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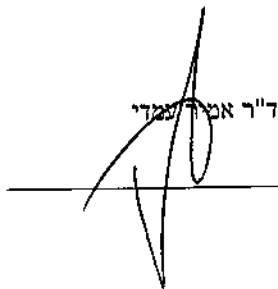
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נוירופלסטיסיות בעוורים והתמרה חושית לראיה

Neuroplasticity in the blind and sensory substitution for vision

הריני מאשר את הנושא ואת התוכנית, ומסכים להדריך את המועמדת בביצוע עבודה זו,

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Abstract

Sight restoration may aid millions of blind individuals worldwide, but its application is hindered by the lack of deep understanding of the neuroplasticity and learning effects in the blind and the processing in the brain of the blind, especially in their occipital cortex. Sensory substitution devices (SSDs) aim to help compensating for blindness while harnessing the same neuroplasticity for learning novel sensory transformations. Here I suggest a research plan looking into the effects of plasticity in congenitally blind individuals in the auditory system, and looking at the plastic changes resulting from learning to use a visual-to-auditory SSD. Specifically, I will investigate the normal auditory low-level (cochleotopic) activation in sighted people, and compare it to organization of the auditory system in the blind. This will look into possible occipital involvement and reorganization in low-level auditory processing. Later I will inspect the differences between the recruitment of the occipital cortex of the blind to such low-level auditory processing and its recruitment in trans-modal shape reconstruction (i.e. reconstructing shape from auditory-to-visual translated information) in SSD. Additionally, I will inspect the neuroplasticity generated by short and long term training in SSD use (i.e. the long-term dynamics of the learning process), and the possible functional specialization which may emerge for different "visual" stimuli categories. This will enable me to test central theories about brain organization. For instance, I will look into 1. The topographical nature of sensory processing and the similarities or differences of organization of the visual and auditory modality. 2. I will test various theories and ideas about the nature and principles of brain plasticity such the meta-modal theory of brain function and the inverted hierarchy theory.

Background

Sight restoration poses enormous scientific and technical challenges. The World Health Organization estimates there are approximately 45 million people suffering from blindness worldwide (WHO report 2009 fact sheet 282). There have been very few surgical vision restoration attempts, and these have shown limited success (Gregory and Wallace, 1963; Ackroyd et al., 1974; Fine et al., 2003), especially in respect to functional object and face recognition. It is currently not clear if this is the result of the lack of visual input during a critical period in early development (Wiesel and Hubel, 1963, 1965; Maurer et al., 2005) or the result of reorganization of the blind individual's brain (Rauschecker, 1995; Sadato et al., 1996; Burton et al., 2002; Amedi et al., 2003; Noppeney et al., 2003; Pascual-Leone et al., 2005; Sathian, 2005) which may interfere with future vision processing. The blind might encounter similar difficulties using neuroprostheses (in addition to many yet unresolved technical features). The development of such visual prostheses was motivated by early studies in which visual percepts (phosphenes, visual light dots or patterns) were successfully generated by electrical stimulation of the visual cortex (Penfield and Rasmussen, 1950). Today, different approaches are under investigation or are being tested in clinical trials in which visual information is recorded by external (or implanted) devices and transmitted to the sensory tract or secondary processing cells in the retina, ganglion cells, thalamus or the visual cortex, thereby replacing the healthy receptors of the sensory organs (for several recent reviews of current technologies and remaining challenges see, (Merabet et al., 2005 Somers, & Pascual-Leone, 2005; Weiland et al., 2005 2005; Rizzo et al., 2007 2007; Dagnelie, 2008; Dowling, 2008). However, although offering great promise, there are still several major issues currently preventing these approaches from becoming true clinical solutions, e.g., their invasive nature, low applicability across different etiologies of blindness, high costs, and many technical limitations (e.g. the relatively low resolution of the devices so far). Since surgical visual restoration or neuroprostheses are still applicable to a very small percentage of the blind, sensory substitution devices (SSDs) are currently the best direction for sight restoration or 'visual' orientation. In visual SSDs (Meijer, 1992; Bach-y-Rita and Kerchel, 2003; Renier and De Volder, 2005), visual information captured by an artificial receptor is delivered to the brain using a non-visual sensory information carrier via a human-machine interface, therefore bypassing the dysfunctional eyes or neural tracts. But how are such artificially-constructed stimuli processed in the blind brain? What are the putative plastic changes associated with learning to use such sensory transformation and how do they evolve with expertise and experience? Successful use of SSDs without a systematic training program has proved to be quite limited, and practically little is known about how the brain makes sense of such cross-modal "visual" information, or whether this information is processed in the visual cortex *similar* to natural visual stimulation (and more philosophically – if it is indeed perceived and experienced as vision; e.g. see : Renier and De Volder, 2005; Renier et al., 2005; Renier et al., 2006; Poirier et al., 2007). Moreover, the brain of congenitally blind individuals undergoes vast reorganization, which results in the employment of the occipital cortex in many different non-visual cognitive processes – from percepts of other modalities to memory and verbal functions. So is the

congenitally blind “visual” cortex still able to process visual percepts, even those provided by other modalities (i.e. by means of sensory substitution)?

Recent studies show that when sighted individuals learn to use a visual-to-auditory SSD (the vOICE; Meijer, 1992, see methods for further details) for object recognition a key area in the occipito-temporal cortex (lateral occipital tactile-visual area, LOtv), is activated (Amedi et al., 2007). LOtv is activated by object recognition when presented either as a visual or as tactile stimulus in sighted individuals (Amedi et al., 2001; Amedi et al., 2002). These findings indicate that extracting shape information, in either modality, including visual-to-auditory sensory substitution soundscapes, activates LOtv. Moreover, this study showed that the activation in LOtv in two blind proficient SSD users (one congenitally blind and one late-blind) was comparable to that of sighted in response to object recognition. But could these results be generalized to the blind population level by inspecting many more blind subjects? More importantly, how is this activation achieved? Is the occipital cortex of the blind be activated due to the low-level auditory properties of the stimuli (as a result of reorganization of the visual cortex to process sounds), or by their “visual” shape? And finally what is the short-term (online) dynamics and long-term (offline, over days and weeks of training) dynamics of the process of learning to extract shapes from sounds?

Several studies show that the occipital cortex in congenitally blind can be activated by sounds (Kujala et al., 1995; Bookheimer et al., 1998; Liotti et al., 1998; Gougoux et al., 2005; Kujala et al., 2005; Poirier et al., 2006; Collignon et al., 2008; Renier et al., 2008). But does this auditory reactivity of the visual cortex of the congenitally blind result from low-level or high-level auditory properties? How does the general auditory activation differ from activation generated by trans-modal (or multisensory, auditory-to-visual) SSD stimuli? Can such findings give indication to the organization of the occipital cortex of the congenitally blind and its ability to de-organize itself back to process visual properties?

To investigate these questions, I suggest performing a series of functional magnetic resonance imaging (fMRI) studies aimed at answering those questions regarding auditory reorganization, plasticity in blindness and sensory substitution. I will begin by investigating the normal auditory processing system, and the “purely” auditory cortical processing, in sighted subjects (including testing for robust auditory maps in visual cortex), and in comparison, in congenitally blind individuals. This will be done by testing the activation resulting from perception of natural (pure tones) auditory stimuli. This study will allow us to have a better understanding of low-level auditory processing in temporal and occipital cortex (and across the entire cerebral cortex), before studying blind and then engaging in more complex stimuli and processing (due to plasticity and cross-modal interactions) such as the ones used in sensory substitution devices in the blind. Additionally, in this project I will examine methods of assessing the neural activity dynamics using spectral analysis and cross-correlation techniques. These methods are commonly used for the study of topographic mapping in vision and audition. In order to apply them to a more complex and less predictable design, such as the dynamics of sensory

substitution processing, I will first apply and test these methods in the auditory system, in which the results regarding the primary auditory cortex are more predictable.

This work will establish in whole-brain coverage the auditory areas which are cochleotopic in nature in normally sighted humans (at least those which are large enough for fMRI resolution), a question which only partially answered so far. In normally sighted people, only the auditory core regions (A1 and an adjacent area R) are known to be cochleotopic, demonstrating topographic mirror symmetry organization in Heschl's gyrus, but not beyond it (Wessinger et al., 1997; Schonwiesner et al., 2002; Formisano et al., 2003; Hall et al., 2003; Talavage et al., 2004; Upadhyay et al., 2007), with hints of cochleotopic mapping in some of the auditory belt regions immediately surrounding the core regions (Talavage et al., 2004). Studies in primates (Merzenich and Brugge, 1973; Imig et al., 1977; Morel and Kaas, 1992; Kaas et al., 1999; Kaas and Hackett, 2000; Hackett et al., 2001; Petkov et al., 2006) and other mammals (Merzenich et al., 1975; Reale and Imig, 1980; Nelken et al., 2004) suggest that cochleotopic mapping may exist in multiple areas of the auditory belt areas. Recently, however, retinotopic maps were also discovered in the higher-order visual, parietal and prefrontal cortices (Levy et al., 2001; Sereno et al., 2001; Malach et al., 2002; Hasson et al., 2003; Schluppeck et al., 2005; Silver et al., 2005; Hagler and Sereno, 2006; Larsson and Heeger, 2006; Pitzalis et al., 2006; Schluppeck et al., 2006; Hagler et al., 2007; Kastner et al., 2007; Swisher et al., 2007; Gardner et al., 2008; Saygin and Sereno, 2008). The discovery of these maps enabled the distinction between visual regions and clarified their function and hierarchical processing. In this study, I will look into the possibility that such extension of topographical mapping to high-order processing regions may apply to the auditory modality as well, in sighted subjects (in which the cochleotopic characterization of high-order auditory cortex had not been previously attempted). The study of cochleotopic mapping in itself therefore has important implications in the definition of auditory fields in sighted individuals, similarly to retinotopic definition of the visual fields.

