good for newborn babies and that Westerners in particular were "touch hungry". Maître et al. (2017) measured somatosensory responses using EEG and predicted the degree of atypical attenuation of sensory evoked potentials (ie responses) as a function of the kinds of tactile experiences which the newborn or preterm baby has in the neonatal intensive care unit. This degree appeared to be predicted by the number of positive/noxious tactile experiences: the more positive experiences – chances to interact with parents, soothing, stroking, the less atypically attenuated the sensory responses were; on the other side, the more noxious experiences, the more atypically attenuated the response was.

Regarding chemosensation as well, Schaal and colleagues put forward the transnatal chemosensory hypothesis: they demonstrated that newborn babies and newborn animals have some marked preferential orienting responses to specific odorants (the mother's amniotic fluid or colostrum, as opposed to a stranger's one). They argue that it is the *in utero* experience of the chemosensory environment that prepares the infant to preferentially orientate in an adaptive way in the outside postnatal environment.

Yet, very little amount of research on tactile or olfactory senses is done, compared to visual and auditory, and this might be due to the fact that for the latter, new techniques are available in infants.

One particular feature of interest in understanding the development of an integrative multisensory system is the cross-modal binding problem: how does one learn to integrate the information coming from different sensory channels ?

To this purpose, Bremner et al. (2008) did research on the babies' ability to localise tactile stimuli. Before six months of age, babies experienced stimuli physically first, and move the stimulated limb before even watching it. Whereas after ten months, they watched first where they were touched, before moving. Therefore, there seems to be crucial changes in the ways touch interacts with other senses during this timeframe. Babies seem to learn around this period that the visual world they see is somehow linked to the tactile world of the body, which they have experienced *in utero*. This was further confirmed by an experience showing that four-month-old babies, upon feeling a touch on their body, do not relate that to a place in the external world (left/right for instance). Indeed, at that age, they do not make any mistake in localising the stimulus, for instance on the foot, even when their feet are crossed. Conversely, six months old are duped by the crossing of the legs and make mistakes in correctly localising the stimulus, thus suggesting that they already expect the stimulus to be on a particular place in the external visual space, which the four months old don't (Beguma Ali, Spence and Bremner, 2015). Therefore, it almost seems as there are completely separate sensory worlds for touch and vision in the first months of post-natal life.

Such complex crossmodal integration requires synthesizing different spatial and temporal information, learning different latencies and acuities of perception: first the vision, then the sound, the smells arriving even later in an even less precise format. This is complicated by the fact that all sensory channels move relatively to one another (the eyes and the hands for instance). Therefore, this complexity creates a hard problem for sensory development, which is likely to be susceptible to disorder. Any perturbations in the way in which we can respond to these kinds of sensory challenges in the early development are likely to be influencial downstream in the way in which we learn to make links between the senses. Brigitte Röder's work with blind adults demonstrates that developmental vision is necessary for the automatic referral of touch to external space – congenital blind adults do not show indeed any effect on the cross-hand experiment, they are just as accurate. This seems to indicate that they do not refer touch to a place in the external space, as sighted adults do. In addition, Monica Gori's work with blind children showed that visual impairments lead to poorer tactile, proprioceptive, auditory spatial abilities, probably because in typical development, vision calibrates the ways in which the other sensory information works – giving spatial acuity to spatial tasks.

Therefore, multisensory impairments are implicated in a wide range of neurodevelopmental disorders: developmental dyslexia, autism spectrum disorder, attention deficit and hyperactivity disorder, developmental coordination disorder. Only very recently, attention was given to this, to understand the ontogeny of sensory impairments in developmental disorders. For instance, Ryan Stevenson's work on audiovisual integration in ASD, demonstrating that children with ASD have different temporal binding windows for auditory and visual stimuli, or Carissa Cascio's work, finding atypical body representations and multisensory interactions in perceiving one's own limbs in ASD. So both unisensory and multisensory deficits are likely to be developmentally related, with impacts of impairments downstream from one to the other. In these disorders, there are patterns of hypo/hypersensitivity to particular sense modalities indicative of multisensory impairment, and probably linked to a difference in the balance or weight of salience given to a particular stimulus. So sensory and multisensory dysfunction may be a particular vulnerability, risk factor, in neurodevelopmental disorders.

Gaps in research and proposed topics to be funded

The “other senses”, other than vision and audition, are understudied. Touch, chemosensation and interoception need more research, given their wide-reaching functional roles, developmental primacy and multisensory interactions.
Multisensory processes are also of key relevance for understanding sensory dysfunction, as virtually no perceptual act is unisensory. Multisensory functions are a product of development, and their dysfunction needs to be considered developmentally.
Therefore, topics to be funded are:
- the multisensory dysfunction and multisensory aspects of disorders of sense organs;
- the atypical and typical development of multisensory processes;
- the capitalisation on intact senses to optimize and calibrate multisensory interactions (enrichment of stimuli and cues from intact senses, as in Monica Gori’s work);
- basic as well as applied research, especially given that so little is known about chemosensory, somatosensory functions in typical development).

Interaction between sensory organs and the central nervous system

Andrej Kral, Hannover Medical School, Germany

Hearing loss can be seen as a “growing epidemic” problem: in 2018, 466 million people suffer from a hearing loss requiring treatment, and they are predicted to amount up to 900 million people in 2050. It is therefore an important medical issue. Furthermore, in the context of an increase of cognitive decline with age in Western societies, leading to immense healthcare expenses, it is important to target the available modifying factors, and hearing impairment in midlife periods is indeed the largest modifiable risk factor for cognitive decline.

Mechanisms of cochlear implants and their interaction with the central nervous system

The development of cochlear implants had a revolutionnary consequence on orientation and communication: thirty years ago, doctors would have considered a hearing loss beyond 90 dD irremediable; now, a cochlear implant can restore hearing to various degrees.
Cochlear implants have an external part, with a microphone, a battery part, electronics and a transmitter coil which generates the magnetic field providing energy for the internal part that is inside the body, a receiver coil, receiving this energy and the signal that controls it, and then there is a connection into the inner ear where the cochlear implant is located. The electrodes on the implant are used to stimulate the surviving auditory nerve (since sensorineural hearing loss is mainly due to a loss of hair cells, and nerve is often preserved). Cochlear implants lead to remarkable speech performances – measured by the percent of correctly perceived sentences, up to 2 years after implantation. 90 to 100 % of patients at 2 years understand 90 to 100 % of sentences. In addition, the number of implanted subjects raises exponentially: next year, it is expected that a million patients will be implanted (Kral et al., 2016, Lancet Neurology).
Furthermore, such an implant provides the possibility to investigate sensory loss in parallel on human and animal models, allowing to investigate the development of language, cognition, higher functions or perception, so not only is it a hearing aid device for patients, it is also a scientific tool.

The mechanisms of a cochlear implant rely on its capacity to mimick the different codes of the inner ear, namely, the place coding, known as tonotopy, and the temporal coding.
Tonotopy is the fact that a stimulation with different frequencies activate the cochlea in different parts: fibers that innervate the apex of the cochlea are activated by sounds of low frequences and fibers that innervate the base respond best to high frequencies, like a series of bandpass filters. The cochlear implant can mimick this by placing electrodes at different positions along the cochlea and differentially activating them. At the moment, conventional methods such as monopolar stimulation need

improvement as their place coding is not precise enough (this can be measured as sound pressure level, or current level, as a function of position along the cochlea). Various techniques exist to limit the spread of excitation within a critical band, but they are not used in clinic yet (Hartmann and Kral, 2004, SHAR).
Temporal coding represents the firing of the auditory nerve, which follows the frequency timecourse of the acoustic stimulus. A tone is immediately followed by a response of the nerve fiber to it, with action potentials appearing in certain temporal distances from each other. They are phase locked to the stimulus, and this is an information that the brain can use. The quality of their phase-locking can be computed from a period histogram and quantified by a synchronization index (a synchronization index of 1 would mean that all spikes occur exactly at the same point in the stimulus cycle). An acoustic cochlear implant could thus achieve maximum values of 0.85. However, electric stimulation does even better and can reliably transmit temporal information too (Tillein et al. 2015, Hear Res.).

The topics for funding in the field of cochlear implants are therefore:
1) research to understand and adapt to the variability in the morphology of the cochlea in humans and animals, which is probably dependent on the size of the heads, and the differences are huge, up to 30% variation;
2) ways to prevent impact of implantation trauma. Presently analytical models of the shape of the cochlea are developed, in order to predict in each individual subject with clinical imaging how large his cochlea is and where to locate the implant
3) combined cellular therapies, where cellular genetic therapy could be used with implants that would hold the cells;
4) investigation in more therapeutic approaches, in particular for the less frequent cases where the auditory nerve is damaged – one might consider central auditory implants, such as penetrating high-density electrodes, new brain/prosthesis interface (nonpolarizing electrodes), or approaches with patterned microstimulation
5) improving channel separation and reducing current spread
6) using implants as biomarkers, for diagnostics of cochlear “health” (hair-cells) and the surviving auditory nerve.

