NEUROPLASTICITY IN THE BLIND AND SENSORY SUBSTITUTION FOR VISION

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By

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Abstract

We live in a society based on vision. Visual information is used for orienting in our environment, identifying objects in our surroundings, alerting us to important events which require our attention, engaging in social interactions, and many more functions that are necessary to efficiently function in everyday life. Thus, the loss of vision decreases the quality of life and poses a severe challenge to efficient functioning for millions of individuals worldwide.

Despite some medical progress, the restoration of visual information to the blind still faces multiple technical and scientific difficulties. "Bionic eyes" or visual prostheses are being developed mostly for specific blindness etiologies and target only a subpopulation of the visually impaired. Even these devices have yet to reach the stage where the technology can provide high-resolution, detailed visual information.

More importantly, these approaches take for granted the ability of the human brain, following long-term or even life-long blindness, to interpret vision once the input from the eyes becomes available.

The current scientific consensus regarding the development of the visual cortex is that visual deprivation during critical or sensitive periods in early development may result in functional blindness, as the brain is not organized to process visual information properly, and this may be irreversible later in life. In fact, the rare reported cases of late-onset surgical sight restoration (by means of cataract removal in early blind patients) show severe visual impairments that persist even following long-term exposure to vision. Furthermore, studies of early-onset and congenitally blind people have shown that their visual cortex may have plastically reorganized to process information from other sensory modalities. Recent studies showed that even short term visual deprivation in adulthood may cause some functional chances in the visual system. Thus, sight restoration may indeed be severely limited by the reorganization of the visual cortex.

In this dissertation I test this theory by using an alternative approach to visual rehabilitation, in which the visual information is conveyed non-invasively using the remaining senses of the blind. We used a sensory substitution device (SSD) that translates visual information using a consistent algorithm to sounds (The vOICe). Because SSD soundscape translations of natural visual input are very complex, we developed a structured training protocol (Striem-Amit et al., 2012b) where congenitally blind people are gradually taught how to interpret

the sounds carrying the visual information. This training paradigm also made it possible to test whether the congenitally blind can learn to perceive complex visual information without having had visual experience during early infancy, and to better identify the neural correlates of processing such information in the blind.

Specifically, this dissertation aimed to study:

1. Whether and how SSDs may be applied for visual rehabilitation to reach sufficient practical visual acuity and functional abilities. Can we restore complex visual capacities such as object categorization (a visual ability which requires feature binding within visual objects as well as their segregation from their background) beyond the critical developmental period in the congenitally blind?
2. How are such visual-in-nature artificially-constructed stimuli processed in the blind brain? Can we find evidence for the functional specializations of the normal visual cortex in the absence of visual experience during the critical periods of early development?

We found that the blind were able to learn to perceive high-acuity visual information, and could even exceed the Snellen acuity test threshold of the World Health Organization for blindness (Striem-Amit et al., 2012d) and the 'visual' acuity possible using any other current means of visual rehabilitation. Furthermore, they were able to perceive and categorize images of visual categories, and carry out certain visual tasks (Striem-Amit et al., 2012b).

A neuroimaging investigation of the processing of SSD information showed that despite their lack of visual experience during development, the visual cortex of the congenitally blind was activated during the processing of soundscapes (images represented by sounds). More importantly, its activation pattern mimicked the task- and category- selectivities of the normally developed visual cortex. Specifically, we found that the blind showed a double-dissociation between processing image shape and location in the ventral and dorsal processing streams (Striem-Amit et al., 2012c), which constitutes the large-scale organization principle in the visual cortex. Furthermore, we found that within the ventral stream, category-selectivity for one visual category over all others tested can be seen in the visual word-form area (VWFA) which, as in the normally sighted, showed a robust preference for letters over textures and other visual categories (Striem-Amit et al., 2012b).

In both studies, the visual cortex showed retention of functional selectivity despite the a-

typical auditory sensory-modality input, the lack of visual experience, the limited training duration (dozens of hours) and the fact that such training was applied only in adulthood. These findings support a controversial organization theory which suggests that instead of being divided according to the sensory modalities which elicit it, the cortex area may be better defined by the tasks or computations it conducts, whereas the input sense organ is irrelevant. Specifically, this model suggests that a combination of top-down connectivity with an innate preference for computation- type may generate the same task-selectivities even in the absence of bottom-up visual input. This theory has interesting bearings on the ability to restore sight later in life, as it suggests that the blind brain may not have lost its ability to process some aspects of visual information and may learn to do so if this information is delivered to the brain either via SSDs, as we show possible here, or using other more invasive means.

Contents

Abstract I

1. Introduction 2

  1.1 Rehabilitation following sensory loss 5

    1.1.1. Sensory restoration approaches 5

    1.1.2. Sensory substitution devices 7

    1.1.3 Current challenges in sight restoration 10

  1.2. Neural aspects of functional visual rehabilitation 12

    1.2.1. Neural and cognitive consequences of sensory loss 13

    1.2.2. Evidence for robust task switching plasticity promoted by sensory loss 15

    1.2.3. Critical/sensitive developmental periods and sensory loss 18

    1.2.4 Cross-modal takeover of the visual cortex: can the blind brain switch back to the original visual task specialization? 21

2. Methodology 24

3. Results 28

  3.1 'Visual' acuity of the congenitally blind using visual-to-auditory sensory substitution 28

  3.2 The large-scale organization of "visual" streams emerges without visual experience 29

  3.3 Reading with sounds: Sensory substitution selectively activates the visual word form area in the blind 30

4. Discussion and conclusions 31

  4.1 Summary of the findings 31

  4.2 Task-selective operators in the visual cortex 32

  4.3 Brain organization in the absence of visual experience 35

  4.4 How can “visual” task-selectivity arise in the blind brain? 39

  4.5 Limitations and open questions regarding the task-selective model 42

  4.6 Implications for visual rehabilitation using SSDs 44

  4.7. Conclusions 50

5. References 52

6. Appendix: Extensive Cochleotopic Mapping of Human Auditory Cortical Fields Obtained with Phase-Encoding fMRI 75

תקציר I

1. Introduction

We live in a society based on vision. Visual information is used for orienting in our environment, identifying objects in our surroundings, alerting us to important events that require our attention, engaging in social interactions, and many more functions that are necessary to efficiently function in everyday life. Thus, the loss of vision decreases the quality of life and represents a severe challenge to efficient functioning for millions of individuals worldwide (314 million individuals are visually impaired worldwide; WHO, 2009). Furthermore, it has a significant economic impact on society.

It is therefore not surprising that numerous approaches and potential solutions designed to overcome these difficulties have been put forward to help the visually impaired. However, while the use of compensation devices such as highly sensitive hearing aids, volume enhancing devices and cochlear implants has already greatly improved the lives of many auditorily impaired, compensation and technological aids for the visually-impaired are currently much less effective. At this point in time, the most commonly used rehabilitation techniques for blindness are sensory aids such as the Braille reading system, mobility aids such as canes, or more contemporary devices such as obstacle detectors, laser canes or ultrasonic echolocating devices. All of these devices derive from the premise that the blind are deprived of numerous important types of information typically transferred through vision and each attempts to supply one such information type through other sensory systems. Typically, these attempts “play by the processing rules” of the system they exploit for communicating the relevant information. For example, Braille uses palpable tactile script to compensate for the absence of visual script.