Moreover, this cochleotopic organization may be the basis on which auditory processing in the blind is expanded to traditionally visual cortex (Kujala et al., 1995; Bookheimer et al., 1998; Liotti et al., 1998; Gougoux et al., 2005; Kujala et al., 2005; Poirier et al., 2006; Collignon et al., 2008; Renier et al., 2008). Demonstrating the plastic changes in the cortical cochleotopic maps in the congenitally blind may help understand the functional organization of the auditory and visual cortices in these individuals. It might also contribute to the understanding of trans-modal processing which employs auditory stimuli. In the next study I will therefore examine the cochleotopic activations in congenitally blind subjects, looking for possible differences in cochleotopic maps in the auditory cortex (which have not been seen in the past in the primary auditory cortex; Stevens and Weaver, 2009), and particularly focusing on low-level cochleotopic responses in the occipital cortex, which have not been investigated before.

Following the establishment of general auditory responsiveness in the blind and sighted, I will examine the activations which are unique to sensorily-transformed auditory-to-visual stimuli, which result from extracting "visual" shape and location information. As a prerequisite for some of these studies, I plan to develop and apply an SSD-use training

method. This training paradigm will serve two purposes: First, constructing a training paradigm will enable me to study longitudinally the changes involved in learning such trans-modal transformations, and provide a group of proficient SSD users for the planned neuroimaging work. Additionally, it may demonstrate what are the behavioral abilities blind individuals can reach using such devices, with appropriate training (which has implications for testing their feasibility in the clinical setting). I will then use neuroimaging to look into the dynamics of the slow processing of shape (using many various categories such as tools, faces, letter etc.) in both sighted and blind, and the time in which each area, especially in the occipital cortex, is engaged in these tasks. I will look both into division of labor between various categories and visual tasks (shape recognition vs. location detection, normally better engaging the ventral vs. dorsal visual streams; Ungerleider and Mishkin, 1982) and convergence of information obtained by different stimuli. Later, I will look into the plastic changes resulting from short and long-term training in SSD use, which may reoccupy the occipital cortex of the blind to process vision, via sensory substitution.

Objectives

A. Auditory processing of low-level (non-sensory-transformed) stimuli:

- a. **Mapping the representation of auditory stimuli in the normally sighted brain.** What areas are contained in the low level auditory network in sighted and how is the auditory cortex organized? Is its organization based on a simple cochleotopic mapping outside the primary auditory cortex? Can this organization be used to distinguish and define different auditory areas? Are there any cochleotopic maps in the visual cortex of sighted?
- b. **Mapping the representation of standard auditory stimuli in the congenitally blind brain.** Does the cortex of congenitally blind humans undergo adaptations that change or add to its auditory processing network, particularly within the occipital lobe? If so, can such novel auditory fields be identified and mapped using cochleotopic mapping?

B. Trans-modal processing of auditory stimuli – visual-to-auditory sensory substitution

- a. Teaching blind individuals to process visual-to-auditory sensory substitution, and assessing their ability to process trans-modal visual stimuli
- b. Studying the neural networks involved in processing trans-modal auditory stimuli
 - i. What are the neural networks involved in processing visual shape and location in SSD in blind compared to sighted individuals? Do they include cortical and subcortical regions which are not activated by pure tones? What is the extent of activation of the visual cortex in processing trans-modal visual percepts in congenitally blind individuals? And can we find a division of labor between the ventral and dorsal streams in both groups?

- ii. What is the dynamics of the trans-modal shape processing, during single-item processing? When in the perceptual process are regions within the occipital lobe involved in sensory substitution?
- iii. What is the dynamics of the trans-modal shape processing in time, while learning to process trans-modal percepts? Are there changes in activation pattern in the occipital lobe during short and long term training?
- iv. What is the topography or division of labor of trans-modal “visual” percepts? Do they conform to the regular functional segregation to visual areas in sighted? And does such functional distinction exist in congenitally blind individuals? Does it evolve following prolonged SSD use?

Research plan

1. Auditory processing of non-sensory-transformed stimuli:

a. *Mapping the representation of auditory pure-tone stimuli in the normally sighted brain.*

To answer this question in humans, I chose fMRI as my main research tool, due to its optimal spatial resolution compared to other imaging tools available today. The visual cortex has been characterized in past years using spectral analysis methods (Wandell et al., 2007), allowing analysis of continuous, cyclic stimuli. This non-invasive technique has greatly assisted in the definition of visual areas and their bounds in the human brain. In my research, I chose to use methods based on spectral analysis (Engel et al., 1994; Sereno et al., 1995; Engel et al., 1997), in order to observe the response to simple tonal stimulation, thus mapping the auditory-responsive cortex. We also used multiple cross-correlation maps and standard GLM to validate this relatively cutting-edge approach. The tonal stimulation will be delivered as a logarithmically rising tone chirp, spanning a large frequency range (250 Hz – 4 KHz) which can be clearly perceivable in the scanner environment. In this experiment, stimuli will be delivered in both directions and in repeated measures to obtain test-retest reliability. In one session the stimulus will be a rising chirp (cochleotopic exp. 1), which will be repeated a second time in some subjects (cochleotopic exp. 2), and in another session I will use a dropping chirp (from higher to lower tonal frequencies, cochleotopic exp. 3). For each run, this auditory stimulation will be repeated several times, with pauses between each series of stimuli to the next. For a more detailed description of analysis methods, see materials and methods, spectral analysis and protocol design of the experiments sections. In order to address the question of the auditory-responsive areas, I may examine correlation maps that will delineate the sensory area (**Fig. 2D**). Correlation maps reflect the areas in which the hemodynamic response is locked to the stimulation repetition frequency. In order to explore the specific tonal

preference of each region, I may examine each voxel's phase, synchronized with the timing of stimulation applied to a certain auditory frequency. This can give us insight into the organization, and whether this organization extends beyond regions seen in previous literature, which contain, in humans, only the core auditory cortex (Formisano et al., 2003) and parts of the auditory belt immediately surrounding it (Talavage et al., 2004).

b. Mapping the representation of standard auditory stimuli in the congenitally blind brain.

Similarly to the mapping of the auditory responsiveness in normally sighted controls, I will utilize fMRI spectral analysis in a similar design to look into the auditory responsiveness in the auditory and in the occipital ("visual") cortex of congenitally blind individuals. I will particularly look for auditory responses outside the activation scope of the sighted controls (by comparing the activation between the groups using a standard GLM or ANOVA approach), which represents reorganization of the congenitally blind cortex. I anticipate seeing at least one focus of auditory activation in the occipital lobe, due to several past studies (Kujala et al., 1995; Bookheimer et al., 1998; Liotti et al., 1998; Gougoux et al., 2005; Kujala et al., 2005; Poirier et al., 2006; Collignon et al., 2008; Renier et al., 2008) that indicate auditory responses to more complex auditory stimuli and tasks. If these auditory responses are the result of a general auditory responsiveness, I also expect to see cochleotopic preferences, which would further support this reorganization.

2. Trans-modal processing of auditory stimuli – visual-to-auditory sensory substitution

Sensory substitution devices (SSDs) involve translating the sensory input of one modality, in this case vision, to that of another. While visual-to-tactile SSDs are also under research (Bach-Y-Rita et al., 1969; Bach-y-Rita et al., 1998; Chebat et al., 2007), their potential scope may be smaller than that of auditory SSDs. This is due to the low possible "visual acuity" provided by the tactile devices, which is limited by the number of electrodes and tactile 2-point-discrimination. Additionally, Tactile devices high cost lowers its potential in providing a visual aid to many blind individuals. In my study I will use the vOICe (Meijer, 1992; see Fig. 1), a visual-to-auditory SSD which converts 2-dimensional grayscale pictures to sounds according to a fixed transformation algorithm. Time and stereo panning constitute the horizontal axis in the sound representation of an image, tone frequency makes up the vertical axis, and loudness corresponds to pixel brightness. Visual information in the sound representations of complex gray-scale images is preserved up to a resolution of about 144x176 pixels for a 1 s sound scan and a 5 kHz audio bandwidth. The vOICe can be easily and cheaply used in an everyday manner, using a small webcam, laptop and earphones, making it widely available to many blind people worldwide.

a. Teaching blind individuals to process visual-to-auditory sensory substitution:

Recently, a short training program was developed facilitating the learning and efficient use of the vOICe in sighted subjects, with success rates (for novel objects) far above chance level following 40 hours of training (Amedi et al., 2007). In order to create a group of proficient vOICe users as well as

monitor the neuroplasticity resulting from learning to interpret trans-modal stimuli, I will attempt to adapt this training method for the blind. Currently there is no structured training program for using such SSDs, and blind individuals that use these devices reported that learning to make sense of the input of the device took many months and was very difficult. This suggests that applying an organized training method may greatly improve the outcome and efficiency of using SSDs. In addition to the neuroimaging studies involving learning, long-term training may demonstrate the behavioral abilities blind individuals can reach using such devices, which has implications for testing their feasibility in the clinical setting.

b. *Studying the neural networks involved in processing trans-modal auditory stimuli*

- i. What are the neural networks involved in processing visual shape and location in SSD in blind compared to sighted individuals? Do they include cortical and subcortical regions which are not activated by pure tones? What is the extent of activation of the visual cortex in processing trans-modal visual percepts?*

To answer this I will conduct an fMRI study requiring the blind and sighted subjects to identify simple and complex shapes of objects or their location and investigate the resulting brain activations.