The developmental aspect of hearing loss.

Cochlear implants also allow investigating the developmental aspect of hearing loss. Indeed the period of language acquisition is critical for the therapy of hearing, in children born deaf. Inborn hearing loss is one of the 3 more frequent inherited disorders in mankind. Therefore, the question is to understand how this population can benefit from the implants.
Notably, it was observed that earliest implanted children reach 100 % correct bisyllabic words recognition after four years of implant use, while later implanted children reach only 70% or less and hardly improve later. Considering both groups have the same electric hearing threshold, they both hear, but the later implanted group has troubles in decoding complex sounds. Therefore, it means there is a critical period for the therapy of hearing. However, differences in synaptic plasticity do not explain such a discrepancy between the groups. Of course, synaptic plasticity is higher at a juvenile age and children learn better, easier, and faster. But synaptic plasticity still exists at the adult age, although it is reduced compared to the juvenile age. Thus, this can not explain the critical nature of the sensitive period because this would only suggest that late implanted subjects simply need more time to improve, when in fact they never achieve hearing improvements, even many years after the implant.
To explore this critical period, the use of a white cat model has been very helpful. Since Darwin, congenital deafness is known to be much more prevalent in blue-eyed white cats. Moreover, generally speaking, higher mammal models are important as there are quantitative (the size) and qualitative (much more inhibitory neurons) differences in a mammal’s brain such as a cat’s one, compared to one of a rodent. Congenital deaf white cats lose hair cells before the onset of hearing but they have an excellent preservation of spiral ganglion cells, so they can be equiped with a cochlear implant and their

auditory system's function can be tested. They can be trained to respond to acoustic stimuli, which they learn quite fast, and early implanted cats do a little better than late implanted cats. Furthermore, it is possible to investigate the brain, map out the cortex and look for electrophysiological correlates of responses. Thus, we know that even deaf cats show responses in the cortex, meaning that the auditory path develops and is in a way functional even in the absence of hearing experience – this development of the auditory path is genetically determined, which is explained by the fact the auditory pathway has to be ready when hearing starts. However, if a cochlear implant is placed and stimulated chronically during 2, 3, 5 months after early implantation, there is a slow but important expansion of the responding area, increased amplitudes and maturation of response, with more diverse responses to different types of stimuli. There is, therefore, a maturation of the auditory cortex due to auditory experience. However, later implanted animals show less effect of the stimulation, confirming there is a critical period in this animal model as well, similar to what is seen in children (Kral and Lomber, 2015, Curr Biol).

Both in deaf children and in the cat model, a mechanism other than plasticity needs to be found to explain this critical window. And this might be synaptic pruning, the physiological selective elimination of neurons and synapses around the ages of 4 to 6, to improve computational power by losing unused neuronal connections. Indeed, in deafness, most of the synapses in the auditory cortex are not used, and thus might be suppressed, explaining why a later stimulation of the auditory system would then lead to very poor results (Kral and O'Donoghue, 2010, NEJM). To test this hypothesis, the cats' functional cortical columns' activity was analysed, and based on cortical layer and time, this allowed predicting functional connections between layers. In addition, it appeared that in deaf cats, there was a functional empoverishment, with much less activity in the auditory cortex. The synaptic pruning that happens in the auditory cortex of cats might correspond to approximatively 36 months in humans, explaining why later cochlear implants for congenital deafness are not so efficient.

This discovery further highlighted the role of the very deep layers of cortical columns in auditory processing. Hearing is processed at a cortical level by primary and secondary areas: primary areas feature maps that analyse the features of the sounds – which frequency, intensity or location for instance, while secondary areas analyse the context and make predictions of objects based on this context. Both are in tight interaction in a functional unit, whose top-down connections might be compromised by synaptic pruning in congenital deafness. Therefore, a double recording in primary and secondary auditory areas in the brain of cats was done during the application of a repetitive stimulus. Two responses were recorded: first, an immediate time-locked response, then another, 150 ms later, that was not in phase with the stimulus. The first one, the "evoked response" is the consequence of the thalamo-cortical stimulation. The second one, the "induced response" is the consequence of the integration process, the interaction of the sensory input with ongoing activity of other cortical influences, cortico-cortical interactions, including cortico-cortical feedback and therefore is considered to be a trace of top-down influences on bottom-up processing. These later signals might thus be more important than the first ones. After computational extraction of the expected evoked signals from the total signal recorded in the auditory areas, it is possible to isolate the induced part of the signal. Thus, it was shown that although the evoked part was relatively similar in deaf and hearing cats, there was an important difference in the induced signal, which was nearly absent in congenitaly deaf cats. This means that deaf cats are not able to perform the corticocortical processing and the topdown effects. In conclusion, when the brain is not developmentaly trained, it is not able to incorporate context and other cortical activity with auditory processing, not bringing any substrate to prediction-error based learning, thus closing the sensory period (Kral et al, 2019, Ann Rev Neurosci).

In summary, congenital deafness delays cortical functional synaptogenesis and later eliminates too many cortical synapses, leading to dysfunctional cortical networks - both within cortical columns and between cortical areas. Auditory deprivation leads to smeared cortical feature representation, complicating discrimination of complex sounds. Cochlear implants allow auditory maturation and compensate the developmental effects of deafness. In congenital deafness, therapy has to take place

within an early critical period – the earlier, the better. The mechanisms for the critical period are due to synaptic pruning in absence of hearing. Dysfunctional cortical microcircuits prevent the possibility of integrating bottom-up and top-down processing, compromising learning based on predictions. Finally, cross-modal reorganization in congenital deafness is specific to cortical areas and likely does not close the critical period.

Challenges and proposed topics for funding

The main objective in the field is the development of personalized medicine, giving to each patient a precise diagnosis and adapting a unique set of interventions. Indeed, there is still a huge variability in outcomes (up to 5 years) after cochlear implantation. To implement personalized medicine, it is crucial to take into account the factors already known as being important (genetic, environmental, anatomic, socio-economic, etc).
When looking at implanted children in terms of working memory, factual memory or novel problem solving, children implanted can be as good as the best hearing children. However, there is still an important variability in functional scores that can be explained by an equivalent variability, not only in hearing, but also in non-auditory functions and their connections with auditory areas. Thus, deafness needs to be considered from a connectome perspective.
In addition, one can ask whether it is possible to repair cortical circuits, or repair cortical circuits through microstimulation (Voigt et al, 2018).

The proposed topics to be funded are therefore:

- the consequences of sensory loss for the central nervous system;
- the development of objective biomarkers for central nervous adaptation and maladaptation following sensory loss;
- innovative solutions for restoration of central nervous function following sensory loss;
- innovative solutions for restoration of sensory function using multi-channel stimulation approaches;
- the cortical multi-channel microstimulation for restoration of physiological activity patterns following sensory loss;
- individual variations of sensory organs with focus on prosthetic restoration of sensory function;
- uncovering multifactorial dependencies for predicting outcomes following neurosensory restoration (prospective and retrospective studies on large cohorts).

Disability rehabilitation: Neuroprothesis with a focus on cochlear implants

Tobias Moser, University Medical Center Göttingen, Germany

When compared with the visual system that is part of the brain, the ear is in the peripheral neural system, and thus gives more room for rehabilitation therapies, as it might be a bit more isolated. However, it is not possible to generate hair cells yet, as it is with photoreceptors. Both the eye and the ear share the concept of a (partial) immune privilege, as they are, more or less, separated by membranes from the blood. In either cases, gene therapy is increasingly researched, but this applies to only a few genetic sensory disorders, and one needs no to overlook the importance of treatments that do not target specific genetic etiologies, such as cochlear or retinal implants.
Therefore, the current presentation will address the unmet needs to improve sensory rehabilitation beyond the current state of the art.