In contrast, the new generation of sensory aids takes one step further, in that it aims to deliver full visual information about the surroundings to the brains of the blind. One way to accomplish this is by surgically restoring the missing functionality of the eyes and brain areas typically exploited for visual processing. Conventional sight restoration includes surgical removal of cataracts and treatment of vision loss caused by glaucoma. Although highly practical and frequently used in the developed world following short periods of sight deterioration (and also rarely following longer term blindness with much more limited success; see details in section 1.2.3), these solutions are only applicable to specific causes and stages of vision loss. Sight restoration in blindness due to other etiologies, such as congenital or late-onset degeneration (for example age-related macular degeneration) of the retina or optic tract has only started to be addressed. This is done mostly by the development of new generation techniques, neuroprosthetic medical solutions aimed at restoring the missing sense by replacing the retina with a bionic component that can transmit the visual information directly via the optic tracts to the brain (as is already done in audition using cochlear implants; Fallon et al., 2008; Geers, 2006; Spelman, 2006). However, these novel approaches still have several major disadvantages. These are invasive, expensive techniques which offer very limited visual perception, and currently have only been somewhat successful in very restricted populations of the blind, since they typically depend on stimulating retinal ganglion cells (which are not always intact in different etiologies) to transmit their signal. However, once several technological obstacles (detailed below) are resolved, these may hold great promise for restoring natural vision to many blind individuals, similar to the enormous progress in the treatment of deafness that has been made since the development of cochlear implants.

The second group of rehabilitation approaches takes a different methodology of translating full visual information of the environment to another, non-visual modality. Such sensory substitution devices (SSD) are non-invasive, cheap and relatively accessible. These devices are designed to deliver visual information to the blind using their remaining and fully-functioning sensory modalities, in the hope that the brains of such individuals will learn to exploit this information, similarly to the way the sighted use equivalent information transmitted though the visual pathway. Although this hope may appear unintuitive or even unrealistic, SSDs, when used with targeted training (see methodology section and results section 3.3) are starting to show, as presented here, some very encouraging and in some cases even remarkable outcomes, while still facing many challenges (see discussion). Such efficiency combined with their low cost and broad applicability to different types or ages at sensory loss make them highly attractive sensory aids. This is especially important in blindness, given that 87% of the blind reside in developing countries and therefore need cheap and widely applicable solutions.

However, even if the best optimal technological rehabilitation-aid is designed, an additional, perhaps more critical, challenge facing sight restoration efforts is that of the neural and cognitive capacities required to process vision. In a sense, when first introduced to the brain of a congenitally blind individual, the visual information is meaningless because that individual lacks any previous experience against which to interpret this information interpreted (Held et al., 2008). The study of early-onset and congenitally blind people has shown that their visual cortex may have plastically reorganized to process information from other sensory modalities (see section 1.2.2); thus, the brain of such individuals may lack a functioning visual system needed for interpreting this newly introduced information and giving it functional meaning. Currently, the scientific consensus regarding visual cortex development is that visual deprivation during critical or sensitive periods in early development may result in functional blindness, because the brain is not organized to process visual information properly, and this may be irreversible later in life (see section 1.2.3). Indeed, the rare reported cases of late-onset surgical sight restoration (e.g. by means of cataract removal) following long visual deprivation periods show severe visual impairments that persist even following long-term exposure to vision, suggesting that sight restoration may be severely limited by the reorganization of the visual cortex. Therefore, it is both of clinical importance as well as of vital interest in terms of our basic understanding of brain processing and organization to determine whether the visual cortex of the blind can functionally interpret visual information, and if so, whether can it utilize a similar functional organization to that of the complex normally developed sighted brain (section 1.2.4).

In this thesis I present the current methods of visual rehabilitation, and expand on the effective use of a specific visual-to-auditory SSD (The vOICe; Meijer, 1992) for this purpose. I detail the challenges of using SSDs; namely how we provide the training required and the visual abilities they afford following such targeted training, in terms of both visual acuity and the functional abilities in every-day settings (results sections 3.1 and 3.3). Given the lack of visual experience of our congenitally blind participants, their ability to process multiple features of the visual scene is especially important.

Furthermore, I discuss the way in which such sensorily-transformed information is processed by the congenitally blind brain. I report evidence that the congenitally blind brain, despite many previous studies showing robust functional reorganization to the extent of functional task switching (Striem-Amit et al., 2011a; from vision to language and memory), may still tap some of the neural networks and functional organization that relates to the “visual” nature of different stimuli and tasks (results sections 3.2 and 3.3). I discuss the significance of these findings both clinically for the restoration of vision in adulthood (section 4.6), and for our understanding of the underlying principles of brain organization in the “visual” cortex (sections 4.2-4.5).

1.1 Rehabilitation following sensory loss

1.1.1. Sensory restoration approaches

Restoration of sensory input to the visually impaired using visual implants appears to be an attractive alternative to sensory substitution devices, as they provide a sense of “real” vision, visual qualia (as compared to providing only visual information without the sensation of sight). The development of visual prostheses was prompted 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). The idea of channeling these findings into clinical applications was suggested years ago by a handful of researchers (Dobelle et al., 1974; Haddock and Berlin, 1950; Newman et al., 1987), but their ideas are only now being pursued, as shown by the extensive development of visual prostheses. Today, different approaches in which visual information is recorded by external (or implanted) devices and transmitted to the sensory tract (Brelen et al., 2005; Delbeke et al., 2002; Veraart et al., 2003), secondary processing cells in the retina (ganglion cells; Weiland et al., 2011), thalamus (Pezaris and Reid, 2005, 2009) or the visual cortex (Fernandez et al., 2002; Schmidt et al., 1996; Troyk et al., 2003) thereby replacing the healthy receptors and relay pathways of the sensory organs, are being studied or tested in clinical trials (for recent reviews of current technologies and the remaining challenges see Dowling, 2008; Weiland and Humayun, 2013; Weiland et al., 2011). The most advanced approach today is that of the retinal implants, which is mainly useful in cases of retinitis pigmentosa and age-related macular degeneration (ARMD) which cause selective degeneration of the photoreceptor layer of the outer retina. In this case the information sent to the visual cortex can still be transmitted over minimally damaged retinal ganglion cells.