Specifically, I intend to look into differences in occipital activation between the blind and sighted groups, and between the two processing streams in the occipital cortex (Ungerleider and Mishkin, 1982). I will do so following a short standardized training in shape identification using the vOICE, so that both blind and sighted users will be able to identify basic shapes using soundscapes to a comparable degree.

- ii. What is the dynamics of the trans-modal shape processing, during single-item processing?*

The vOICE generates a slow-motion process of object shape reconstruction and identification, which can be utilized to study the dynamics of trans-modal object recognition using high-spatial-resolution fMRI. This is particularly interesting for two reasons: the first its relevance to studying object recognition in sighted people, which is normally too short a process to be studied using such methods. Secondly, the involvement of the occipital cortex in the blind can be attributed to many parts of the perceptual process: to the auditory perception, to visual-like shape reconstruction or even to motor planning of the response. Studying the dynamics of the process will enable me to differentiate between parts of the occipital cortex which are engaged at different stages of the trans-modal processing, and thus better identify their functions in this process. Specifically, while it was demonstrated that the ventral visual cortex is involved in SSD object recognition (Amedi et al., 2007), the earlier visual cortex is activated in blind individuals but the nature of its involvement is unclear. Two competing models suggest that the early visual cortex of the congenitally blind may be involved either in very early sensory processing, or in later stages of more complex cognitive processing. The metamodal model, suggests that each cortical area may operate in a metamodal fashion (Pascual-Leone and Hamilton, 2001), being specialized in a particular type of computation rather than being tied to a specific input modality. Thus it predicts early

visual cortex will retain its function or characteristic computation regardless of its input, and in the case of congenital blindness it may be involved in low-level auditory or tactile processing (due to direct connectivity between V1 and early auditory and somatosensory cortices or even thalamic nuclei; Robitaille et al., ; Wittenberg et al., 2004; Karlen et al., 2006; Laemle et al., 2006; Piche et al., 2007). An alternative model, the inverted hierarchy theory (Amedi et al., 2003; Buchel, 2003; Raz et al., 2005) suggests that, due to the dysfunctional main bottom-up geniculo-striatal pathway in the blind (Noppeney et al., 2005; Shimony et al., 2006), the retinotopic areas (especially V1) will be much farther (in terms of the number of synapses) from the remaining functional sense organs (in the tactile or auditory modalities). This, in turn, would lead to V1 resembling more the prefrontal cortex (which is similarly remote from any direct sensory input) than becoming a primary sensory area in the blind. To study this and look into the time of activation I will apply a slow-event-related fMRI design, in which each soundscape will be delivered and processed separately, enabling the investigation of the onset of activation of each cortical region separately. For this type of analysis I will apply linear correlation analysis and phase analysis, similarly to the ones I will apply for cochleotopic mapping.

iii. What is the dynamics of the trans-modal shape processing in time, while learning to process trans-modal percepts?

The dynamics in the longer timetable refer to the learning process of trans-modal perception. I expect that as the sighted subjects train for longer in trans-modal processing, the percept will become more natural, and more reliant on neural networks involved in visual perception in the sighted. In the blind, I will see if the visual-like processing generates any short-term and long-term plastic changes in the brain. For that purpose, I will compare the activations generated in an fMRI study of trans-modal shape perception before training, following short training and following the entire training program.

iv. What is the topography of trans-modal "visual" percepts? Do they conform to the regular functional segregation to visual areas in sighted? Furthermore, does such functional distinction exist in congenital blind individuals? Does the same neural tissue process different object categories, or does a new division of labor emerges? And most interesting, does any division of labor evolve following prolonged SSD use?

Following extensive training, processing of soundscapes may involve dynamic interactions between distant brain areas. In the sighted, I expect these will include the visual cortex, utilizing its highly specialized functional architecture (spatial topography, visual streams and object categories (Zeki, 1978; Ungerleider and Mishkin, 1982; Grill-Spector and Malach, 2004)). Its involvement will be either by pure multisensory interactions or with the aid of visual imagery. The blind may also use the occipital lobe to process soundscapes, increasingly as training progresses. In the blind, the occipital lobe may either show the same regional specialized functional preferences of the sighted through multisensory processing, or the occipital lobe's ability to process vision was lost, and will be regained for artificial vision using

another mechanism (generating different functional specializations). I will test these hypotheses using fMRI studies of the cortical responses to soundscapes and visual “tasks” that are processed by different specialized regions of the visual system. I will look into the activation generated by soundscapes in shape versus localization tasks (processed by the ventral vs. dorsal streams correspondingly), and object recognition using different categories based on object-related visual cortex topography (Reddy and Kanwisher, 2006): faces (Fusiform face area; FFA), scenes (including buildings, Parahippocampal place area; PPA), body-parts (Extrastriate body area; EBA), Letters (Word form area) and tools/all other objects (Lateral-occipital complex; LOC). For some of the studies I will apply slow-event-related designs in order to look into the timing of activation of different regions of the visual cortex, and in some, use a standard block-design, which has a larger signal-to-noise ratio.

Materials and methods

1. Functional MRI

One of the few non-invasive ways to study the aims and questions detailed above in humans is by using imaging techniques (functional Magnetic Resonance Imaging, fMRI), which will constitute the main methodology (in addition to psychophysics and behavior) I will use in my research. fMRI is a well-established tool, used to identify brain areas or large-scale networks associated with a given function. In Magnetic Resonance Imaging (MRI), the phenomenon of Nuclear Magnetic Resonance (NMR) is utilized for imaging purposes. The technique involves use of a strong magnetic field that is constant in time, in conjunction with time-dependent, radio-frequency electromagnetic pulses to manipulate nuclear spin dynamics. The pulse sequence normally used in the context of functional brain mapping is that yielding the Blood Oxygenation Level Dependent (BOLD) contrast. This map describes differences in the ratio of the oxygenated and deoxygenated forms of hemoglobin (Kwong et al., 1992; Ogawa et al., 1992), which in turn is believed to be directly related to the underlying, time-dependent neuronal activity (Logothetis et al., 2001; Logothetis and Wandell, 2004) – hence “functional” MRI (fMRI). In this work, I will use the BOLD fMRI measurements obtained in a whole-body, 3-T Magnetom Trio scanner (Siemens, Germany), and a whole-body, 3-T Signa scanner (General Electric, USA). The fMRI protocols will be based on multi-slice gradient echoplanar imaging (EPI) and a standard head coil. The functional data will be collected under the following parameters: TR = 1.5 s, TE = 30 ms, FA = 70°, imaging matrix = 64 X 64, FOV = 20 X 20 cm (i.e. in-plane resolution of 3.125 mm). I will use a relatively short TR value in order to apply the phase-locking spectral analysis approaches (see below). 23-29 slices of slice thickness = 4-4.5 mm and 0.5mm gap will be oriented in the axial position, for complete coverage of the whole cortex, at a maximal spatial resolution under these conditions. For

data analysis I will primarily use the Brain Voyager QX software package (Brain Innovation, Maastricht, Netherlands), coupled with lab in-house software generated in Matlab.

2. Spectral and cross-correlation analyses

The time-resolved fMRI measurements provide topographical and temporal information about the brain areas subserving a cognitive task. Following standard retinotopy procedures (Engel et al., 1994; Sereno et al., 1995; Engel et al., 1997), I will apply spectral analysis to the responses locked to the stimulus presentation frequency (Fig. 2A). This will be done both for cochleotopic mapping in the sighted and blind subjects, and for mapping the dynamics of trans-modal processing. This analysis, in effect, computes the latency of a hemodynamic response to single events throughout the brain, and thus creates a map of the chronometry of a complex neural response. Prior to frequency analysis, the time courses will be de-trended to remove mean and linear drifts. The complex Fourier at the repetition frequency f_{rep} is denoted by:

$$[1] \quad F(f_{rep}) \equiv a(f_{rep}) \cdot e^{i\phi(f_{rep})}$$

Where $a(f_{rep})$ represents the amplitude and $\phi(f_{rep})$ the phase, and calculated by:

$$[2] \quad F(f_{rep}) = \sum_{k=1}^N TC_k \cdot e^{-i2\pi \cdot (k \cdot f_{rep})}$$

Where TC represents the sample time course, and N is the number of sampled time points.