Sensorineural hearing impairment

Hair cells regenerate in birds, but not in mammals, where no treatment is available yet for hearing dysfunctions, whether it is gene therapy, pharmacology or cellular therapy. However, some studies showed it was possible to partially restore hearing by transfecting genes of synaptic proteins required at the hair-cell synapse. Indeed, the AAV-mediated otoferlin gene replacement in a rodent's model that was knocked-out for otoferlin led to restoration of hearing. Such experiments hold good promise for translation to clinical trials.
The majority of the profoundly hearing impaired and deaf people benefit however from cochlear implants, and the main issue is the quality of speech recognition by the users. This depends on our understanding of the tonotopic and temporal coding of the neurons receiving the information from the cochlea. Although the tonotopic organisation of the cochlea is known – a circular stair with each step being a frequency, from 20 kHz to 20 Hz, the performance of central prostheses remains still very poor compared to peripheral ones, as the neuronal coding is not entirely elucidated, and the way we print electrical stimulation to the neurons demands implementation.
Efforts to further improve the cochlear implant include advanced analysis, preprocessing of acoustic information, biomimetic coding, integration of multiple devices, directional hearing, mimicking spike rate adaptation… Connectivity and signal to noise improvement require bluetooth communication with phones, as well as FM receivers. Furthermore, the improved coding of fine temporal information demands ameliorated cortical implants. But one major bottleneck subsists nevertheless: how to improve coding of spectral information? Conceptually, placing the electrode exactly where the neuron sits would actually achieve natural hearing. This is why efforts are made to bring more focal stimulation to the neuron, through multipolar stimulation, current steering, electrode-neural interfacing, or even optical stimulation, as it is possible to confine light better than electric current. Importantly, it is crucial to preserve as much as possiblethe original cochlear structure and function during implantation, leading to less traumatic combination therapies. In addition, adding glucocorticoids on the electrodes, or improving the flexibility of the electrodes might reduce the implantation trauma. Overall, the aim is to preserve low frequency cochlear range with electrical hearing for the base of the cochlea, and this can be achieved in hybrid electro-acoustic stimulation devices.

Implementation of cochlear implants with microLEDs

One technological implementation done by Prof. Moser's team was to use microLEDs to improve the resolution of the stimulus. About a hundred microLEDs, each being 15 microns in size, fitting on a fingertip, are put in place around this tonotopic map. Thus, trying to map the sound frequency is amounting to activating a specific microLED at a particular place.
As a way of comparing, an electrical implant would be equivalent to playing the piano with the fist, while the microLED optical stimulation technology might refine the approach, by bringing back more focal stimulation closer to physiological hearing. The motivation for such an endeavour is great, as current devices allow hearing, but still at a rather coarse level, making sound recognition difficult in noiser environments, such as group conversations on a big background noise, forcing hearing impaired people to resort to lip reading or other cues to make sense of what they hear, despite their current devices. The appreciation of music is also complicated, as mainly strong beats are understood, due to their easy temporal coding.
This is why optogenics were introduced in the field. Channel rhodopsins, which are light-gated ion channels that can respond to a light stimulation, appear as essential tools to control the excitation and inhibition of neurons. In a gerbil model, clinician scientists injected a viral vector transporting the channel rhodopsin gene, associated to a specific promoter of the targeted cell, the bipolar spiral ganglion neurons, which expressed the channel rhodopsin in the soma and in its neurites. A demonstration of the real efficacy of light stimulation was obtained by inserting an electrode array in the midbrain auditory layers that correspond to the tonotopic cochlear layers, and observing their response to various stimuli. For acoustic hearing, the superficial layers of the midbrain were

responding the best, and higher frequencies were closer to the base. This allowed for a calibration of the system and measurements of the stimulus' spread in the cochlea, leading to benchmark frequencies resolution to compare artificial stimulation with natural hearing. In this setting, natural hearing appeared very well tuned according to its frequency. Then placing optical fibers into the apex, the low frequency part of the cochlea, or the midfrequency part then the high frequency part, a very similar spread of excitation as in natural hearing was obtained. When the spread of excitation for low and modest stimulations was compared between modalities, no statistical difference was found between sound and optical stimulation. Overall, optical stimulation achieves better frequency resolution than electrical bipolar stimulation, which itself was more performant than the monopolar one.
Following these electrophysiological recordings, the next step was to prove that such light stimulation could lead to sound, prove that it could be perceived as a sound stimulus by the animals. They were therefore conditionned to leave a platform when a stimulus came in (either acoustic or optic), which the animals learnt over a few days to reach performance over 80% in either modality, meaning optical stimulation of the cochlea could be used as a sensory cue to do a behavioural test. Finally, the question of how similar the perception of a light stimulus to an acoustic sound was addressed. This has been explored by testing the animals' ability to generalize their learning, from light percept to acoustic stimulation and vice versa. When stimulated by light in one ear, and then later with acoustic stimulation in the other ear, they did not require more learning, they did the task right away, thus proving their light-hearing percept could generalize to acoustical hearing.
However, one main issue initially arose: the timeframe of ion channels rhodopsin to turn off and on according to light switching was a millisecond, much too slow compared to the auditory nerver fibers' precision when locking their spike to a stimulus, under the millisecond. This led to the development of ultra-fast opsins, which were tested by evaluating how often a unit responded to light pulse as a function of frequency. In addition, it appeared ultra-fast opsins such as f-Chrimson had a time constant of deactivation in the range of 2 milliseconds, and Chronos opsins achieved even better, below a millisecond in deactivation speed.

Such work needed of course many transdisciplinary collaborations, in particular with people who specialize in microsystems engineering and semi-conductor lightening. This led to the development and insertion of flexible microLED cochlear implants, which can even be placed in the smallest cochlea, the one of the mouse, and is sufficiently soft to go across different turns. The results are therefore very promising, and are ready for implantation.

Certain controversies need however to be mentioned: optical stimulation without opsins, the concept of direct infrared neural stimulation, has been aluded in the scientific literature. The delivery of a very brief, high-energy light pulse into the cochlea was suggested to be sufficient to stimulate the spiral ganglion neurons, without needing gene therapy to introduce channel rhodopsins. However, infrared light might in fact lead to a partial click in the air, which is actually heard by the the neurons. Moreover, other studies never reproduced the results after having properly deafened the cochlea. Nevertheless, this brought the idea of using the opto-acoustic effect as a hearing aid based on optical light pulse delivery to the cochlea.

Balance restoration

Likewise, cochlear neuroprostheses were considered for balance restoration. Bilateral vestibulopathy is indeed a very disabling condition, where there is a difficulty stabilizing the gaze while moving, due to an impaired vestibulo-ocular reflex.
So it was thought to use cochlear implant technology combined with motion sensors and processing information on motion to drive the semi-circular canals that give information on the three dimensional movements to restore the vestibular ocular reflex and improve acuity of vision when walking. In addition, indeed in a lab setting, research groups in Geneva and Maastricht achieved these objectives

of improved acuity with vestibular implants. However, this implant has not been used outside a lab setting yet, as it inactivated at home.

Gaps in reseach and proposed topics to be funded

There is a need to improve sensitivity, which is one of the issues there currently is in optogenetics vision restoration. There is a need for more light and to palliate to this issue, people test chimeric proteins associated to metabotropic receptors, whose signaling cascade would be more performant to transduct the signal after a light stimulus.
Non-genetic approaches to restore vision using photopharmacology are also considered.
In other fields of neuroprostheses, fantastic work is done with motor prostheses, with groups working on somatosensory feedback, increasing the precision of the grip of the prosthesis with feedback from the somatosensory pathway to the brain and then back to the prosthesis.

Overall, using molecular physiology and genetics led to great steps forward, great successes already in the field of hearing, while there is still potential for balance and somatosensation. There are proofs of concept and clinical trials for vision restoration but not for hearing yet, and to keep improving our understanding, there is a need to consider not just the sensory organs each at a time, but the entire multisensory system. Therefore, one needs better animal models, early and improved diagnostics, genetics and improved clinical phenotyping.

Disability rehabilitation: Molecular and cell therapies

Francine Behar-Cohen, INSERM UMR 1138, Paris, France

Common challenges faced by visual and hearing systems, in particular the prevention and targeting of environmental risk factors

The visual and hearing systems share common properties: they are both in contact with the outside environment, they are both small organs, complex, compartmented, comprising neuronal tissue and fluidic environment, and these local micro-environments are more or less privileged immunologically. Barriers protect both organs and the systemic routes are not optimal, making systemic drug delivery to these organs a major problem. However, compared to the brain, there is a direct access allowing for local delivery. Both the eye and the ear are exposed to environmental burden (light, noise, particles, and allergens) and in these organs, there are diseases associated with pathological ageing, genetic diseases, but also complex, multifactorial diseases. However, the main difference between the visual and hearing system is the complexity of the visual signal and the difficulty to develop a visual aid, as it is already the case for cochlear implants in hearing loss. In addition, good animal models are difficult to find for visual pathophysiology, due to the differences in macula (the rodents have none), in vasculature (it is different in the rabbit and in the human) or in immunity (different in any animal, including between non-human and human primates), for instance. Nevertheless, the eye can benefit of much more developed local delivery drugs.
Regarding the causes of blindness, cataract is prevalent in the world, especially in developing countries, whereas age-related macular degeneration (AMD) and retinal disease are the most frequent diseases in Western societies, representing up to 50% causes of blindness. Regarding retinal disease, AMD is the main cause of blindness, followed by diabetic retinopathy and glaucoma, and in 2040 the number of individuals in Europe with early AMD is predicted to reach 20 million and for late AMD, around 5 million, thus representing an important health problem. Although the number of patients with visual impairment due to diabetes is not going to increase in proportion, the number of diabetic