Devices based on these approaches have so far shown some promising results, as experienced blind users can, to some extent, utilize visual phosphenes generated by some of these devices to experience meaningful visual percepts. However, although they are at the cutting edge of medical, technological and scientific advances, there are still several major issues currently preventing these approaches from becoming true clinical solutions. First of all, their invasive nature makes them prone to risks related to surgical procedures, such as inflammation, hemorrhage, and increased patient mortality. For example, in the 32 patients implanted with an Argus II retinal implant up to March 1, 2010, there were 17 SAEs (serious adverse events) that were determined to be device or surgery related (Humayun et al., 2012). Moreover, retinal prostheses are not applicable to all populations of the blind, as they require the existence of residual functional retinal ganglion cells and visual tracts, whereas multiple blindness etiologies result in their injury or absence. Additionally, these techniques are expensive: the single type of retinal implant which has recently (February 2013) acquired the first FDA approval for chronic implantation, Second Sight's Argus II, which is now the first commercial visual implant, is available at a price of approximately $100,000 per unit (without the cost of the implantation operation itself). Furthermore, retinal implants have severe technical limitations which include a narrow field of view and the need for complicated image processing algorithms compensating for the visual processing taking place in the retina itself.

Functionally, these devices typically do not take advantage of eye movements (with one exception; Palanker et al., 2005), and require large and slow head movements to scan entire visual patterns (Brelen et al., 2005; Chen et al., 2007; Veraart et al., 2003). The visual percept they provide is thus also slower than natural vision: for example the average time for recognizing letters for the subjects who are capable of this task is ∼100 seconds (Humayun et al., 2012). Lastly (but importantly), these devices are currently greatly limited by the visual resolution they offer, providing only relatively poor visual acuity and sight even to those who overcome the immense cost and operation risks. This problem is further detailed in section 1.1.3 and in results section 3.1.

Thus, the visual abilities exhibited by the implantation patients include only simple visual tasks such as reading Braille letters (up to 4 letters at a time; Lauritzen et al., 2012) and normal letters (Ahuja and Behrend, 2013; Brelen et al., 2005; da Cruz et al., 2013; Dobelle, 2000; Weiland and Humayun, 2008), detecting motion direction of a large a high-contrast moving bar (Dorn et al., 2013; Weiland and Humayun, 2008), and localizing a simple large visual shape (Ahuja and Behrend, 2013).

Therefore, visual prostheses (which are only now becoming commercially available beyond preliminary clinical trials) do not yet provide sight that resembles natural vision and a key milestone in this field, namely generating truly useful and functional vision, at affordable costs has yet to be reached. If, however, visual prosthesis research can overcome these obstacles, these approaches could provide a real visual experience and not merely the ‘visual’ information or orientation provided by SSDs. Similarly, even newer solutions such as gene therapy (den Hollander et al., 2010) and stem cell therapy (Bull and Martin, 2011) will hopefully become available in the future and enable the treatment of wider etiologies.

1.1.2. Sensory substitution devices

An alternative approach to visual transmission to the blind is that of sensory substitution. Sensory substitution refers to the transformation of the characteristics of one sensory modality into the stimuli of another modality (for a clarification of the concept see Figure 1 in results section 3.2). For example it is possible to replace vision by touch or audition, audition or vestibular senses by touch, etc. In the case of blindness, SSDs represent a non-invasive rehabilitation approach in which visual information is captured by an external device such as a video camera and communicated to the blind via a human-machine interface in the form of auditory or tactile input. Louis Braille (1809-1852) who developed Braille writing pioneered the work that paved the way for modern SSDs by substituting visually read letters by a raised dot code. However, Braille can only work for material transformed offline from printed visual letters to Braille dots, and cannot be used for online reading of regular letters. In recent years other reading substitutions have been developed for online reading such as the Optacon (a print-to-tactual-image device devised for reading embossed letters; Goldish and Taylor, 1974; Linvill and Bliss, 1966), or various versions of dedicated text-to-speech engines (from the Kurzweil reading machine; Kleiner and Kurzweil, 1977 to current talking software). In addition to these reading aids, a great deal of effort has been invested in developing devices aimed at improving the mobility of the blind. The white cane used to mechanically probe for obstacles represents the simplest, most commonly used device. Both the Braille system and the cane solutions, which were quickly adapted by blind users, suggest that at times the simplest solution might be the one that is the most widely used. However, in recent years more advanced counterparts of the cane have become available, such as electronic travel aids designed to be used along with the white cane in order to extend the distance for environmental preview and thus increase speed and efficiency of travel. The Sonic Pathfinder (Heyes, 1984), the Sonicguide (Kay and Kay, 1983) and the EyeCane (Maidenbaum et al., 2013) typically scan the environment acoustically (ultrasonically) or optically (laser light or IR sensors), and transmit spatial information on obstacles and objects in the surroundings via vibrotactile or auditory signals.

In contrast to these devices which are typically designed for a limited purpose and are successful in replacing only certain functional aspects of vision, more sophisticated techniques that replace vision through tactile or auditory information have been developed over the last few decades. The first targeted modality for substituting vision was touch, due to the simplicity and ease of transforming visual into tactile signals which are both characterized by 2-dimensional spatial representations. Pioneering work in this field was done in the 1970s by Paul Bach-y-Rita who devised a tactile display which mapped images from a video camera to a vibrotactile device worn on the subject's back. This device (Bach-y-Rita, 2004; Bach-Y-Rita et al., 1969,; Bach-y-Rita and Kercel, 2003), dubbed the Tactile Vision Substitution System (TVSS) provided tactile transformation of black-and-white images at a resolution of 20×20 pixels and enabled the blind to perform sufficiently well in some visual tasks, for example a ball-rolling task and objects localization. However, it was extremely large and non-mobile which motivated the development of smaller mobile tactile devices placed on the tongue and forehead (for a review see Bach-y-Rita, 2004) which are also characterized by better spatial somatosensory resolution. One of these, the Tongue display unit, or TDU (Bach-y-Rita, 2004; Bach-Y-Rita et al., 1969), is an electrotactile device comprised of a 12x12 matrix of stimulators (measuring approximately 3 cm^2) placed on the subject's tongue (a newer version of this device, the BrainPort V100 device, is commercially sold by Wicab, Inc.). Studies that investigated this device suggest that at least a subgroup of early-onset blind may particularly benefit from its use (Chebat, 2007; Kupers, & Ptito 2007).