Both amplitude and phase parameters will be used to construct a pure cosine serving as a model of the activation (Fig. 2B, C). A Pearson correlation coefficient will then be calculated between the model and the original time course of the activation (Engel et al., 1997). This procedure will yield a correlation coefficient for each voxel.

The correlation coefficient will be used as a direct measure of the voxel's response to the stimulus. The correlation

coefficient (R) will be transformed $\left(\frac{R \cdot \sqrt{N-2}}{1-R^2} \right)$ and used as t statistic with N-2 degrees of freedom (in our case N=300), to calculate the significance of the cortical response to the auditory stimulus.

In regions showing high correlation to the stimulus repetition frequency, the phase value will be inspected. The phase corresponds to the latency of the voxel's response to the stimulus at hand. For example, in cochleotopic mapping if each voxel has tonal selectivity (resulting from the tuning curves of the neurons in that voxel), its response should correspond to the preferred tone (auditory frequency) of that voxel. In the dynamics of SSD processing the phase will correspond to the timing in relation to stimulus onset, in which each voxel is activated, i.e. the processing stage of the trans-modal stimulus. Phase values will be distributed between $-\pi$ and π , and linearly transformed to represent time points in each stimulus cycle.

As a complementary analysis, I will apply a standard cross-correlation analysis using the Brain Voyager QX 1.9.10 software package to the individual time-courses. I will use the predicted hemodynamic signal time course for the beginning of a stimulation cycle and shift this reference function successively in time (time steps corresponded to the recording time for one volume, TR). The resulting lag value maps show the highest cross-correlation value lag for a particular voxel. Group analysis (Fig. 3ii, Fig. 4C, Fig. 6A) was conducted on the averaged data of the individual subjects for each experiment.

3. Group level GLM analysis

Statistical group analysis in the general linear model (GLM, Friston, 1994; Friston et al., 1999) will be calculated using hierarchical random effect model analysis allowing for generalization of the results to the population level. The average time course of activation will also be sampled from each individual subject in relevant regions-of-interest and averaged to extract the average percent signal change for each experimental condition.

4. Protocol Design of the Experiments

1.a, b. Mapping the representation of auditory stimuli in the normally sighted and blind brain: In this fMRI study the tonal stimulation will be delivered as a logarithmically rising tone chirp, spanning a large frequency range (250 Hz – 4 KHz) in 18 seconds, followed by a 12 second rest baseline period. The 30 seconds complete cycle will be repeated 15 times, resulting in a stimulus frequency of 0.033 Hz. Thirty seconds silence periods will be added before and after the 15 cycles of auditory stimulation. Sighted subjects will be blindfolded and all subjects will be asked to shut their eyes for the duration of the scan, and instructed to concentrate on the sounds. In some subjects, stimuli will be delivered in both directions: in one session the stimulus will be a rising chirp, which may be scanned twice to look for test-retest reliability, and in another – a dropping chirp (from higher to lower tonal frequencies), in order to control for the effect of frequency modulation direction.

2.a. Trans-modal processing of auditory stimuli – Teaching blind individuals to process visual-to-auditory sensory substitution: As a prerequisite for conducting fMRI studies on expert users in sensory transformation, I will attempt to adapt the vOICe training method originally designed for sighted individuals (Amedi et al., 2007) for the blind. This will include the introduction of the conversion algorithm, followed by training in object recognition (from simple to complex shapes) and localization using a multiple choice paradigm combined with corrective feedback. This method will be especially adapted to the blind using several modifications: the first is a simplistic explanation of the visual characteristics of 2-dimensional object pictures, as the congenitally blind are not accustomed to perceiving 2-dimensional information regarding object shapes. This will be conducted using real small objects which can be palpated and explored, and a demonstration of their 2D outline using a picture of them presented on a tactile display. The training will be performed in a standardized manner in 15 weekly meetings of 3 hours each. It will mostly focus on

recognizing shapes, in several functional categories: geometric shapes, textures, faces, every-day-objects, houses, human figures and body parts, letters and words, animals and tools. These categories represent types of objects that have specifically designated cortical regions in the normal visual cortex (e.g. FFA for faces, PPA for scenes including houses, LOC for objects), and will thus enable me to see if such functional differentiation exists in the blind brain, either originally or due to extensive training with visual stimuli via SSD (see exp **2.b.iv**)

2.b.i-ii. Trans-modal processing of auditory stimuli – identifying the neural networks involved in vOICe shape

recognition and their dynamics: In this slow-event-related fMRI study I will, in each event, present blind and sighted subjects with a simple soundscape repeating 4 times, and request that they identify if that sound included a circular shape. Following the soundscape, the subject will have to construct the shape for 5 seconds and at an auditory cue, answer using a response box. The experiment will include 20 events, each followed by a 9 second baseline rest period. Additional baseline rest periods of 21 seconds will occur before and after the entire experiment. This study will be conducted following a short standardized training in shape identification using the vOICe in both groups, which should result in a controlled and similar performance.

2.b.iii. Trans-modal processing of auditory stimuli – the plasticity in vOICe learning on short and long time scales: In this longitudinal fMRI study I will examine the short and long term plastic changes resulting from training in visual substitution. For that aim, I will repeat experiment **2.b.i.** in three different stages of vOICe training: first before training (in fully naïve subjects, who are not familiar with the visual-to-auditory transformation algorithm), then immediately after a short standardized training (short term effect of training, following 1 hour of training, exp **2.b.i.**), and a third time following extensive standardized training (approximately 45 hours of training). In the blind subjects that will continue using the vOICe in every-day life, I will periodically perform additional studies to examine even longer-term possible effects of years (which may exist according to anecdotal reports of vOICe users; Ward and Meijer, 2009). In analyzing these results I will compare the first, second and third scans of the subjects in a repeated-measures ANOVA design, and also look for brain regions whose activation is correlated (in terms of individual subject or individual event level) to successfully performing trans-modal shape recognition.

2.b.iv. Trans-modal processing of auditory stimuli – the topography of trans-modal “visual” processing: in these fMRI studies I will examine the functional specialization of the occipital cortex to different trans-modal stimuli and tasks.

- I. Following extensive training, I will present soundscapes of different object categories (faces, houses, every-day objects, body parts, letters) in an fMRI block design. In each block 3 stimuli of a specific category will be presented (each lasting 2 seconds and repeating twice). Baseline rest periods of 21 seconds will occur at the beginning and end of the experiment, as well as 12 seconds baseline rest in between blocks. Each object category will be repeated on 5 blocks in a random order.

- II. In addition to the block design fMRI study, I will include a slow-event-related fMRI study of faces, houses and letters in a similar design to that described in experiment *2.b.i.*, in order to identify the differential dynamics of perceiving visual objects of different types.
- III. In order to compare the differential activation of the different visual object categories to that of the normal visual topography, I will conduct a visual object localizer in the sighted participants of the study. Images of faces, houses, objects and patterns will be presented for 800ms (+200ms intervals). Each block will include 9 stimuli, and will be followed by a 6 second baseline rest period. Each condition will be repeated 7 times, and the experiment will begin and end with a 24 second baseline rest period.

5. Ethics

The Tel-Aviv Sourasky Medical Center and Hadassah Medical Center ethics committees approved the experimental procedure and written informed consent is obtained from each subject. Only adults or children above the age of 14 will be scanned in this project

Preliminary results

1.a. Mapping the representation of basic pure-tones auditory stimuli in the normally sighted brain.

This study is nearing completion, and a paper describing its results is under review in Cerebral Cortex journal.

For my first study I looked at the auditory cochleotopic mapping in the brain of sighted individuals. For the main analysis method, I use spectral analysis (Serenio et al., 1995; Engel et al., 1997) to extract the correlation coefficient of each voxel's response to a model of the auditory stimulus repetition frequency and its phase (see Fig. 2). The correlation coefficient (R) was used as a statistic to calculate the significance of the cortical response to the auditory stimulus. While the peak of the correlation to the auditory stimulation is indeed located in the primary auditory cortex region, the significantly responsive area (Fig. 2D, $p < 0.05$, Bonf. corrected) extended well beyond core areas all the way to the superior temporal sulcus, and parts of the middle temporal gyrus, regions considered to be higher-order auditory cortices responsive to complex sounds or even multisensory integration. Each voxel within the responsive area is assigned a color representing the phase of the response, which, as sound frequency varied systematically with time during the auditory stimulus, was indicative of the preferred tone (see Fig. 2) of that voxel. Phase analysis of these areas revealed gradients between multiple bands of tone frequency selectivity (see Fig. 2E, Fig. 3A). In the superior temporal plane a topographical mapping pattern of tone-preference shift from high-frequency tones to low-frequency tones and back along can be seen with Heschl's gyrus (HG) located within this mirror-symmetric large scale organization. This is

highly consistent with the general pattern found in primates (Petkov et al., 2006) and in recent neuroimaging studies in humans (Formisano et al., 2003; Upadhyay et al., 2007). Thus our results confirm the suggestion of Formisano and colleagues (2003) that this mirror-symmetric mapping corresponds to the human analogues of the core auditory areas A1 and R. Outside the auditory core, large-scale mirror-symmetric tone-selective bands which have never been reported in humans extend along the superior-to-inferior axis to the superior temporal sulcus. Although both hemispheres exhibited at least two new mirror symmetry maps with a superior-inferior axis, there are indications of additional maps extending as far as the middle temporal sulcus in the left hemisphere. These maps are consistent in group maps and in single subjects (not presented here), across experiments (rising and falling tone chirps) and across analysis methods in spectral analysis, cross-correlation analysis and standard GLM maps (Fig. 3). These maps suggest that the auditory cortex is, similarly to the visual cortex, topographical in nature, comprised of multiple cochleotopic regions which form mirror-symmetric reversal maps. Moreover, the cochleotopic mapping characterizes regions even in multimodal regions such as the superior temporal sulcus (STS).