patients itself is going to significantly increase all over the world, and also in Europe, so it will increase the overall number of diabetic retinopathies.
Often neglected, myopia is becoming a major problem for young individuals. Already very prevalent in Asia, where in some countries like in Korea, it reaches 94% of the whole population, it is also increasing in Europe and presently, we witness for the first time, a higher number of myopic than non-myopic individuals. In 2050, 50% of world population will be myopic. Myopia is associated with macular complications, called myopic maculopathy, leading to blindness and such myopic-related blindness is predicted to soon affect almost 20 millions of people worldwide. Therefore, many efforts are done to identify factors responsible of this ocular axial length change. One of the major factors having been recognized is the lighting environment, which plays an important role: doing the same activity but being outside decreases the evolution and the onset of myopia for children. At a time when new lighting systems (i. e. LEDs) modify our dayly environment, spectral composition of the light and the circadian rhythm are modified, playing a role in the occurrence and progression of myopia.
Likewise, in hearing loss, there are frequent but actionable risk factors that can be controlled (such as noise). Accessible preventive strategies might be more cost-effective than complex replacement and treatment strategies, which remain necessary. Therefore, both visual and hearing diseases affect large populations, are multifactorial and involve complex genetic predispositions, ageing, environmental factors (noise, light, food, pollution, allergens, toxic agents, stress, shift work). There is therefore a crucial need to act on their “exposome”, to control causative or aggravative factors. Indeed, only a limited number of diseases are simply explained monogenetically: they are rare diseases, affecting small number of patients, although they can be models for more frequent ones.

Major advances in visual rehabilitation

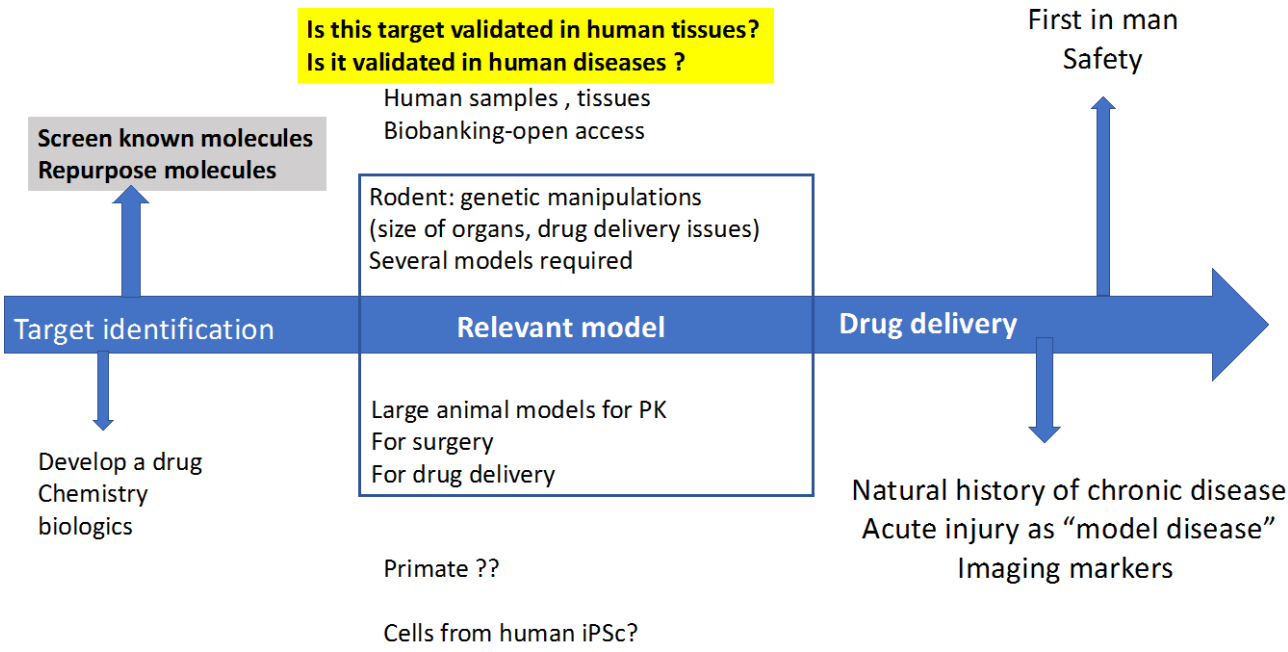
First, the most striking advances come from microsurgery. These advances made possible other therapeutic innovations, like the development of local therapies to treat common retinal diseases, gene therapy and cell therapy, which all need complex surgical procedures. Indeed, eye surgery improved, with miniaturization, simplification, better visualization, and collaboration with industry and doctors. For example, cataract surgery has the highest rate of success amongst all performed surgeries in humans. In addition, the other major advance has been the revolution in imaging technologies. This is probably the reason why in the eye so many therapies were developed: because we can see what we are doing, we can evaluate and quantify the effects of our treatments. For instance, with spectral domain coherence optical tomography, it is possible in a few seconds, without dilating the pupil, to see the morphology of the retina, the macula, like in a retinal histology section. However, this is not enough, changes at earlier time points need to be detected, before irreversible cell death. Should neuroprotective or preventive treatments become available, there is a dire need to be able to evaluate progression of the disease and the effect of treatments and validate correlations between imaging and functional endpoints for clinical trials, or else it will not be possible to test and evaluate therapies in humans. So many efforts focus on improving imagery at the level of the cell, adaptive optics for photoreceptors and other strategy in development, such as transcleral optical phase contrast imaging to image other cell types, like retinal pigmented epithelial cells that cannot be imaged by any other means so far.
More generally, in multifactorial diseases, it is difficult to find one simple etiological treatment. There are three main mechanisms leading to loss of vision: macular edema, cell death, abnormal healing (glial and vascular proliferation). Inflammation and oxidative stress are in the center of all these processes. Macular edema, the accumulation of fluid in the macula, leading to visual distortion and scotoma, is occurring in almost all retinal diseases, such as diabetic retinopathy, wet AMD, vein occlusion, even in retinitis pigmentosa where macular edema develops at the last stage (Daruich et al, Prog Retin Eye Res, 2017). Currently, macular edema is the one and only sign and symptom that is accessible to treatments. Anti-VEGF proteins or glucocorticoids injected repeatedly in the vitreous, are

not curative of the disease but they reduce edema and have changed the fate of disease in millions of individuals.
This treatment, stemming from a fruitful collaboration between technological and biomedecal fields, helped 90 % of wet AMD patients (representing 50 % of all AMD patients) to retain their vision after injection with anti-VEGF. From losing their vision in two years, the majority of patients maintain it. There is however, a high variability and only one third of the patients are really going to regain clinically significant vision, while 50% of the eyes need to be reinjected and still have persistent edema despite the fact they are injected optimally every month. In addition, diagnosis is still done when it is too late, after irreversible pathological changes already occurred. Thus, research is still needed in this field. Furthermore, in diabetic macular edema, there is an effect of anti-VEGF treatment, but it requires extremely frequent injections and again here, 40% of the cases do not reach five letters of improvement. Similar results have been obtained using slow release glucocorticoids in diabetic macular edema, but they do not work in AMD.
In summary, local intraocular treatments have revolutionized the management of these diseases (biologics or corticoids repurposed, slow release systems), but it is still not perfect, as not all patients respond to the treatment, and important gaps remain to be solved. Indeed, results are much worse in real life studies, and this might be due to under-treatment and the constraints pertaining to local and slow delivery, as well as the need of having the drug in the eye permanently. Another problem lies in the fact that there are no biomarkers to select patients amenable to specific treatments. So there is a high cost for the health system (with 1000 € per injection) and insufficient benefits for patients. There is therefore a need for personalized medicine, to identify those biological and imaging factors that could tell which patient will benefit from one treatment or another.
Of course, finding other targeted treatments is another important challenge. For instance, Prof. Béhar-Cohen's team focused on understanding why corticosteroids were not effective in wet AMD and are aggravating it, despite the fact it is an inflammatory disease, with edema and neovascularization that one might expect to respond to corticosteroids. Knowing that when corticoids bind to glucocorticoid receptors, they are anti-inflammatory, anti-edematous and anti-angiogenic, and that when they bind to mineralocorticoid receptors, they induce inflammation, edema and fibrosis, her team used an antagonist of mineralocorticoid receptors in transgenic animal models, and also in patients with wet AMD resistant to anti-VEGF. They added oral spironolactone and during the combination of treatment, the patients improved their vision and restored their retinal anatomy, and there was a recurrence when the treatment was stopped. Her team is now working on slow release systems to deliver the drug directly into the eye so that the patient can have one treatment every few months (Zhao et al, Nat Comm).
Unfortunately, despite transient improvement with anti-VEGF treatment, wet AMD will ineluctably lead to cell death and fibroglial sacring, which cannot be treated yet. Regarding cell death, there are however, general mechanisms that could be targeted for many different types of neuronal cell deaths. For instance, iron toxicity is known to be associated, in the brain and the eye, with many retinal diseases, diabetes or AMD. In addition, it is possible to use human model of diseases, such as retinal detachment, where the acute detachment of the neuro-retina is associated with the death of photoreceptors through a variety of mechanisms: necrosis, apoptosis, autophagy, necroptosis, ferroptosis, so it can make for a good pathophysiological human model. If these patients keep the detachment for more than five days they are going to lose definitively their vision, even if they are re-attached. Taking the fluid of these patients that have been detached as compared to patients that have not been, and comparing vitreous as well as subretinal fluids, showed that there was an accumulation of iron. More importantly, the visual recovery after surgery was correlated to the level of iron – an increase of iron led to poorer visual recovery. Therefore, an animal model modified genetically to overexpress transferrin (binding to the iron) was developed and showed that it led to protection of the photoreceptors. This strategy is now in development to chelate iron through transferrin for patients with retinal degeneration (Daruich et al, Sci Adv, 2019).