Audition was the second candidate to substitute for vision. The development of auditory-based devices was triggered by certain limitations of tactile SSDs; namely, their price and the fact that they are inherently limited by the spatial resolution of touch and relatively lower information content due to a cap on the number of electrodes and on the spatial resolution (2-point discrimination) of the skin. The first auditory SSD device was The vOICe system (Meijer, 1992), which initially used a default resolution of 176x64 sampling points, which was later expanded to 176X144 sampling points. This mobile and inexpensive device uses a video camera which provides the visual input, a small computer running the conversion program, and stereo headphones that provide the resulting sound patterns to the user. Given the high percentage of the world's visually impaired in developing countries (WHO, 2009), the importance of providing solutions which are not just high-resolution, but also cheap and accessible, cannot be underestimated. To some extent, visual-to-auditory SSDs fulfill all of these criteria. However, these devices still pose great challenges both to the developers and the brains of blind individuals using them, as they rely on conversion algorithms which are much less intuitive than those employed by visual-to-tactile SSDs. For example, in the visual-to-auditory The vOICe SSD (Meijer, 1992) the conversion program transforms visual into auditory information ('soundscapes') based upon 3 simple rules: the vertical axis (i.e. elevation of the object) is represented by frequency, the horizontal axis by time and stereo panning, and the brightness of the image is encoded by loudness. Although these conversion rules appear relatively simple, explicit and quite extensive training is required to learn how to interpret even simple shapes. Similar but not identical transformations are implemented in two more recently developed auditory SSDs, the Prosthesis Substituting Vision with Audition (PSVA; (Capelle et al., 1998); providing a resolution of 124 pixels), and SmartSight (Cronly-Dillon et al., 1999; Cronly-Dillon et al., 2000). PSVA uses different tones to provide horizontal location directly, whereas SmartSight presents the vertical location information in terms of musical notes. PSVA can break down the "visual sound" into components of vertically and horizontally oriented edges. Additionally, PSVA applies a magnification to the center of the image to simulate the better resolution (magnification factor) of the human fovea. A newer visual-to-auditory SSD (The EyeMusic; providing a resolution of 24x40 pixels; Abboud et al., In Press; Levy-Tzedek et al., 2012) also conveys color information by using different musical instruments for each of the five colors: white, blue, red, green, yellow; black is represented by silence.

Although extremely different, both auditory and tactile SSDs can potentially be very useful for the blind (but see details about their disadvantages in the next section and discussion section 4.6; mainly the need for explicit training, the potential interruption of auditory inputs and the low temporal resolution). Recent tests show that blindfolded sighted individuals, and in some cases even the blind can learn to interpret the transmitted information and use it in several simple visual tasks, especially after training or prolonged use of the device (Poirier et al., 2006b). These include simple visual discrimination and recognition of patterns (Arno et al., 1999; Arno et al., 2001; Poirier et al., 2006b; Sampaio et al., 2001), motion discrimination (Matteau et al., 2010; Ptito et al., 2009), extracting depth cues and estimating object distance or location (Auvray et al., 2007; Proulx et al., 2008; Renier et al., 2005; Renier and De Volder, 2010), and even recognizing objects (Amedi et al., 2007; Auvray et al., 2007; for a full review of the behavioral abilities using SSDs see Maidenbaum et al., In Press).

1.1.3 Current challenges in sight restoration

Current sight restoration efforts, whether via invasive or non-invasive methods, still face several challenges to be applicable to the general visually-impaired population.

These may be divided to two main features:

1. Conveying information with sufficient practical visual resolution, or acuity.
2. Enabling visual functional processing of every-day complex scenes and tasks

Although the two may seem to be somewhat interchangeable, they stem from very different sources.

The first, while not trivial, is in essence a technical problem of transmitting and more importantly of deciphering a high-resolution visual matrix. Both the visual prostheses and most sensory substitution devices offer relatively low pixel resolution to begin with: up to 1500 pixels in visual prostheses and up to 400 pixels in the most updated version of the TDU (except for the vOICe SSD and new EyeMusic, see details below).

Furthermore, currently the most advanced version of visual implants, retinal prostheses, are technically limited to providing a very narrow field of view due to problems in creating concave implants to fit the anatomical structure of the retina. The current versions provide a maximal resolution of 60 electrodes and 20˚ visual field-of-view (Argus II; Second Sight Inc., Sylmar, CA, USA; http://2-sight.eu/ee/benefits-of-argus-ii) and a newer competing model contains 1000-1500 electrodes, but with a more limited, 11˚, visual field-of-view; Zrenner et al., 2010; Retina Implant AG, Reutlingen, Germany).

Perhaps more importantly, the resulting acuity is lower than predicted given the number of pixels, because the translation from technical resolution to functional acuity is highly complex. For instance, the newest subretinal prosthesis technically has 1500 pixels, but provides a much lower than expected functional acuity, with a maximal measurable acuity of only 20/1000 (Zrenner et al., 2010); the numerator refers to the distance in feet from which the tested person can reliably distinguish a pair of objects. The denominator is the distance from which a person with standard visual acuity would be able to distinguish them. Thus the smallest letter implant patients can see at 20 feet could be seen by a normally sighted person at 1000 feet (i.e. they can discern only extremely large letters). Interestingly, although the TDU maximal technical resolution was only 144 pixels at the time visual acuity was estimated using this device, it enabled better acuity than the highest 1500-electrode technical resolution retinal implant (up to 20/860; Chebat et al., 2007; Sampaio et al., 2001), stressing the need to test for functional acuity beyond potential pixel resolution. However, this acuity was still functionally quite poor. For purposes of comparison, the blindness threshold of the World Health Organization (WHO) is set at a best corrected sight of 20/400 acuity (and a 10˚ visual field; 10th revision of the WHO international classification of diseases, update 2007), and up to now retinal prostheses and tactile-to-visual SSDs remain far below such levels of acuity.

Since no visual rehabilitation tool has been able to provide a high-resolution visual matrix to the blind, it also remains an open question whether people who are blind from an early age or from birth can even process such a complex “visual” sensory-transformed matrix after many years of blindness.

This problem and a suggested implementation of the vOICe SSD is described in the results section 3.1 (Striem-Amit et al., 2012d). The vOICe SSD provides a-priori the highest theoretical resolution (up to 25,344 pixels), and is thus a leading candidate for visual rehabilitation. Its main disadvantages lie in the complexity of understanding the shapes underlying the complex soundscapes it produces and the relatively low temporal resolution (see full detail in section 4.6). Although the SSD conversion rules are relatively simple (see Figure 1 in results section 3.3), interpreting images requires explicit and quite extensive training, which was not in existence at the onset of my research. As part of the research project, I helped develop a targeted training protocol in “learning to see” using the vOICe (see details in the methodology section). In results section 3.1 and 3.3 I describe the functional visual acuity perceivable (as assessed by an adapted visual-to-auditory version of the Snellen E-chart visual acuity test used by ophthalmologists) by congenitally blind people who underwent this training. I show that the training of a high-resolution visual-to-auditory SSD can lead to the highest reported functional visual acuity in the visually impaired with any visual rehabilitation approach, exceeding even the World Health Organization (WHO) blindness acuity threshold.

The second problem, which will be detailed in the next section, has to do with brain organization, plasticity and neuro-rehabilitation, which is more complex, and pertains to our understanding of brain function.