While several regions outside the temporal lobe, including bilateral activation in the posterior-inferior frontal lobe, medial superior frontal gyrus\ premotor cortex, precuneus, and a left inferior parietal cluster showed significant responses to the experimental design at the group level, these regions did not display cochleotopic mapping. No cochleotopic regions or auditory responses were observed in the occipital cortex in sighted subjects.

1.b. Mapping the representation of basic pure-tones auditory stimuli in the congenitally blind brain.

This study is underway, data collection has been completed for Cochleotopy exp. 1 (rising chirp) for 11 congenitally blind, and for control Cochleotopy exp 2 (dropping chirp) for 3 (out of 5 planned) subjects so far. Data acquisition is expected to be completed by February 2010. Preliminary data analysis shows promising results as detailed below, and full analysis and is expected around June 2010.

In a preliminary comparison between the activation pattern elicited by simple auditory chirp in sighted and in congenitally blind individuals several interesting preliminary results start to emerge: 1. it appears that generally speaking the temporal lobe auditory cortex, is similarly activated in both groups, and yielding similar cochleotopic gradients and mirror-symmetry maps. 2. The correlation coefficient, signifying the strength of the response is somewhat weaker in the auditory cortex in the blind. Interesting similar results of weaker activation for language and verbal memory in the prefrontal cortex of blind, and less interference in transcranial magnetic stimulation (TMS) in blind vs. sighted for tactile recognition in S1 and verb generation in prefrontal cortex (Amedi et al., 2004). This might suggest that the plasticity in the visual cortex of blind (see below) is accompanied by weaker responses in the cortical areas typically dedicated to each function. 3. Conversely, other regions, including some in the occipital lobe, are more strongly activated in the congenitally blind group (Fig. 4A). These regions include clusters in the posterior STS, and particularly, in the right

hemisphere middle temporal sulcus (MTS). This auditory cluster is overlapping in Talairach normalized coordinates to sighted area MT (middle temporal visual area), which, in sighted, is dedicated to the analysis of visual motion. Displaying the result of an MT localizer (comparison of moving and stationary visual stimuli, Fig. 4B) conducted in a sighted group ($n=10$) shows that the auditory activation in the blind is indeed localized in the anatomical location of area MT of sighted. Interestingly this auditory responsive area shows some cochleotopic preferences (Fig. 4C) but this result is yet to be validated by demonstrating the same cochleotopic gradient in the falling chirp experiment (similarly to the sighted, to prevent order confounds), an experiment for which data acquisition and analysis are underway. Should these results show consistency across studies, it would appear that at least a part of the occipital cortex, MT, has reorganized to become perceptual, low-level auditory region in the blind.

2.a.i-ii. Teaching blind individuals to process visual-to-auditory sensory substitution

Long-term vOICe training is underway. So far 3 sighted and 5 blind participants have completed this training, and 4 sighted and 6 additional blind individuals are currently being trained, and should complete their training until April 2010. This will result in a group of 11 blind subjects for experiments 2.b2iii-iv, which can construct a sufficiently large group for group hierarchical random effect model analysis allowing for generalization of the results to the population level (Holmes and Friston, 1998; Friston et al., 1999).

I supervised the construction of a training program which teaches blind individuals to view and interpret pictures transformed via the vOICe SSD to sounds. This program provides tactile feedback to the blind participants that are parallel to the visual feedback provided to sighted participants. Participants are trained in a standardized manner in 15 weekly meetings of 3 hours each in recognizing shapes of items of growing visual complexity. Stimulus complexity ranged from stimuli comparable to receptive fields of cells in V1, such as lines in different orientations, to more complex shapes imitating higher-order stations in the visual hierarchy, such as complex living and non-living objects, in several functional categories (some of which were chosen to specifically activate specializing regions within the normal visual system): geometric shapes, textures, faces, every-day-objects, houses, human figures and body parts, letters and words, animals and tools. This part of the training was designed to enable the mapping of different regions within the normally developed visual cortex, and to compare it to that of the visually-deprived occipital cortex of the congenitally blind. This training enables the subjects (blind and sighted alike) to recognize, for example (see Fig. 5 for examples of images included in the vOICe training), that an image includes a face, and recognize features regarding it (that it has long/short hair, if the face is smiling), count the number of windows and doors in a picture of a house, read 5-letter words, identify pictures of every-day objects and identify the posture of a human body. An additional spatial-orientation directed training has thus far enabled blind individuals to walk freely in corridors while avoiding obstacles, recognize items while

walking in their street (such as benches, trees etc.) and applying hand-“eye” coordination in tasks such as puzzle completion and inserting rings on a narrow cone.

2.b.i-iii. Trans-modal processing of auditory stimuli – identifying the neural networks involved in vOICE shape recognition and their dynamics during single-object perception and in short-term plasticity

This study is underway, data collection has been completed for 10 sighted and 11 congenitally blind, and analyzed for 9 subjects of each group. Preliminary data analysis shows promising results as detailed below, and full analysis and is expected around October 2010.

Following a 1-hour training session, both sighted and blind groups reached similar (though relatively low) performance level, enabling the direct comparison of neuroimaging results between the groups. Following the training (Fig. 6A), both blind and sighted groups demonstrated significant activation in the ventral prefrontal cortex, superior parietal lobe (IPS) and occipital-temporal cortex, areas observed in the past in the perception of sensorily-transformed stimuli in the sighted (Amedi et al., 2007). In the blind group, robust activation is also observed more posteriorly in the occipital lobe bilaterally. Direct comparison between the blind and sighted group activations with regard to sensory substitution shape processing shows that the difference in the activation of the visual cortex is highly significant (Fig. 6B). This is another interesting example of brain plasticity in the occipital cortex of blind. The preferential occipital response is bilateral and extremely robust suggesting blind use the visual cortex for this task to a very large extent.

Analysis of the brain dynamics (using cross-correlation analysis at this stage) underlying the shape recognition process demonstrated that the occipital cortex is involved during the late analysis of the stimulus rather than during the early auditory perception (Fig. 6A), suggesting its involvement is during shape analysis and not during auditory perception per-se. Specifically, a gradient of processing onset can be seen between the high-order auditory cortex, ventral occipital lobe and posterior occipital lobe, suggesting that information is transferred backwards compared to the normal visual hierarchy, supporting the inverted hierarchy model (Amedi et al., 2003; Büchel, 2003).

Furthermore, in order to test whether the occipital cortex involvement is functionally relevant to shape processing, I compared the activation evoked by successful versus unsuccessful trials in the blind group (Fig. 6C). The results show that the activation in the ventral occipital lobe modulated by performance level on a trial by trial basis, demonstrating its relevance for the shape recognition task. This functionally-relevant focus of activation does not overlap with the area shown in exp. 2.a.ii to be a novel cochleotopic area in the blind, and is thus not engaged in low-level auditory processing. Preliminary results of the comparison between the shape recognition and location detection tasks (Fig. 7) shows that the sensory substitution tasks activate the ventral and dorsal streams of the sighted subjects as expected according to the normal division of labor between the visual streams (Ungerleider and Mishkin, 1982). In contrast, the occipital cortex of the blind subjects does not show preferential activation for the location task, but rather a global shape-processing

preference in the occipital cortex of the congenitally blind group mainly in the ventral occipital lobe. These results demonstrate that though some functional preferences exist in the occipital cortex of the congenitally blind, visual deprivation may result in a different division of labor than that generated in the normally developing visual cortex. The functional differentiation in the ventral stream will be further tested in visual topography experiments (2.b.iv) which are currently being conducted. Furthermore, repeating the shape-location task following long term training (2.b.iii) will test if a dorsal-ventral differentiation may arise following long-term use of sensory substitution.

Another goal of this experiment was to test for the effect of short-term learning. For this, I compared the activation generated by the vOICe soundscapes before the subjects know the auditory-to-visual transformation algorithm, and after the short training session (Fig. 6D). Short training did not significantly improve the behavioral results (on average), but despite that, following short training most of the network involved in perception of the vOICe soundscapes demonstrated increased activation, including regions within the ventral and posterior occipital lobe. This suggests that visual cortex plasticity and recruitment for sensory substitution analysis can be seen in extremely short time scales in blind individuals.

These results suggest that in blind individuals (and on a group level analysis) the occipital cortex is functionally involved in late stages of SSD shape recognition. This involvement can arise in a short duration, even before generating a large behavioral effect, showing that in this case neuroplasticity and the recruitment of occipital cortex for trans-modal visual processing precedes overt learning.