Nevertheless, important gaps remain: there is no treatment for dry AMD (all anti complement therapies have failed), no treatment for retinal cell death in ischemic diseases of sensory organs, no treatment for toxic or traumatic injury (ear and eye) and no treatment for ganglion cell death (glaucoma, diabetic).

How to improve models and their translationability

Numerous drugs are efficient in models but there has been no translation in humans so far. It is therefore important to re-think drug development strategies. Target identification and development of a drug require intensive chemistry and biological research that might take twenty years. On the other side, it is possible to test molecules that are already known, in order to repurpose them. In either case, the major bottleneck is whether these targets are validated in human tissues and human disease. In addition, this needs to be known quickly for any drug development because if there is no validation in human, this drug development in animals becomes pointless and needs to be stopped. Validation in humans requires performant and open biobanking, with human samples of ocular tissues.
Regarding the currently available models, rodents are used because they are easily available, cheap and can be genetically manipulated but they are very small, with a small eye in the range of the millimeter, on which it is difficult to perform surgery. Moreover, it is difficult to know if the drug is achieving its target within such a model. Larger animal models, such as non-human primates, might be better for pharmacokinetic studies, surgery and drug delivery but they still present problems for translationability: although primates have a macula, it is different from the human one and the immune systems are different in primates and humans. Another solution would be to use cells from human iPScs. Overall, there is a need for collaborative work to define different types of models that could answer different types of questions and validate these models. Drug delivery remains a major issue, both in humans and in animals. Thus, first-in-man safety trials as well as validation of the efficacy of treatments in humans are direly needed. Therefore, a better understanding of the disease's natural history and imaging markers are crucial. Working with agencies so that they accept these imaging markers as validating markers and not just wait for functional efficacy is thus an important step to take. Therefore screening small molecules, repurposing known drugs, reformulation for ocular / ear delivery, and methods to evaluate the effects in relevant models (animal but also cellular) are recommended.



Different available therapies: viral and non-viral gene therapy, and stem cell therapy

Gene therapy is particularly adapted for retinitis pigmentosa, affecting 1.5 million patients worldwide, and a major cause of total blindness. Nevertheless, there are numerous genes leading to retinitis pigmentosa, other affecting also the cilia, leading to retinal dystrophy and deafness as well, and many efforts are directed towards identification of unknown genes. So viral vectors are probably good candidates to deliver these genes, in the case of a target cell where gene replacement and augmentation are required. They have been so far injected subretinally, in many clinical trials, amongst which two are promising. First, the Luxturna treatment, FDA-approved, which provides a functional RPE 65 gene in congenital Leber amaurosis. It leads to an increase in the navigational ability in dim light conditions only in half of the patients, and improvements might not persist long-term, while two patients experienced permanent vision loss. It could treat about 60 000 patients in the world, probably two thousand in Europe, but the price is very high. The other clinical trial using viral vectors is the phase 2 trial for choroideremia (CHM), an X-linked chorioretinal dystrophy characterized by progressive degeneration of the choroid, retinal pigment epithelium and retina-mutation in REP1 gene. It seems that visual acuity in the 14 treated eyes was increased as compared to the controls, in a cohort of predominantly late-stage choroideremia patients in whom rapid visual acuity loss would ordinarily be predicted. However, a phase 3 trial is needed to confirm these results.
There are however important gaps that still need to be overcome: subretinal injection remains at high risks and low reproducibility, it is difficult to evaluate pharmacokinetics and pharmacodynamics, the delivery of vectors and their production needs to be improved and has a high cost, and it is limited to small number of patients with this specific genotype. In addition, efficacy so far has been limited and the duration of efficacy is not known. Therefore, it is not adapted for large number of patients and for the production of secreted proteins.
Gene editing is a recent topic of research, at its early stage, and will not be addressed in this presentation.

If for gene replacement, in the setting of personalized treatment associated with genotyping viral vectors is appropriated, when gene therapy aim is the sustained production of secreted therapeutic proteins, for instance anti-VEGF, they are not the optimal option. Indeed, it is not recommended to have a permanent definitive expression of anti-VEGF the eye, and there is a need to be able to evaluate the dose and have an efficient exit strategy. In addition, the cost of 5 millions patients receiving subretinal injections of viral vectors itself is redhibitory.
Non-viral vectors appear as an interesting possibility for a large number of patients, with better cost, efficacy and accessibility, better safety of procedures, and the possibility of a temporary expression modulation according to clinical response. For instance, electroporation of plasmids in the ciliary muscle turns it into a biofactory, producing therapeutic proteins for a long term in the eye. This has already been used to target TNF to decrease inflammation. The device is a combination therapy of a coupled electric system with plasmid – combination therapy (Eyevensys). Preliminary results are encouraging. They should be confirmed in larger trials. So non-viral vectors are a good strategy, considering the number of patients that there are to treat.

Major advances made in the last decades to rehabilitate sensory organ disabilities: Focus on the visual system **GENE THERAPY**

To deliver genetic material to the tissues , viral and non viral vectors can be used

For gene replacement
- Limited number of patients
- Personalized treatment/ genotyping
- Reduce the frequency of sub-retinal procedures
- Permament expression

Viral

For sustained proteic therapy
- Large number of patients
- Cost/ efficacy/ accessibilty
- Safety of procedures and vectors
- Temporary expression/ modulation according to clinical response

Non-viral

Regarding cell therapy, a good example is the surgery of the corneal endothelium graft. When the cornea is blurred because of a pathological endothelium, which does not regenerate, this 20 microns thick layer of endothelium can be removed and replaced with the apposition of the endothelial from a dead donor, without any suture nor immunosuppression, thus taking advantage of the immune privilege of the eye. It is more complicated for retinal diseases however. Removing dead tissues is a first step, and then there is the possibility of introducing embryonic stem cells, cells differentiated from pluripotent stem cells, that can either be free, on a material or on a biologic membrane. Some under-retinal injections of free cells from human embryonics stem cells have been performed, but they were not completely conclusive and will not be discussed here.More recently there have been attempts to insert polarized cells on membrane or on biomaterials under the retina. One cell implant from a UK team was tested in two patients with late atrophic AMD. There was evidence that the cell survived and expanded under the retina. An increase in vision seemed to be reported in these two patients but one had severe retinal detachment and the other complications from the graft, needing to be suppressed by immunosteroids. Others have used parylene membrane with human embryonic stem cells, while using tacrolimus for systemic immunosuppression. The implants were stable in four of the five eyes tested, at 180 days; the implant is present and there is restauration of the photoreceptor compared to the beginning, so this might be working.
One important caution is to control the origin of stem cells as some cases of patients having become blind after inadequate procedures, were reported. There is therefore a need to regulate these cells and control their origin and how they are used.

Gaps and proposed topics to be funded

The gaps in knowledge that need to be overcome are:
- the immune response and immunosuppression issues,
- the risk of carcinogenesis with the iPSC
- the production, quality control, reproducibility, preservation of viral, non-viral and stem cells,
- the long-term survival of cells in a pathologic environment
- the surgical techniques; because we want to intervene earlier, the current high rate of complications can not be accepted in a patient that is still seeing.

- the strategies for late intervention
- the implementation of combination therapies, as they are a good option to work on the micro-environment to allow those cells to survive

Therefore, the proposed topics to be funded are:

- the role of the environmental burden on sensory organs (light, noise…), to define thresholds and strategies to protect the population;
- *in vivo* imaging technology, in the eye and possibly in the ear, at cellular levels, for earlier intervention and testing new drug; this would help surgery but also follow-up;
- the correlation between imaging and function to define and validate new endpoints for clinical trials (because for the moment, only late phase patients are treated)
- the improvement of drug, gene delivery and surgical techniques
- the better understanding of immune responses to therapies
- the standardization of models for translation to human diseases (primates are not going to answer all the questions; there is a need to understand in each animal model what can be gained and share this experience)
- the screening of small molecules and their repurposing for sensory organs with an adapted drug delivery for the eye, requiring a multidisciplinary network.