1.2. Neural aspects of functional visual rehabilitation

While further developing and improving rehabilitation techniques is still an enormous technological challenge, sensory restoration efforts may require more than simply transmitting the visual information, either via other modalities as in SSDs or by providing vision through the natural visual system to the brain. In a way, when first introduced to the brain of a congenitally blind individual, the visual information is meaningless because that individual lacks any previous experience on which such information can be interpreted. Furthermore, the brain of such individuals may lack a functioning visual system for interpreting the newly introduced information and giving it functional meaning. Even in the case of non-congenitally blind who have had some previous visual experience, one cannot expect that re-introducing visual information to their brains will automatically result in fully sophisticated visual perception, since their “visual” brain regions may now be integrated into other, non-visual brain networks. This lesson emerges from the relatively successful rehabilitation of deaf and auditorily impaired individuals using cochlear implants (Spelman, 2006), which also requires explicit teaching for people to learn to generate new associations between sounds and their sources. Moreover, such rehabilitation is accompanied and enabled by corresponding plasticity in the auditory cortex (Lee et al., 2001) to respond to the newly delivered input.

Indeed, several early attempts at surgical sight restoration after long-term visual deprivation (Ackroyd et al., 1974; Fine et al., 2003; Gregory, 2003; Gregory and Wallace, 1963; Ostrovsky et al., 2006; Ostrovsky et al., 2009; Sinha, 2003) suggested that pure restoration of the lost sensory visual input may also not suffice in case of vision. The patients in all of these studies showed profound difficulty in recognizing natural objects and environments, even after a long period of sight and visual training. This was especially true for ‘ventral stream functions’ such as shape and form recognition, figure ground segregation, depth, size, etc. These visual impairments remained so drastic that in some reported cases the technically “visually restored” individual receded to living in functional self-defined blindness (Ackroyd et al., 1974; Carlson et al., 1986), without any ability to utilize the visual input now available to them. This is true even for people who have lost their sight at older ages: a recent late-onset blind sight restoration patient whose sight was lost at the age of 17 and restored 51 years later also showed major deficits in visual perception (Šikl et al., 2013). This indicates that allowing the visual information to enter the brain via a functional retina does not guarantee or enable full or natural visual perception.

It is currently not clear whether this is the result of the lack of visual input during a critical period in early development (discussed in section1.2.3; Maurer et al., 2005; Wiesel and Hubel, 1963, 1965), which does not allow for the development of the normally functional neural architecture of the visual cortex, the result of reorganization of the blind individual's brain (see detail in the section below) which may interfere with future vision processing, or a combination of these factors as they are not mutually exclusive. Thus, achieving full functional sensory restoration will only be possible if we take into account the specificities of cognitive and neural functioning of the sensory impaired, a topic which will be presented next.

1.2.1. Neural and cognitive consequences of sensory loss

When attempting to understand the minds and brains of individuals who have lost a sensory modality, it is important to note the multiple factors that affect the organization of our brains. These are combined from our genetic dispositions and the brain's natural developmental path, channeled depending on environmental factors and specific individual experiences and activities, and through more unique cognitive challenges and demands imposed by nonstandard sensory inputs. Specifically, in order to achieve the same functional level in their everyday life, those who suffer from sensory loss need to develop strategies which enable them to extract information to achieve their goals from alternative sources to compensate for their blindness. Such adjustments are mediated through restructuring in other sensory or higher-order cognitive functions (for example excessive use of memory strategies, see details below). Thus, different cognitive demands lead to different individual experiences and activities, which in turn promote a certain pattern of plastic reorganization within the nervous system.

In addition, it is important to keep in mind that various subpopulations of individuals suffering from visual loss and differing in etiology or onset of sensory loss differ in their potential for plasticity. The early onset of sensory loss encountered in congenital blindness triggers the most dramatic cases of plasticity and enables extensive brain restructuring which compensates for the deficits, generating a remarkably different functional network than the one seen in normally-sighted individuals or individuals who have sustained brain or peripheral injuries later in life. Congenital or early-onset blindness affects large portions of the brain, especially when resulting from peripheral damage (i.e. dysfunctional retina or the sensory tracts), which do not injure the brain itself, but instead withhold parts of the brain from their natural input, leaving it essentially unemployed. It is estimated that more than 20% of the cerebral cortex is devoted to analyzing visual information (but note that some of these cortical areas might show overlap to some extent with those of other sensory modalities: Beauchamp, 2005; Calvert, 2001; Cappe and Barone, 2005; Clavagnier et al., 2004; Schroeder and Foxe, 2005; van Atteveldt et al., 2004; see also Striem-Amit et al., 2011c in the Appendix section 6). Despite the lack of visual input, the visual cortices of the blind do not degenerate. Rather, they undergo extensive plasticity resulting in significantly changed neural responsiveness as well as functional involvement in non-visual cognitive functions. Significant, although typically less extensive plastic changes, also occur in populations suffering from non-congenital sensory loss. This neuroplasticity is evident both in non-typical brain activation in the blind when compared with that of the sighted, as well as in its behavioral manifestations, e.g., sensory hyperacuity and specific cognitive skills, all of which are crucial to the ability to restore sight later in life.