2.b.iii. Trans-modal processing of auditory stimuli – the plasticity in vOICe learning on long time scales

An additional scan of the same shape recognition task (designated to show the effect of long-term plasticity) is conducted following the completion of the training procedure. So far 3 sighted and 3 blind subjects have been scanned, and full data acquisition is expected to be completed in a group level (11 subjects) around June 2010, and analyzed by October 2010.

2.b.iv. Trans-modal processing of auditory stimuli – the topography of trans-modal “visual” processing

Functional trans-modal “visual” localizers and their dynamics, as well as their visual control experiments are conducted following the completion of the training procedure. So far 3 sighted and 3 blind subjects have been scanned, and full data acquisition is expected to be completed in a group level (11 blind, 7 sighted subjects) around June 2010, and analyzed by December 2010.

Preliminary single subject results suggest that SSD “visual localizers” can be used to define the FFA, PPA etc. in sighted subjects. In congenitally blind subjects some functional preferences can be seen in the occipital lobe: regions in the

ventral occipital cortex show preferences for specific object categories, but no conclusive results can yet be made regarding their consistency across subjects.

Future directions

Other possible directions I may pursue given sufficient time, include looking into the behavioral abilities of the blind in SSD-use, in adults, and perhaps in children. vOICe training will be accompanied by behavioral testing of the learning curves and final behavioral outcome in identifying complex visual objects, object locations and end-result “visual” acuity test. Testing will be done at least twice during the training: once following basic shapes training and once after extensive training in identifying complex visual stimuli. Testing will include displaying the subject a vOICe soundscape 4 times, and then asking a 9-alternative-forced-choice question, requesting a categorization of the heard image to one of the 9 learned object categories. A similar test will be applied to object location, identifying the location of a soundscape out of 9 possible positions. Additionally, to test the “visual acuity” of SSD use, I may apply a version of the Snellen visual acuity test at various stages of the vOICe training. While data acquisition in this study is already underway, due to the longitudinal nature of this study and the slow accumulation of behavioral results, behavioral data analysis may be completed only pending the recruitment of a sufficient number of subjects.

In addition to testing the behavioral and neuroplasticity in blind adults, I may compare their abilities to those obtained by blind children. The brain of blind children is more plastic than that of adults (Neville and Bavelier, 2002), and children might learn to see even after years of blindness if sight is restored surgically (a very rare event) and training is given (Ostrovsky et al., 2006). A recent study found that in sighted children, parts of the ventral visual stream continue to develop until adolescence (Golarai et al., 2007). All of this suggests that using SSDs with blind children for artificial vision is very promising. Though there have been preliminary attempts to study infants using a sonar sensory aid (Kay and Kay, 1983; Sampaio, 1989), surprisingly no one has attempted (to the best of my knowledge) to systematically teach detailed synthetic vision using SSDs to blind children and to study their brain in relation to this process using neuroimaging and other techniques.

Figures

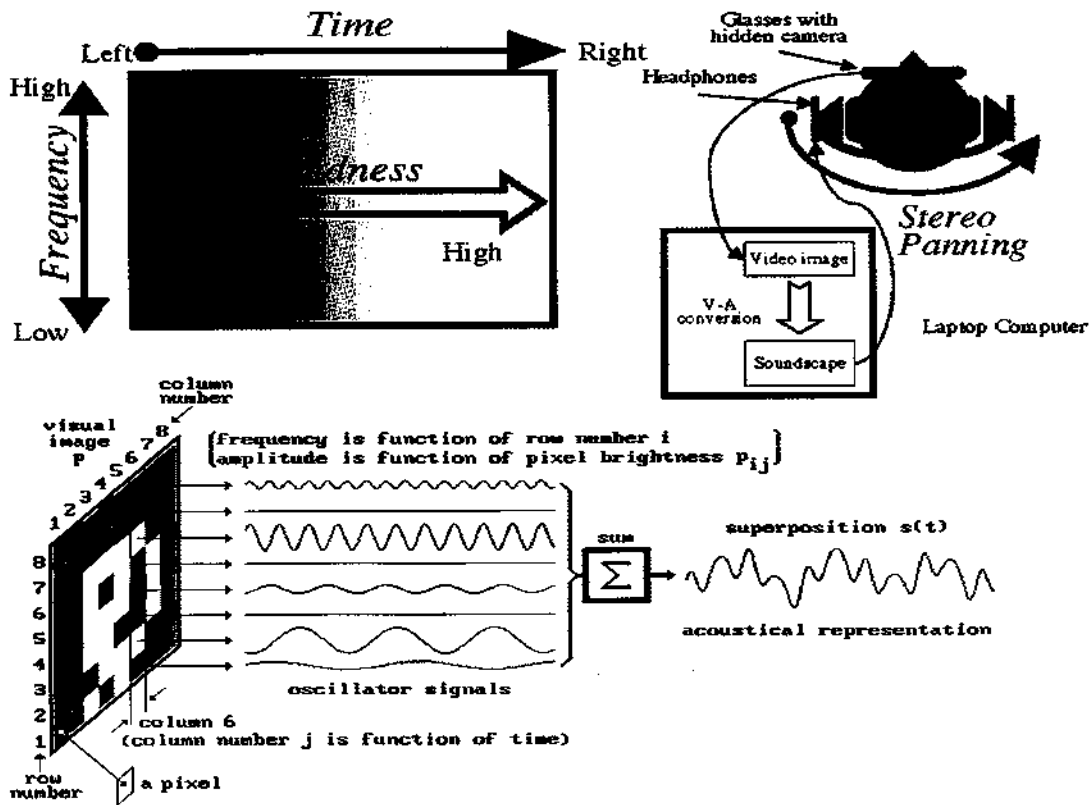


Figure 1: The vOICE algorithm: a visual-to-auditory SSD.

Schematic summary of the algorithm employed for the visuo-auditory conversion and the components of the system (adapted from Meijer, 1992). The functional basis of the visuo-auditory transformation employed lies in spectrographic sound synthesis from any input image, which is then further perceptually enhanced through stereo panning and other techniques. Time and stereo panning constitute the horizontal axis in the sound representation of an image, tone frequency makes up the vertical axis, and loudness corresponds to pixel brightness. Visual information in the sound representations of complicated gray-scale images is preserved up to a resolution of about 60x60 pixels for a 1 s sound scan and a 5 kHz audio bandwidth. Further technical details can be obtained at <http://www.seeingwithsound.com>.

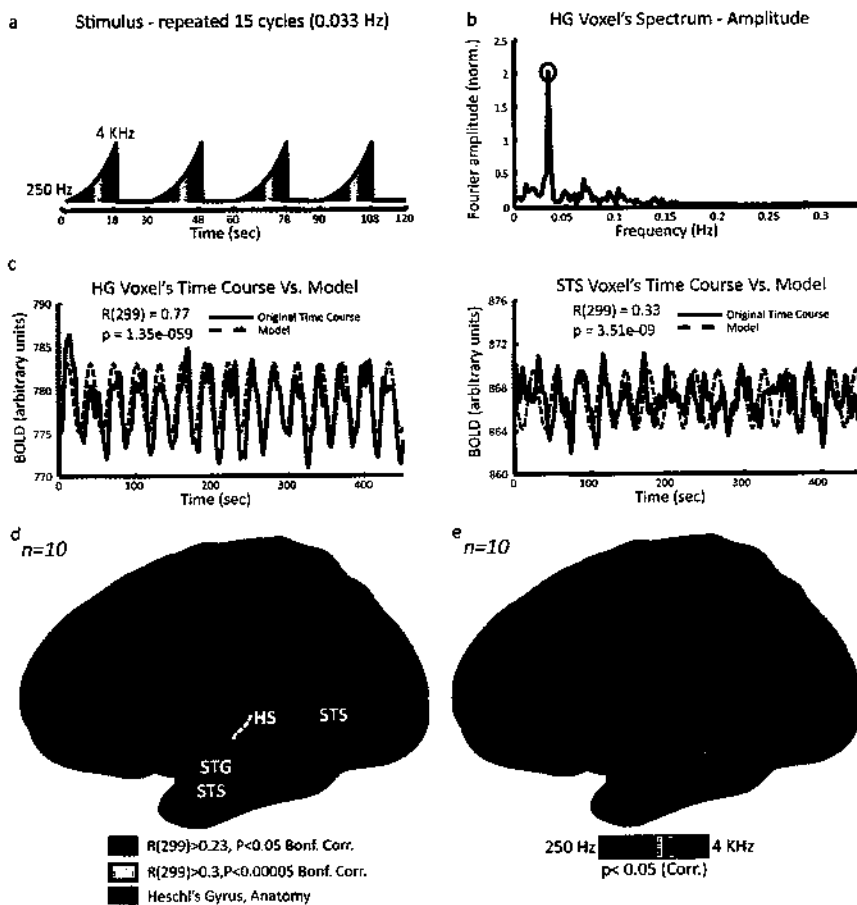


Figure 2: Cochleotopy experimental design and spectral analysis.