Social aspects ans health economics

Diego Santana-Hernández, CBM International, Canarias, Spain

CBM[1] is an international Christian development organisation, committed to improving the quality of life of persons with disabilities in the poorest countries of the world, in particular in communities where there is not the same public health network as in wealthier states. This presentation will therefore address the ways of supporting governments to develop ear and hearing care.

Ear and hearing care (EHC), as recognized by the World Health Organization (WHO) entails more than purely Ear, Nose and Throat (ENT surgery) approaches or audiology, and extends to all socio-economical and cultural considerations related to disability. CBM is presently reducing its portfolio, aiming to work with fewer countries but in a more intensely and comprehensive approach. This includes working with partners in service delivery, in national public health programmes, in community based programms and inter-regional programs like the WHO itself. CBM has been a non-state actor in official relationships with the WHO since 1989, and academically its main partner is the London School of Hygiene and Tropical Medicine. Their EHC work extends to other areas as well, including global advocacy alongside the World Hearing Forum, the Coalition for Global Hearing Health, Worldwide Wearing Foundation International, and helping to develop regional forums as well, in the Americas, East, Central and Southern Africa, and South East Asia, among other areas.

The social and economic aspects of hearing loss, and the way we relate to sound in everyday life are essential to be taken in consideration, from all perspectives: of the individual, the family, and the society. The person's experience is important as a hearing loss affects everything, from one's education and future work, to empowerment as a person and social relationships. Deafness implies a change in communication. While a blind person can use oral language on television, radio, any meetings, and become a leader in any area without having to change the means of communication, a deaf person who has sign language as mother tongue cannot do that, unless he/she benefited from early re/habilitation, interventions or cochlear implantation. The family is affected in the same way the individual is, all the same aspects of life. The issue of discrimination may not start in the society, but in the family, when sibling or parents reject or ignore what is happening. Even with accepting relatives, there is a mourning process when the family finds out a child is born deaf, a grieving process which many families, many parents, never actually overcome. In the broader society, the issue is the same, but it is much more difficult to pin down the factors that need to be changed, due to lack of awareness,

knowledge and/or interest. This is why CBM intervenes at all these levels, to identify realistic and practical indicators and outputs that could be targeted to make a change.
According to WHO estimates 466 million people, 6.1% of the world's population, live with a hearing disability [2]. But the main issue is that it is associated with a high rate of years lived with disability (YLDs), just after low back and neck pain, depressive disorders and iron-deficiency anaemia[3], which lead to huge personal burden and very high societal costs. Even in most developed countries, in North America, Europe and Australia, it affects 3% of the population at the very lowest, which is still significant. Indeed, the WHO recognizes any prevalence rate that is above 4% as a public health emergency. Although 6,1% of world population is affected, very little is done about it. Moreover, these estimates will rise to 630 millions by 2030, and by 2050, to 900 millions, concerning developed countries as well, as it is associated to an increase in life expectancy: more than one third of persons over 65 years old will have a hearing disability, complicated by all the associated conditions, including cognitive decline.

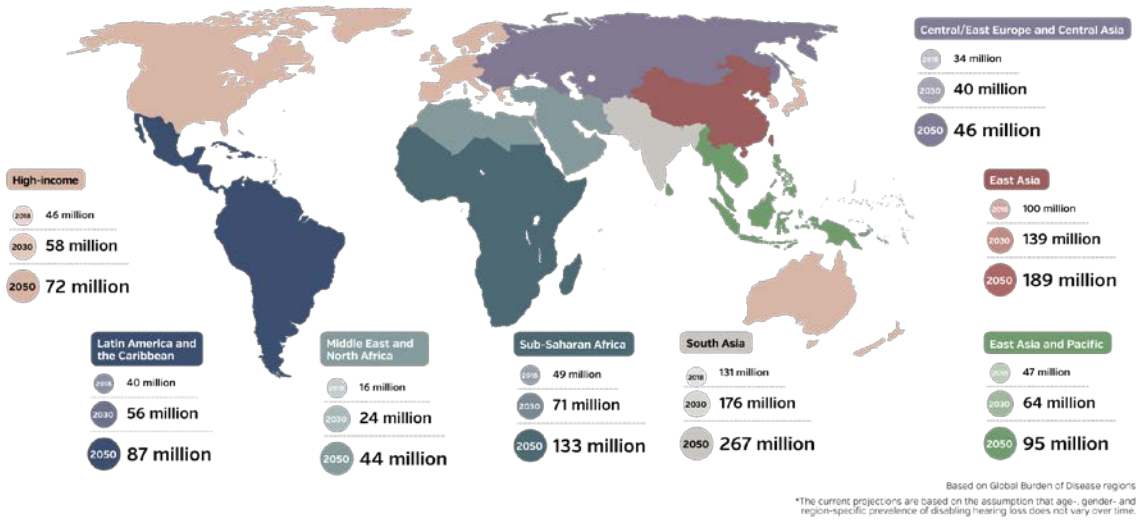


Figure 1:
The map shows current and projected number of people with hearing loss in different world regions by 2050. Projections show that people with disabling hearing loss will increase in all regions.
World Health Organization. World Hearing Day 2018.

Progress can be made in the field of disability through rights-based global public health programmes. In the area of vision, the number of persons with visual impairment in the world decreased from 311 million in 2004 to 285 million current estimation.[4]
This happened in the context of VISION 2020, a global initiative aiming to eliminate avoidable blindness by the year 2020. It was launched in 1999, but with a lead-time of over a decade of heavy investment in advocacy at government level and international agencies, public health planning and so on. Projections about the number of blind persons for 2020 show a significant difference between the estimated 80 million people without sight if Vision 2020 would not have been implemented, compared to more recent estimations: 39 million blind people by 2010, and even predict a decrease to around 22 million blind people by 2020. Therefore, public health at the global level does make a difference when it is met with adequate investments and political will.

In the area of hearing loss, around half of causes leading to hearing impairment could be avoided. The adequate technology exists for early diagnosis, from birth or early childhood, however, it is not available everywhere. This is where differences appear between middle-high and high income countries, where medical, audiological, educational and psychological interventions are well defined. These would include, among others: medical care of middle ear pathology and cochlear, middle ear

and bone anchored implants; audiological interventions for hearing aid fitting and programming of cochlear and other implants; educational integration/inclusion and special education, – although even in Europe, it is difficult to find, strictly speaking, comprehensive inclusive education with full support services for deaf students); – and psychological support for students and parents, behavior management and family counseling. In low and middle-low income countries, the approach is often not strategic nor comprehensive, and interventions remain inconsistent and opportunistic. In situations with a high proportion of the population being poor and not having access to these services, where sometimes only by spending the salary of a whole year one can afford to purchase a hearing aid, and cochlear implants are simply unaffordable; these approaches seem at first difficult to put in place. Especially as prices for hearing devices are often the same as in richer countries. This is why one cannot separate the social model from the health economics, to deal with hearing loss.Therefore, a change of paradigm is needed, going from a hospital-based service delivery setting to an inclusive public health approach, by re-orientating thinking towards the public health approach, especially by clinicians in ENT and audiology. Indeed, while clinical medicine focuses on the health of individuals (with consultation, and diagnosis, treatment, and follow-up), public health focuses on the health of populations, using surveys, prevention measures, population interventions, and repeated population surveys after five to ten years, etc. These approaches are different, but not mutually exclusive, in fact, they are complimentary. In addition, public health is not an exact science, and replication sometimes doesn't work from one country to another, or one region to another, or even in the same geographical area from one time to another.

Prevention of avoidable deafness and hearing impairment thus requires the development of a public health orientation, finding ways to make a difference in a population and targeting conditions with high prevalence and effective means of prevention and control, which is the first criterion for selecting any public health intervention. There are conditions that should be targeted, among those with high frequency is chronic otitis media, which is fully preventable and still, can lead to severe complication and death, for example through a brain abscess. Among conditions of moderate frequency which are preventable: excessive noise exposure, ototoxic drugs, ante- and peri-natal problems, meningitis, measles, mumps, rubella or foreign bodies in the ear. Among conditions estimated with low frequency, nutritional deficits, trauma and toxic chemicals are also preventable. However, more research is needed in order to produce updated evidence for rating of these conditions in low- and middle- income countries.

Such prevention-centered approach would thus require to shift the main ear and hearing care entry point, from hospitals to primary health care facilities. The WHO stated indeed, in 1978, that "Primary Health Care is essential health care made universally accessible to individuals and families in the community by means acceptable to them, through their full participation and at a cost that the community and country can afford. It forms an integral part of the country's health system of which it is the nucleus and of the overall social and economic development of the community." Of course, when applied to ear and hearing, this definition doesn't appear to work as there isn't sufficient knowledge, medication, equipment and instruments to treat essential ear conditions like, for example, an acute otitis media (no amoxicillin nor otoscope to look into the ear) in many developing countries. While ear drops, or assistive devices such as hearing aids, are on the WHO's priority lists of essential medicines and assistive products any country should have, the majority do not have them. Without a reliable and effective primary health care, the development of secondary and tertiary health care will always be limited by the burden derived from the workload not dealt with at the primary level, and also the delayed diagnosis and intervention for ear and hearing health in the developing world. At the moment, we're very far from achieving universal health coverage in EHC.