1.2.2. Evidence for robust task switching plasticity promoted by sensory loss

The first evidence for the extensive reorganization undergone by the brains of the congenitally blind can be found in the reported enhanced sensory and cognitive abilities of such individuals which compensate for their sensory deficits. Blind individuals need to compensate for their lack of vision, the modality which normally allows one to “know what is where by looking” (Marr, 1982) and is ideal for providing concurrent information about relations of planes and surfaces to each other, drawing attention to relevant external cues and greatly facilitating spatial coding (Millar, 1981). Although the blind cannot acquire information for object localization and recognition by looking, they still need this information to navigate through space or find and recognize the objects around them for example. Therefore, they have to acquire this information through alternative, sensory or other, strategies. For instance, as early as the epoch of the Mishnah (about 350 C.E.) it was known that blind individuals possessed superior memory abilities compared to sighted (“*The traditions cited by Rabbi Sheshet are not subject to doubt as he is a blind man."* − Talmud Yerushalmi, *tractate Shabbat 6b)*, which enables them to remember the exact location and identity of stationary objects and the sequence of steps required to complete paths. Such phenomenal memory of the blind has also been documented in modern scientific studies (D'Angiulli and Waraich, 2002; Hull and Mason, 1995; Noordzij et al., 2006; Pozar, 1982; Pring, 1988; Raz et al., 2007; Röder et al., 2001; Smits and Mommers, 1976; Tillman and Bashaw, 1968; Vanlierde and Wanet-Defalque, 2004). Similarly, it has been shown that the blind have superior tactile and auditory perception abilities: for instance, they are able to better discriminate between small tactile dots or auditory spatial locations than the sighted, and even to better identify smells (Collignon et al., 2006; Doucet et al., 2005; Goldreich and Kanics, 2003, 2006; Grant et al., 2000; Hugdahl et al., 2004; Murphy and Cain, 1986; Röder et al., 1999; Smith et al., 2005; Wakefield et al., 2004). However, the blind do not always perform better on such tasks (Zwiers et al., 2001), suggesting that optimal development of some aspects of sensory processing in the unaffected modalities may depend on, or at least benefit from, concurrent visual input. Furthermore, when comparing different populations of the blind, it becomes clear that the identified benefits in some auditory and tactile tasks depend to a great extent on the age at sight loss. Specifically, these advantages are often, but not always, limited to the congenitally and early-onset blind, whereas the performance of the late blinded tends to resemble that of the sighted (Fine, 2008), reflecting differences in the potential for neuroplastic reorganization and the amount of visual experience between these populations. However, there is also evidence indicating that compensatory benefits also occur in the late blind, in which case they may be mediated by different neurophysiological mechanisms (Fieger et al., 2006 Hillyard, & Neville 2006; Voss et al., 2004), as detailed in the next sections. Importantly, although prolonged experience with a reduced number of available sensory modalities leads to such benefits, these do not appear automatically. For example, it has been shown that blind children have significant difficulties with some tasks, especially those which require reference to external cues, understanding directions and spatial relations between objects. Such tasks are challenging for the blind, as they have compromised spatial representations and rely mostly on self-reference and movement sequences (Millar, 1981; Noordzij et al., 2006; Vanlierde and Wanet-Defalque, 2004). Consequently, the blind have problems recognizing potentially useful information needed to perform these types of tasks and lack the benefits which could arise from simultaneously available vision. For example, concurrent visual input can facilitate recognition and learning of helpful auditory or somatosensory features given that the existence of redundant or overlapping information from more than one modality is generally associated with guiding attention and enhanced learning of amodal stimulus features (Lickliter and Bahrick, 2004). Nevertheless, such recognition of useful cues or the calibration of auditory and tactile space is eventually possible even in the absence of vision, as it may be achieved using different cues, for example those stemming from self-motion (Ashmead et al., 1989; Ashmead et al., 1998). Importantly, although it may require relatively lengthy training to reach a stage in which the missing sensory input is replaced and compensated for by equivalent information from other modalities, spatial representations which are finally generated on the basis of haptic and auditory input of the blind seem to be equivalent to the visually-based ones in the sighted (Röder and Rösler, 1998; Vanlierde and Wanet-Defalque, 2004). Overall, the findings indicate that the blind, once they learn to deal with the available sensory modalities, can show comparable or superior performance in many tasks when compared to the sighted. This advantage can even be compromised by the presence of visual information, as indicated by inferior performance of the partially blind (Lessard et al., 1998). Thus, the available evidence tends to counter the notion that sensory loss leads to general maladjustment and dysfunction in functions outside the missing modality. Quite the contrary, this general-loss hypothesis should be abandoned in favor of the alternative, compensatory hypothesis which suggests that sensory loss leads to the superior development of the remaining senses (Pascual-Leone et al., 2005).

These unique compensatory abilities are the result of plastic changes in the brains of the blind. In the last few decades, neural correlates of reported impairment-induced changes in cognitive functions and strategies have been thoroughly studied, providing a wealth of information regarding the brain's abilities to change. Studies investigating neural processing of congenitally blind individuals, as well as animal models of these conditions, show that the brain is capable of robust plasticity reflected in profoundly modified functioning of entire brain networks. Important evidence pertaining to the altered cognitive processing and the functional status of the occipital cortex in the blind stems from electrophysiological studies which have investigated non-visual sensory functions of the blind. These yielded results showing shorter latencies for event-related potentials (ERP) in auditory and somatosensory tasks in the blind in contrast to the sighted, suggesting more efficient processing in these tasks in this population (Niemeyer and Starlinger, 1981; Röder et al., 2000). Furthermore, different topographies of the elicited ERP components in the sighted and the blind provided first indications of reorganized processing in the blind, such as the engagement of their occipital cortex in non-visual tasks (Kujala et al., 1992 Summala, & Naatanen 1992; Leclerc et al., 2000 Lassonde, & Lepore 2000; Rösler et al., 1993 & Hennighausen 1993; Uhl et al., 1991 Lang, & Deecke 1991). Functional neuroimaging studies have confirmed and extended these findings by showing the functional engagement of the occipital lobe (visual cortex) of congenitally blind individuals in perception in other modalities (i.e. audition and touch, Gougoux et al., 2005 Voss, & Lepore 2005; Kujala et al., 2005, for recent reviews of these findings see Frasnelli et al., 2011; Kupers and Ptito, 2013; Merabet and Pascual-Leone, 2010; Noppeney, 2007), tactile Braille reading (Buchel et al., 1998 & Friston 1998; Burton et al., 2002a; Gizewski et al., 2003 Boehm, & Forsting 2003; Sadato et al., 1998; Sadato et al., 1996), verbal processing (Bedny et al., 2011b; Burton et al., 2003; Burton et al., 2002b & Raichle 2002; Ofan and Zohary, 2006; Röder et al., 2002 Neville, & Rösler 2002) and memory tasks (Amedi et al., 2003 Malach, & Zohary 2003; Raz et al., 2005). Importantly, the reported activations reflect functionally relevant contributions to these tasks, as indicated by studies in which processing within the occipital cortex was transiently disrupted using transcranial magnetic stimulation (TMS) during auditory processing (Collignon et al., 2007), tactile processing including Braille reading (Cohen et al., 1997; Merabet et al., 2004) as well as linguistic functions (Amedi et al., 2004).

It is important to realize that involvement of unimodal brain regions in cross-modal perception is not only limited to individuals with sensory impairments, but can under certain circumstances also be identified in the majority of the population (Amedi et al., 2001; Amedi et al., 2005b; Merabet et al., 2004; Sathian, 2005; Zangaladze et al., 1999; and see discussion in section 4). In the blind this involvement is much stronger (see details in the discussion section, regarding the anatomical bases for plasticity), because sensory areas deprived of their customary sensory input become functionally reintegrated into different circuits which lead to profound changes in the affected modality and the system as a whole.

In the blind, many of these changes start to occur within days following the onset of blindness (Pascual-Leone et al., 2005) and therefore affect not only the congenitally blind but also the late blind, who also show significant reorganization in the occipital cortex (Buchel et al., 1998 & Friston 1998; Burton et al., 2002a; Voss et al., 2004, although to a lesser extent; Cohen et al., 1999). For example, late-onset blind people show activation in their primary visual cortex (and other early visual areas) for language perception (Bedny et al., 2011b; Burton et al., 2003), braille reading (Burton, 2003), sound processing (Collignon et al., 2013), and even specifically for processing echolocation sounds (Thaler et al., 2011), showing the recruitment of the visual cortex for an adaptive compensatory task required due to blindness.

This plasticity, especially in the early-onset blind, may act as a double-edged sword (reviewed in Merabet and Pascual-Leone, 2010). On the one hand, it helps the blind cope better with blindness by supporting compensatory capabilities, but at the same time it might interfere with sight restoration efforts by disturbing the original functions of the visual cortex, as will be detailed in the next section.