- A. Stimulus – the subjects heard a dynamic ascending pure tone chirp, which repeated 15 times (stimulus repetition frequency 0.033Hz).
- B. Each voxel's time course was Fourier transformed. Presented here is the normalized amplitude of the spectrum of a voxel sampled from Heschl's gyrus (HG) of a representative subject. Amplitude at stimulus repetition frequency is marked with a red circle. The voxel's phase at that frequency corresponds to the preferred tone (auditory frequency) of the voxel.
- C. Amplitude and phase parameters were used to construct a pure cosine used as a model of the activation. The original raw time course of two voxels, one from HG and one from the superior temporal sulcus (STS) are drawn in red; the dashed black line shows the model for each voxel. Pearson correlation coefficients were calculated to estimate the significance of the response of each voxel, and phase maps were inspected only in regions showing high and significant correlations.
- D. Mean correlation coefficient (Pearson's R) map of 10 subjects, presented on a partly inflated left cortical hemisphere of the standard MNI brain. Most of the auditory cortex is marked with high R values (marked red, $R(299) > 0.23$, $P < 0.05$ Bonf. Corr.). Within this region R values are the highest in the core area (marked in yellow, $R(299) > 0.3$, $P < 0.00005$ Bonf. Corr.), including HG (marked in green) and its surroundings. HS – Heschl's sulcus, STG – Superior temporal gyrus, STS – Superior temporal sulcus.
- E. Group (Cochleotopic exp. 1, $n = 10$) best frequency map is presented in a lateral view of the partly inflated cortical hemispheres of the standard MNI brain. The map within the auditory-responsive region shows multiple iso-frequency bands, in addition to the mirror-symmetric cochleotopic maps in the auditory core area on the superior temporal plane. These iso-frequency bands extend in a superior-to-inferior axis along the temporal cortex to the superior temporal sulcus.

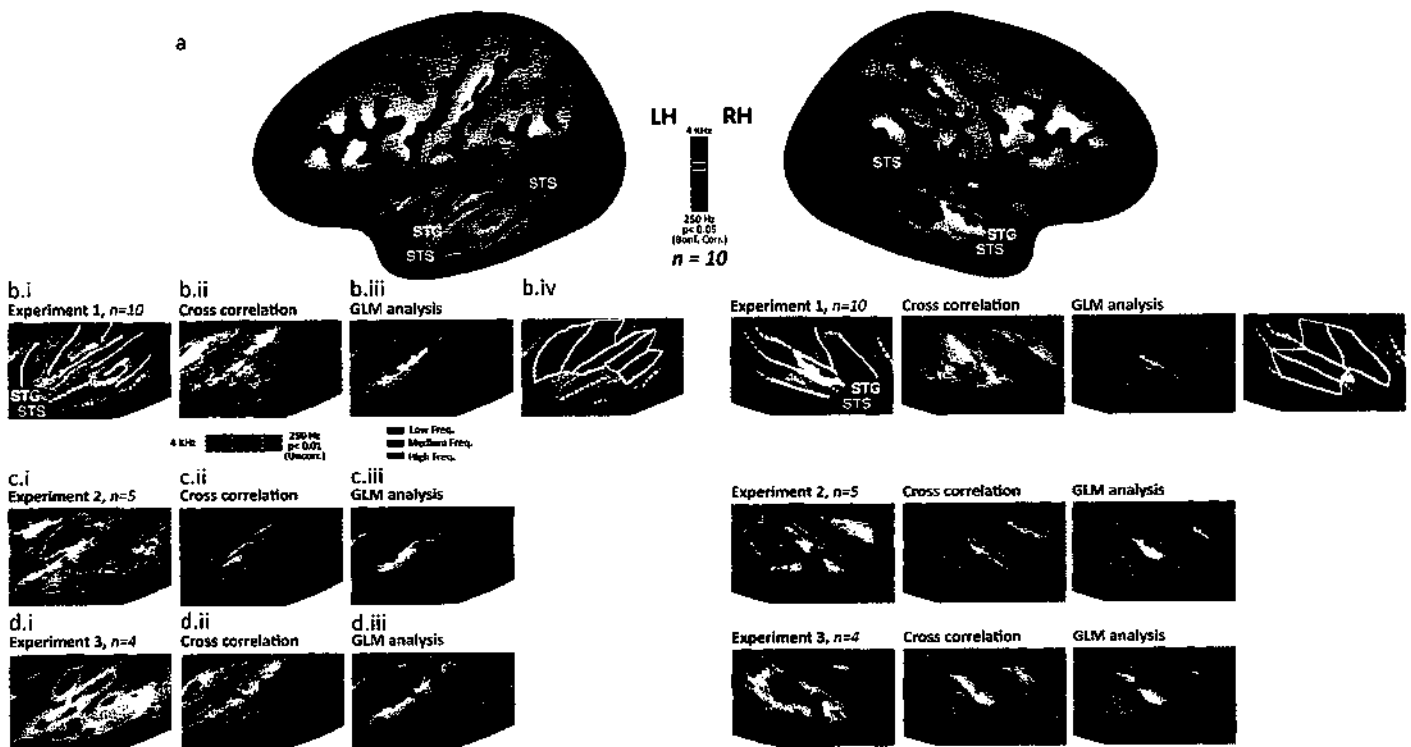


Figure 3: Multiple mirror-symmetric cochleotopic maps in the human auditory cortex.

- A. Group (Exp. 1, $n=10$) best frequency map is presented in a lateral view of the inflated cortical hemispheres of the standard MNI brain, exposing the entire cochleotopic organization of the multiple iso-frequency bands. STG – Superior temporal gyrus, STS – Superior temporal sulcus.
- B. i. The auditory cortex region is magnified, showing Exp. 1 best frequency map on the cortical surface. The estimated border between the putative mirror-symmetric cochleotopic maps is indicated (white line) in the lowest and highest frequency tones which represent the mirror-symmetry flipping lines. ii. Cross-correlation analysis for the averaged single-subject time-course shows remarkably similar trends to that of the spectral analysis. iii. The continuous auditory stimulation was analyzed by dividing it in a random effect general linear model (RFX-GLM) into low, medium and high frequency tone conditions. The GLM map displays the contrast of each frequency band with the other conditions. iv. The putative mirror-symmetric maps in these regions are marked in dark and light purple, highlighting the two core cochleotopic maps in both hemispheres, as well as 3 additional extra-core cochleotopic areas in the left hemisphere and two extra-core areas in the right hemisphere.
- C. Spectral (i), cross-correlation (ii) and GLM (iii) analyses are displayed for Exp. 2 ($n=5$) in which the chirp was reversed (i.e. from high to low frequencies), showing that the auditory fields and cochleotopic gradients displayed for Exp. 1 do not result from the frequency modulation direction.
- D. Spectral (i), cross-correlation (ii) and GLM (iii) analyses are displayed for Exp. 3, in which a subgroup ($n=4$) of subjects was scanned again one month after the original scan, revealing a similar patterns of iso-frequency bands as the original (first scan) map, demonstrating the high test-retest reliability of the auditory fields and their locations.

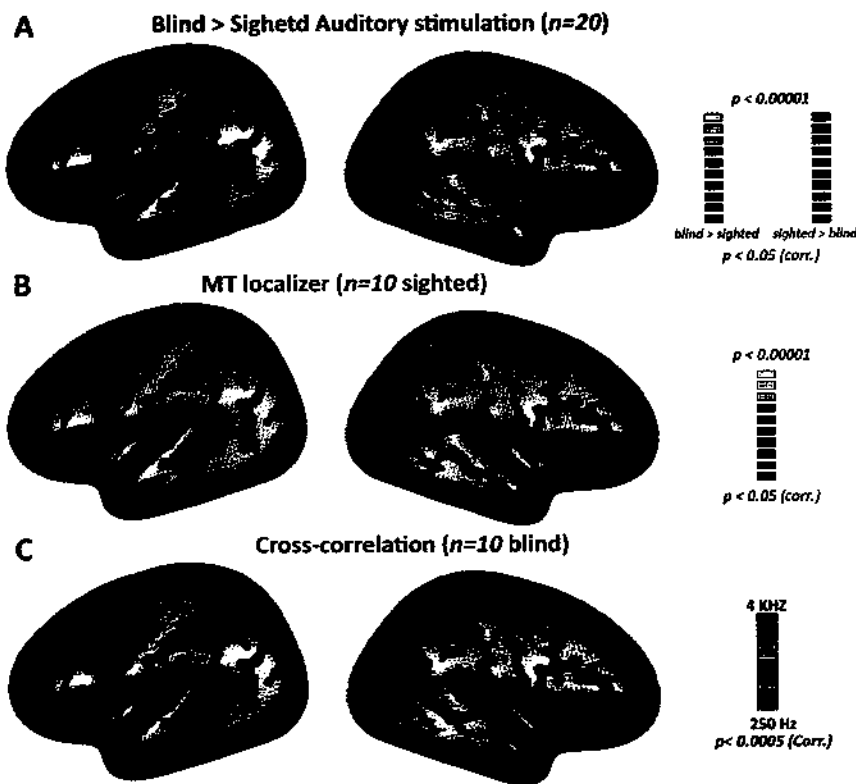


Figure 4: Auditory activation in the congenitally blind occipital lobe

- A. A contrast between the activation generated by simple auditory stimulus (auditory rising chirp) in the blind (n=10) and the sighted (n=10) groups is presented in a lateral view of the inflated cortical hemispheres of the standard MNI brain. While the auditory regions within the temporal lobe are more strongly activated by the sighted group, other regions, including the middle temporal sulcus in the occipital lobe, are more strongly activated in the congenitally blind group.
- B. A visual motion localizer (comparison of moving and stationary visual stimuli) conducted in a sighted subject group (n=10) is displayed on the same brain, showing that the auditory activation in the blind is indeed localized grossly in the anatomical location of sighted area MT. The middle temporal auditory responsive area shows some cochleotopic preferences (differential preferences for high and low-frequency tones), which will be further validated in the control falling chirp experiment.