Regarding costs, the WHO estimates that the cost of not investing in EHC amounts to 750 billion dollars, in order to compensate for barriers to education and social integration, lack of productivity and cognitive decline and depression.[5] This is computed by evaluating the direct and indirect costs of unaddressed interventions related to ear and hearing care derived from the lack of prevention, delayed identification and intervention; including surgical procedures, hearing devices and re/habilitation for

all people who need support, at home, in education and at work. However, more evidence is required regarding the cost of not investing, as it is an important tool to incentivize governments to act. Furthermore, there is strong evidence that poverty and disability are linked.
There is currently a vicious circle in which hearing loss may lead to poverty and poverty to hearing loss, this needs to be address in order to move towards a more inclusive society. It was shown that prevalence of disabling hearing loss in children decreases exponentially as gross national income increases.

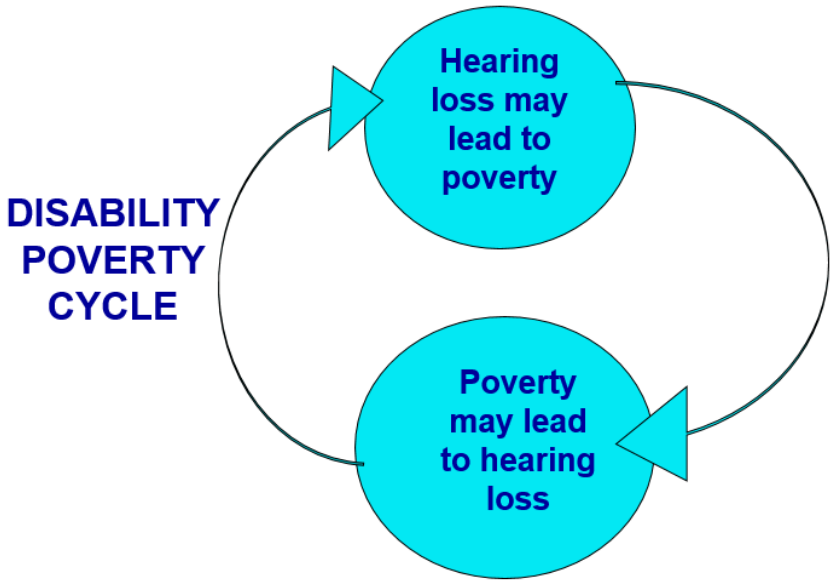
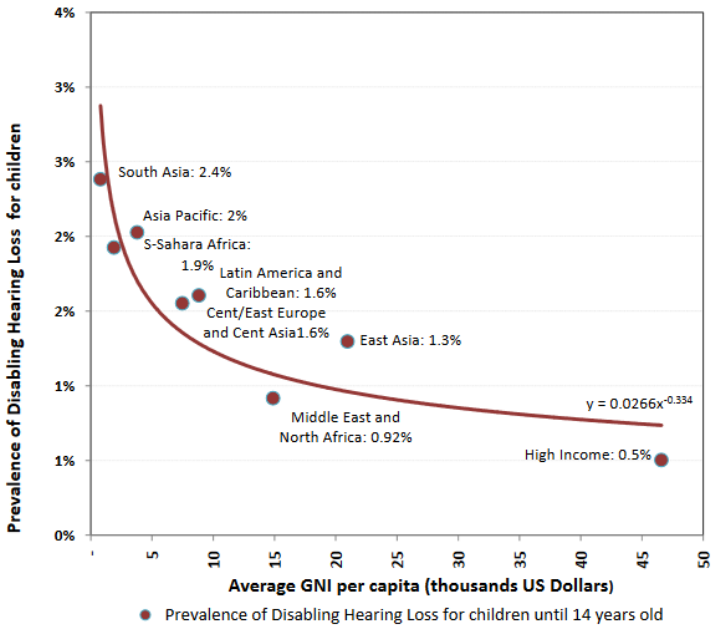


Figure 2: The vicious cycle of hearing disability and poverty

Prevalence of Disabling Hearing Loss for children versus average GNI per capita:*

In children, prevalence decreases exponentially as GNI increases.



*GNI per capita: gross national income per capita

*MBD, WHO, 2012 DHL estimates,

Figure 3: Prevalence of Disabling Hearing Loss for children versus average GNI per capita. MBD, EHO, 2012 HHL estimates [6]

Cost-effective public health programmes are therefore:

- primary ear and hearing care
- providing affordable hearing aids on a massive scale
- global and national programmes to reduce burden of hearing loss
- training for programme planning

Convincing governments that investing in ear care and hearing devices is going to be cost-effective in the long run would be a good start, but more data is needed to better influence national polices and investment. And although countries in Northern America and Europe invest much more than Southern Hemisphere countries in public health in general, there is still a disproportion and very little is allocated to hearing loss. An example from Europe shows that 47.71$ was invested in cardiovascular conditions research for every person affected, compared to only 1.34$ invested into hearing loss research.[7]

Gaps to overcome

The World Health Assembly resolution on the prevention of deafness and hearing loss (WHA70.13) was unanimously adopted on 30 May 2017.[8] This is a milestone for EHC but there is still much work to be done in order for WHO member states to align their health policies with the WHA resolution and its 9-points call on governments, so that the recommendations for activities at country level are adopted, supported and implemented. Indeed, this resolution has 9 points of strong recommendations:

i) to collect quality population data on ear disease & hearing loss;
ii) to integrate EHC strategies within Primary Health Care (PHC) systems;
iii) to establish suitable training programmes in EHC,
iv) to ensure the highest vaccine coverage against MMMR (Meningitis, Mumps, Measles and Rubella),
v) to implement early screening in high-risk populations (eg for CSOM (Chronic Suppurative Otitis Media), infants, children, elderly, noise-exposed),
vi) to improve access to affordable, cost-effective, quality, assistive hearing technologies and products,
vii) to develop and implement regulations for control of work and leisure noise and to control ototoxic medicines,
viii) to promote alternative means of communication (eg SL, captions),
ix) to work towards Sustainable Development Goals: SDG 3 (healthy lives), SDG 4 (education for all).

There are very significant gaps in evidence-based data (particularly prevalence rates of hearing loss per country), training and continuous education, accessible and affordable technology, implementation science in EHC and replicable successful programmes.

Regarding gaps in evidence-based data, , there is a need to develop reviews, updated protocols and software, to develop a survey method and tools for Rapid Assessment of Hearing Loss (RAHL). This RAHL initiative is being developed by the International Centre for Evidence in Disability of the London School of Hygiene and Tropical Medicine (ICED-LSHTM) with CBM support, has already been field-tested in China and Malawi and is due to be tested in the Philippines and Chile in 2019. The aim is to create an efficient and affordable population-based research tool supported by mobile-devices technology both for hearing testing and as simple data entry. This could be used by researchers and epidemiologists, but also by specifically trained primary health care workers, thus allowing automated and distance analysis. Currently, there is planning for 2020 to train trainers in such programmes. This is also included in the curriculum of short courses on EHC; those on Primary Ear and Hearing Care

(PEHC) using the WHO Training Resources (currently under review and field testing); and the high level Public Health Planning for Hearing Impairment courses, delivered by the ICED-LSHTM.

Regarding data gathering, a good example is the initiative of WorldWideHearing (WWH).[9] The organization took on the challenge of gathering global data with a global hearing loss database, which can be found at www.wwhearing.org, where it is possible to see which research has been done in what country, in matters regarding prevalence studies in the field of ear or hearing care. Also, WWH has developed a mobile application for data collection using android technology devices, which can be used for clinical data storage and for population based data analysis and storage.
Moreover, a WWH-commissioned study[9] done in Guatemala and led by the London School of Hygiene and Tropical Medicine (LSHTM), evaluated the impact of using hearing aids in the population, during 9 months: people with hearing disability were twice as likely to have symptoms of depression and they had a significantly poorer quality of life, while having a hearing aid led to significant improvement in mental health and wellbeing, including: significant reduction in moderate to severe symptoms of depression, 86% of case participants reported that hearing aids increased their self-confidence, 88% of case participants reported increased enjoyment of life, 23% felt safer wearing their hearing aids, 56% reported that the most significant benefit of wearing hearing aids had been the ability to communicate with family and friends. However, there was little to no economic impact over the 9-month period of the study period, but this might be due to its short timeframe. There is a need for longer longitudinal studies to measure the economic impact.
The above mentioned study led to various insights in the situation of the target population, in particular by visiting households, and showed that even basic hearing aids can have significant impact. The hearing loss prevalence was much higher than expected, and cases with mild hearing loss were included in control groups. The population surveyed was earning average of $5.70 a day, 82% of people were satisfied with their hearing aids, charging for hearing aids and continuous follow-up care led to significant ongoing usage, 71% used their hearing aids daily, 78% used their hearing aids at least 4 hours a day.
Currently, the next steps for WWH are to seek funding to run a longitudinal study in Guatemala, measuring the impact of hearing aids over a 5-year period, which would be the first study of its kind. Other research areas comprise further research on reduction of depression due to hearing interventions (mental health), measuring impact of charging for hearing aids vs. donating (people take more care of it if they pay), running an impact study with children fitted with hearing aids, validating and publishing new play audiometry hearing screening protocol for children under 5, as it has been developed by earAcces Inc, which already screened over 30,000 children in less than 3 months with this methodology.[10]