1.2.3. Critical/sensitive developmental periods and sensory loss

When discussing different types of neuroplastic changes and possible mechanisms underlying them, and the adverse effects on the normally developing visual system in the context of visual rehabilitation, it is important to emphasize that all of these vary significantly depend on the age at onset of blindness, as well as its duration. These differences reflect several factors: the brain's potential to change at different periods of development, the amount of experience with visual or auditory processing prior to sensory loss and the amount of practice with the remaining senses or some special materials (e.g., Braille letters). The most important of these factors reflects the fact that the general potential for any form of plastic changes varies enormously across the lifespan. Although the brain retains some ability to change throughout life, it is generally believed and experimentally corroborated that the nervous system is most plastic during its development, both in the case of normal development and following brain injury. The developing brain is a highly dynamic system which undergoes several distinct phases from cell formation to the rapid growth and subsequent elimination of un-used synapses before finally entering into a more stable phase following puberty (Chechik et al., 1998). The functional assignment of individual brain regions which occurs during this time is crucially dependent on synaptic development which includes drastic changes that often take place in spurts. In the visual cortex, during the first year after birth, the number of synapses grows tremendously and is subsequently scaled down to the adult level around the age of 11 through extensive decreases in synaptic and spine density, dendritic length or even the number of neurons (Kolb, 1995). This process is primarily determined by experience and neural activity: synapses which are used are strengthened while those which are not reinforced or actively used are eliminated. Synaptic development is highly dependent on competition between incoming inputs, the lack of which can result in a decreased level of synaptic revision and persistence of redundant connections in adulthood (De Volder et al., 1997). This process of synaptic pruning represents a fairly continuous and extended tuning of neural circuits and can be contrasted with other types of changes which occur at very short timescales. During such periods of intensified development, (i.e., critical or, more broadly, sensitive periods; Knudsen, 2004; Michel and Tyler, 2005), the system is the most sensitive to abnormal environmental inputs or injuries (Wiesel and Hubel, 1963). Thus, injuries affecting different stages of development, even when they occur at a roughly similar ages, may trigger distinct patterns of compensatory neuroplastic changes and lead to different levels of recovery. Specifically, early studies of recovery after visual loss in animal models (Wiesel and Hubel, 1963, 1965) suggested that vision is particularly sensitive to receiving natural input during early development, and that visual deprivation even for short durations, but at an early developmental onset, may irreversibly damage the ability to normally perceive vision at older ages. Cases of cataract removal in visually impaired children support these findings. For example, children born with dense bilateral cataracts and then treated during the first year of life later generally develop normal vision, and are not impaired at either low level visual abilities (e.g. normal sensitivity to high rates of flicker) and high-level abilities (e.g. discriminating facial features, and detecting direction of eye gaze; see review in Maurer et al., 2005). Because these skills exceed those present at birth in the visually normal child, the normal performance of cataract-reversal patients probably implies that the neural circuits underlying these capabilities can recover completely from a short period of earlier visual deprivation. However, if the cataracts are not removed early enough, the cataract-reversal patients may later suffer from reduced visual acuity and impairments high-level abilities, such as reduced visual grouping abilities and impaired face processing (Geldart et al., 2002; Lewis et al., 2002; Maurer et al., 2005). It would appear that even after early childhood, visual information is important for the crystallization of visual connections long after the end of pruning, but the deficits generated from short visual deprivation beginning at early adolescence for example are more moderate (Maurer et al., 2005).

Therefore, visual deprivation, especially if manifesting early in life, can have a devastating effect on the ability to process vision. Moreover, the ability of the brain to adapt, or the potential for neuroplasticity after puberty is considered to be much lower than in childhood (Shaw and McEachern, 2000). Furthermore, the plasticity found in adulthood tends to result from different neurophysiological mechanisms, which may not suffice to support visual rehabilitation. For example, the robust, short-term plasticity witnessed in blindfolding for several days may arise from the recruitment of already existing, but commonly unused, inhibited or masked pathways which become available once the source or reason for such masking (e.g., availability of visual input in those who have been blindfolded) is removed. Therefore, some forms of adult plasticity do not reflect “plasticity de novo” which is characterized by the creation of new connectivity patterns (Burton, 2003). In pathological states, injuries, or late sensory loss, plasticity may be mixed. Rapid changes reflecting the unmasking of existing connections occurring in the first phase promote and may enable subsequent slow, but more permanent structural changes (Amedi et al., 2005a & Pascual-Leone 2005; Pascual-Leone et al., 2005 &

Merabet 2005).

However, the brain's ability to process vision may not be possible to restore in adulthood, or following extended periods of blindness.

1.2.4 Cross-modal takeover of the visual cortex: can the blind brain switch back to the original visual task specialization?

Another factor worth considering in this respect is the immense complexity of the visual processing conducted in the brain, and its requisite underlying neural structures.

The normally developed visual system is a complex neural architecture of parallel and intertwined processing, with a complex division-of-labor (Mishkin et al., 1983; Zeki, 1978a) in which different regions specialize in the processing of different visual features, tasks (Goodale and Milner, 1992) and even objects (Kanwisher, 2010). For example, the visual cortex is comprised of two processing streams. The ventral occipito-temporal "what" pathway, or the "ventral stream", has been linked with visual processing of form, object identity and color. Its counterpart is considered to be the dorsal occipito-parietal "where/how" pathway, or the "dorsal stream", which analyzes visuo-spatial information about object location and participates in visuo-motor planning and visually-guided movement (Goodale, 2008; Goodale and Milner, 1992). Within the ventral visual stream specific areas exist which partake in the processing of written script (the Visual Word Form area, VWFA; Cohen et al., 2000), faces (e.g. the fusiform face area, FFA; Kanwisher et al., 1997), visual scenes (the Parahippocampal Place Area, PPA; Aguirre et al., 1998) and the objects (the Lateral Occipital Complex, LOC; Malach et al., 1995).

It has been repeatedly shown that in normally sighted people who have suffered a lesion in one of these supposed neural modules or even processing streams, the perception of objects processed in this region may be severely impaired (Gainotti, 2000; Goodale and Milner, 1992; Kanwisher, 2010; Mahon and Caramazza, 2009). For example, the double dissociation between the processing of the two streams has been thoroughly validated by studies of localized lesions separately affecting visual object identity recognition (visual agnosia) and object visuo-motor spatial manipulation (optic ataxia: for a review see Goodale, 2008), and a lesion or deafferentation of the VWFA may result in alexia, or acquired dyslexia (Cohen et al., 2004).

The anatomical basis for this division has also been studied, and shows a complex pattern of bottom-up connectivity, beginning with the primary visual cortex and creating two parallel (though not completely independent) anatomical connectivity streams, one of which leads dorsally, through the posterior parietal cortex towards the premotor cortex, thus creating a natural “path” towards preparation for motion and spatial processing, whereas the other leads through area V4, which is selective for the color and size of visual objects (Desimone and Schein, 1987; Zeki, 1983a, b), to inferotemporal areas containing complex visual object representations (Desimone, 1991; Tanaka, 1997), and up to the prefrontal cortex (O'Scalaidhe et al., 1997). Similarly, the hierarchical processing of the low-level features of the shapes of letters, their further sequencing to words and then to more abstract semantic representations also manifests in an anatomical processing pathway (Vinckier et al., 2007). This hard-wired bottom-up connectivity pattern creates a strong constraint towards the generation of these streams and regions in the presence of normal visual input during development. However, the creation of two separate visual streams, or that of separate domain-selective regions within the streams, and their functional selectivities may not be so trivial in the absence of visual input, which deprives the visual cortex of its natural input, especially given the different susceptibility to plasticity over the lifespan. Since these streams and regions have been shown to be essential for the proper processing of object shapes, locations as well as finer-grade features such as script (as evidenced by the abovementioned lesion studies), it is plausible to inquire whether visual recognition can occur at all without developing the full extent of the complex visual cortex architecture.