Figure 5: Examples of images used for vOICe training in sighted and congenitally blind subjects.

Following approximately 40 hours of training, trained individuals can recognize, for example, that pictures contain faces, houses, letters, every-day objects or people, and identify specific features regarding them.

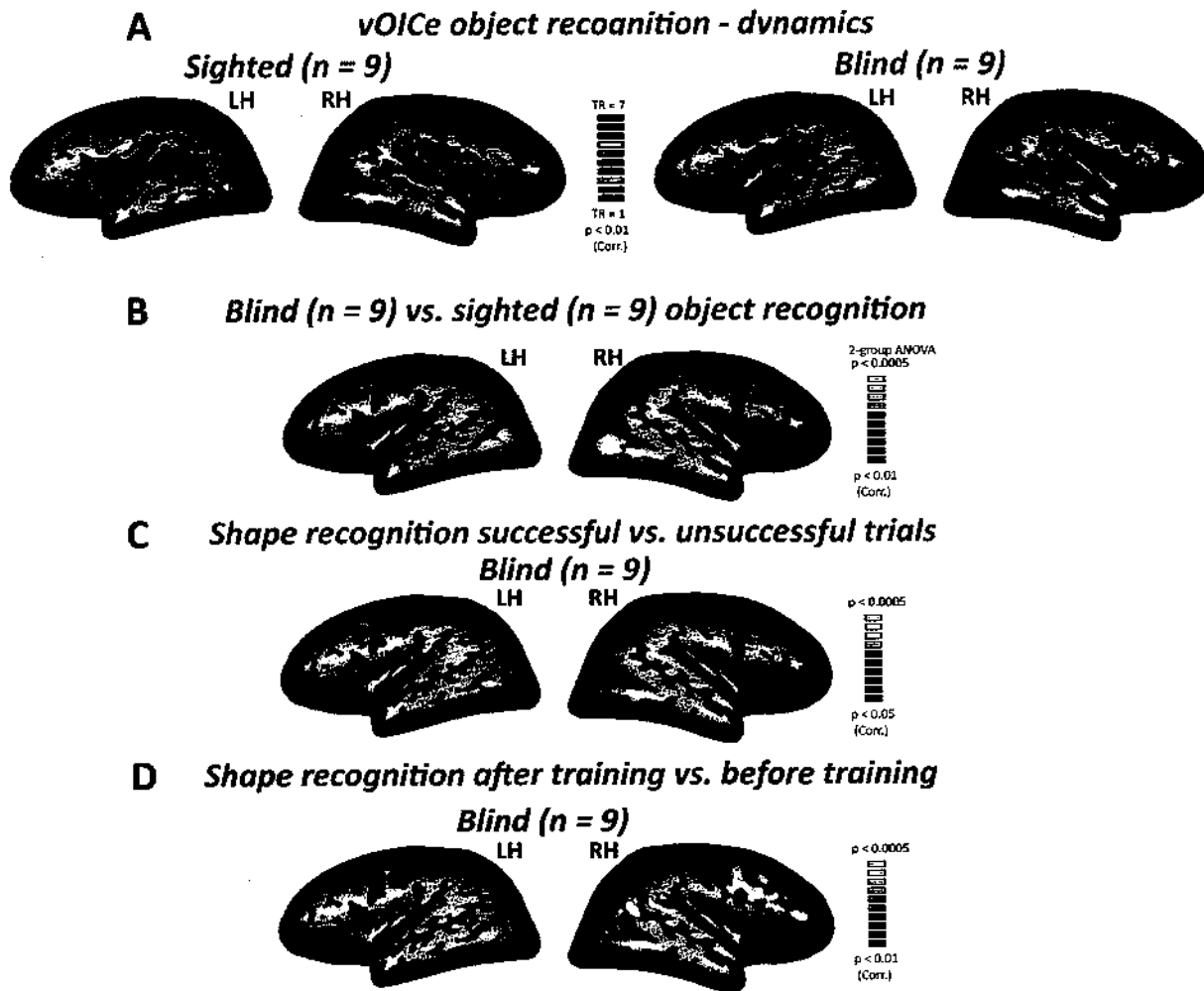


Figure 6: Neural networks, dynamics and the effect of short-term plasticity in vOICe shape recognition

- Following the training, both blind and sighted groups demonstrated significant activation in the ventral prefrontal cortex, superior parietal lobe (IPS) and occipital-temporal cortex. Furthermore, in the blind we additionally observed robust activation in the posterior occipital lobe bilaterally. Analysis of the brain dynamics underlying the shape recognition process demonstrated that the occipital cortex is involved during the late analysis of the stimulus rather than during the early auditory perception.
- Comparison between the blind and sighted groups reveals a significant difference in the activation of the visual cortex in response to sensory substitution shape processing.
- Occipital cortex activation in the blind is also modulated by performance level on a trial by trial basis, demonstrating its relevance for the shape recognition task.
- After the short training most of the network involved in perception of the vOICe soundscapes demonstrated increased activation, including regions within the ventral and posterior occipital lobe.

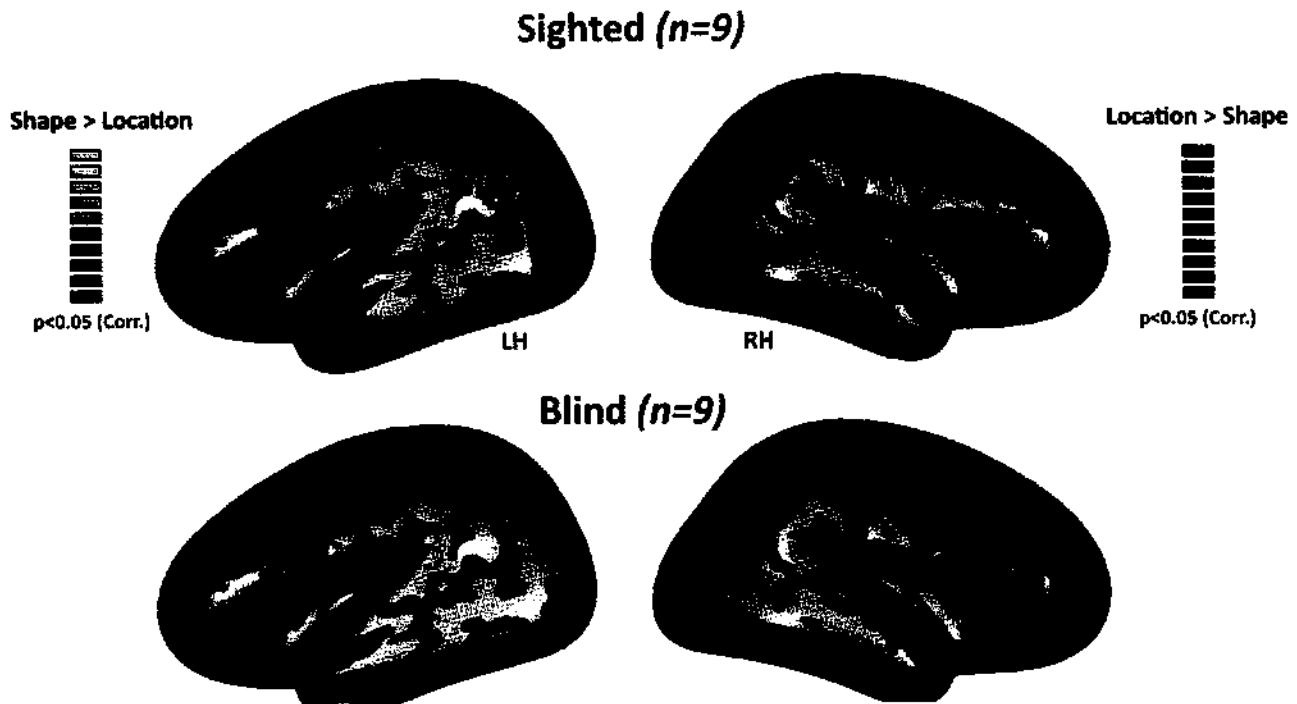


Figure 7: Division of labor in the occipital lobe in vOICe “what” and “where” tasks

The preliminary comparison of the location detection (left vs. right location; depicted in green) and the shape recognition (round – non-round; depicted in orange) tasks reveals the known division of labor between the dorsal and ventral visual streams in the sighted group (upper panel) and a lack of such differentiation, along with a global shape-processing preference in the occipital cortex of the congenitally blind group (lower panel). These results demonstrate that though some functional preferences exist in the occipital cortex of the congenitally blind, visual deprivation may result in a different division of labor than that generated in the normally developing visual cortex.

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