Overall, implementation science is needed to study the methods used to promote uptake of evidence-based interventions into routine clinical practice, to examine the factors surrounding implementation in addition to the outcomes of intervention, and to consider the aspects of interventions that can be modified or added, to better allow use in routine practice. One needs to acknowledge that real world settings are very complex systems, often requiring a change in the approach paradigm, challenging assumptions about how scientific advances reach real world practice. Indeed, the traditional pathways, from research to publications, then systematic reviews and finally clinical guidelines, do not always reach the target consumers. Only 14% of clinical research influences clinical practice and there is an average of 17 years until widespread adoption of new health care practices. In the case of EHC, often research and development of hearing devices stops after producing the intervention, when actually people are not yet wearing the device. Indeed, often the challenge is not in developing interventions but in successfully implementing them in real life settings, as only 20% of adults who could benefit from hearing aids are actually wearing them.

Therefore, one needs to follow the WHO 2014 recommendations, to address implementation bottlenecks, identify optimal approaches for a particular setting, and promote the uptake of research findings, which will lead to improved health care and delivery.[11]

To do so, one needs to consider various factors. For instance, when establishing a hearing aid clinic in a developing country, it is essential to address relevant questions: What are the referral pathways which patients would follow to reach the clinic? What are their financial incentives or disincentives to do so? What socio-cultural determinants will assure that fitting the hearing aid will be accepted? What are the barriers to an evidence-based prescription fitting? How do staff caseloads and staff shortages affect the fitting process? And what are the other health needs of patients and how do they relate to the fitting process? These require input from individuals involved at all the levels of the implementation process: health care providers, managers, policy makers and beneficiaries. Furthermore, success should not be evaluated just as scientific results but also be measured on a larger scale -on sustainability, to what extent the intervention is delivered to the target community- thus going beyond traditional health research boundaries, through transversal approaches. Such a comprehensive programme should thus be supported by a national plan for ENT/EHC, with a network of stakeholders at the national level, regional level, and global level.[12]

The topics to be funded are, therefore:

1. Evidence-based data (prevalence). Rapid Assessment for Hearing Loss (RAHL) survey: field testing and Training of Trainers (TOT) methods, alongside WHO.
2. Training and continuous education. Impact of Primary Ear & Hearing Care (PEHC) and Public Health Planning for Hearing. Impairment (PHPHI) training resources on professionals and communities.
3. Accessible and affordable technology. Longitudinal study measuring the socio-economic impact of hearing aids over a 5-year period.
4. Implementation science in EHC. Determination of standard audiogram sets based on most frequent patterns to allow hearing aids to be pre-programmed for optimal initial fitting in individuals living in low and middle income countries.
5. Replicable successful programmes. Obtain qualitative evidence of EHC comprehensive programmes efficacy as drivers of attitude change regarding hearing loss and towards national EHC strategies and plans.

References:

1. CBM International at https://www.cbm.org/
2. World Hearing Day 2018, World Health Organisation
3. Ranking of years lived with disability (YLDs) in the Global Burden of Disease (GBD) studies. From: Wilson et al, Lancet 2017
4. http://data.worldbank.org/about/country-classifications/country-and-lending-groups
5. World Hearing Day 2017, World Health Organisation
6. Figure 3: Prevalence of Disabling Hearing Loss for children versus average GNI per capita. MBD, EHO, 2012 HHL estimates, from Prof Andrew Smith, ICED/LSHTM.
7. Dr Daksha Patel, International Centre for Evidence in Disability of the London School of Hygiene and Tropical Medicine (ICED/LSHTM), 2017
8. World Health Assembly resolution WHA70.13, WHO 2017. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R13-en.pdf
9. Information and links to Complete Research Summary and Executive Summary of this impact study report can be found at: https://www.wwhearing.org/en/impact
10. Ms Audra Renyi, Executive Director World Wide Hearing Foundation International, Montreal, Canada, 2019. World Wide Hearing at www.wwhearing.org,

11. World Health Organization, 2014.
12. Ethical standards & efficacy measures for hearing health care research in developing countries. Prof Bradley McPherson, Division of Speech and Hearing Sciences, University of Hong Kong, 2019. Presentation at 2nd Society for Sound Hearing 2030 World Congress, Bali, Indonesia, 20-22 February 2019.

Annex I

List of participants

Speakers at the scientific workshop "Sensory Organ Disorders"

1. Francine Behar-Cohen, INSERM UMR 1138, Paris, France
2. Andrew J Bremner, University of London, UK
3. Andrej Kral, Hannover Medical School, Germany
4. Brigitte Malgrange, University of Liège, Belgium
5. Tobias Moser, University Medical Center Göttingen, Germany
6. Serge Picaud, Vision Insitute, Paris, France
7. Diego Santana-Hernández, CBM International, Canarias, Spain

Neuron SAB members and other Pannelists

1. Paola Bovolenta, Madrid, Spain
2. Martin Dichgans, Munich, Germany
3. Chapman Joab, Tel Aviv, Israel
4. Jean-Antoine Girault, Paris, France
5. Ewa Knapska, …., Poland (ERC grantee)
6. Luc Mallet, Paris, France
7. Jean-Paul Selten, Maastricht, NL
8. Fabrizio Tagliavini, Milan, Italy
9. Ana-Maria Zagrean, Bucharest, Romania

Guests

1. Christina Fasser, Switzerland, Patient representative (Retina Interrnational)
2. Anton Iftimovici, Psychiatry Resident, Paris Descartes University, France

Neuron Partners

1. Jan Barancik, SAS, Slovakia
   barancik@up.upsav.sk
2. Ana Barra, MINECO, Spain

neuron@mineco.es

3. Maxime Beaudoin, FRQS, Canada
   Maxime.Beaudoin@frq.gouvqc.ca
4. Maija Bundule,VIAAA, Latvia
   Maija.Bundule@viaa.gov.lv
5. Recep Emrah Cevic, TÜBITAK, Turkey
   emrah.cevik@tubitak.gov.tr
6. Kiri Couchman, ANR, France
   Liri.COUCHMAN@agencerecherche.fr
7. Marlies Dorlöchter, DLR-PT, Germany
   marlies.dorloechter@dlr.de
8. Maria Druet, ICSIII, Spain
   mdruet@isciii.es
9. Liron Even-Faitelson, CSO-MOH, Israel
   liron.ef@moh.gov.il
10. Clara Fons, MRC, UK
    clara.fons@mrc.ukri.org
11. Nathalie Gendron, CIHR, Canada
    Nathalie.Gendron@cihr-irsc.gc.ca
12. Anna Gossen, DLR-PT, Germany
    Anna.Gossen@dlr.de
13. Etienne Hirsch, INSERM, France
    etienne.hirsch@upmc.fr
14. Anabela Isidro, FCT, Portugal
    Anabela.isidro@fct.pt
15. Charlotte Inchley, MRC, UK
    Charlotte.Inschley@mrc.ukri.org
16. Georgia Kosptopoulou, GSRT, Greece
    g.kosptopoulou@gsrt.gr
17. Hannele Lahtinen, AKA, Finland
    hannele.lahtinen@aka.fi
18. Hella Lichtenberg, DLR, Gremany
    Hella.Lichtenberg@dlr.germany
19. Eric Marcotte, FRQS, Canada
    eric.marcotte@cihr-irsc.gc.ca
20. Sheyla Mejia Gervacio, ANR, France
    Sheyla.MEJIA@agencerecherche.fr
21. Herbert Meyer, FWO, Autria
    herbert.mayer@fwf.ac.at
22. Christina Müller, DLR, Germany
    Chr.Mueller@dlr.de
23. Melanie Neijts, NWO, The Netherlands
    M.Neijts@nwo.nl
24. Bernard Poulain, CNRS, France
    bernard.poulain@cnrs-dir.fr
25. Florence Quist, FNRS, Belgium
    Florence.quist@frs-fnrs.be
26. Jesus Miguel Sanz, AEI, Spain
    neuron@aei.gob.es
27. Dace Tirzite, VIAA, Latvia

28. Christine Tuffereau, INSERM, France
    christine.tuffereau@inserm.fr