All the factors detailed so far illustrate the demanding challenges that still need to be tackled by sight restoration efforts. If the blind brain has undergone extensive changes, and the congenitally blind brain may be even more drastically altered since it did not receive the visual inputs directing its normal development to begin with, how can we expect the blind to learn to perceive vision?

Thus, while years of specialized research have established the visual cortex functional segregation into streams and selective modules, what remains unclear is the role of visual experience in shaping this functional architecture of the brain. Does the fundamental large-scale organizational principle of division- of -labor or that of domain- and category-selectivity depend on the availability of visual experience during critical periods in early development? Or are innately determined constraints (for example, anatomical connectivity pathways) sufficient for the emergence of the functional divisions-of-labor, even in the absence of vision? Can category-selective visual areas develop their specialties without visual expertise and exposure to vision? And, in the case of sight restoration, can the blind brain learn in adulthood to process visual information conveyed in a new manner?

These questions pertain not only to the clinical topic of sight rehabilitation, which may be greatly complicated by the lack of a functional visual neural network, but also to our basic understanding of brain processing and organization, its plasticity and development. Moreover, studying the brains of congenitally blind people as they learn to process visual information for the first time is the ideal setup to test whether the visual cortex of the blind can functionally interpret visual information, and if so, whether it utilizes a similar functional organization to that of the normally developed sighted brain.

Therefore, this dissertation aimed to study

1. Whether and how SSDs may be applied for visual rehabilitation to reach sufficient practical visual acuity and functional abilities. Can we restore complex visual capacities such as object categorization (a visual ability which requires feature binding within visual objects as well as their segregation from their background) beyond the critical developmental period in the congenitally blind?
2. How are such visual-in-nature artificially-constructed stimuli processed in the blind brain? Can we find evidence for the functional specializations of the normal visual cortex in the absence of visual experience during the critical periods of early development?

2. Methodology

For purposes of using SSDs for brain research and testing their functional limits in rehabilitation, we developed and implemented a training protocol facilitating the learning and efficient use of “The vOICe” visual-to-auditory SSD in congenitally blind subjects. The Hebrew University’s ethics committee for research involving human subjects approved the experimental training procedure and written informed consent was obtained from each participant.

During the study, nine congenitally blind people were enrolled in a novel unique training program in which they were taught how to effectively extract and interpret high-resolution visual information from the complex soundscapes generated by the vOICe SSD. Each participant was trained for several months in a 2-hour weekly individual training session by a single trainer in accordance with the training protocol guidelines. The training duration and progress rate varied between participants and were determined by the personal achievements and difficulties, but generally took tens of hours: the average training of participants which took place in the final experiment described here (results section 3.3) was 73 hours, and most subjects continued their training past this stage.

The training program was composed of two main components:

1. Structured 2- dimensional training, in which the participants were taught how to process 2- dimensional still (static) images. The structured 2- dimensional training involved learning to process hundreds of images in seven structured categories: geometric shapes, Hebrew letters and digital numbers, body postures, everyday objects, textures (sometimes with geometric shapes placed over a visual texture, used to teach object-background segregation), faces and houses (see Fig. 1E in results section 3.3), introduced with increasing complexity and detail. For example, for teaching letters, we first introduced vertical, horizontal, diagonal and curved lines, and then constructed the letters from these elements (for a demo in English see http://doc.org.il/voice.ppsx). The participants in the study were taught the entire Hebrew alphabet, and also taught how to read whole words (up to 5 letters) in a single soundscape, which could be further sequenced to form longer

words. The main consideration for choosing these particular categories for training in addition to their functional importance in daily life, was that these categories are known to be processed by distinct specialized brain areas in sighted individuals (Kanwisher, 2010). During each training session, the participants heard each soundscape, and tried to describe what it contained, by paying attention to both the location and the shapes of all elements in the image, as well as integrating the details into meaningful wholes. Occasionally, mostly in the first few training sessions, the participants were asked to draw the image they 'saw' (by engraving, thus making the image tangible). This requirement forced them to reach decisive conclusions as to how they imagine the image, and enabled the trainer to completely asses their 'visual' perception. In cases when the participants failed to perfectly describe the image (verbally or by drawing), had mistaken or missed some details, they were asked guiding questions by the trainer, who also directed them as to the processing strategy they could use to interpret the sounds. This active technique enabled the participants to better understand how to avoid mistakes in the future, which aspects of the sounds they should pay careful attention to and which questions they should ask themselves in order to correctly interpret the visual scene. This prepared them for future independent use of the vOICe, without a trainer's guidance. Additionally, whenever possible, we provided the blind subjects with haptic feedback by presenting them with palpable images identical to those they perceived through the SSD (see Fig. 1D in results section 4.3; e.g. for all 2D stimuli and some of the 3D stimuli).

Following the structured 2-D training, participants could tell upon hearing a soundscape which category it represented. This required Gestalt object perception and generalization of the category principles and shape perception to novel stimuli. A rigorous experimental investigation of the participants' object categorization abilities is reported in results section 3.3. A rigorous examination of the participants' visual acuity using the SSD following training is described in results section 3.1.

Anecdotally (although all the participants in the study were able to carry out such tasks and were required to do so to continue to the new image category), they could also determine multiple features of the stimulus (such as hairstyle in a face image, number of floors and windows in a house image, and body posture in a body-shape image), enabling them to differentiate between objects within categories.

2. Live-view training in which visual depth-perception and training in head-eye-hand coordination were taught, using a mobile kit of the vOICe SSD, which was composed of a webcam pasted on sunglasses, connected by USB cable to a laptop with contained the vOICe software, and to earphones. This training was directed toward achieving processing of natural complex visual scenes and environments as well as spatial orientation and navigation abilities. During the live-view training the subjects trained in walking freely (though escorted by the trainer for safety reasons) in the lab corridors, outdoors on the campus and in their own homes and everyday surroundings, and learned to orient themselves in space, identify everyday objects in their homes, identify crosswalks and staircases and avoid obstacles in their paths. This was done while also training in modifying the refresh rate of the vOICe software such that every image was transmitted in a minimal time (as little as 0.5 second per image). A demonstration of a blind participant recognizing emotional facial expressions from soundscapes can be found in the supplementary movie of the third publication (Striem-Amit et al., 2012b). A rigorous investigation of some of these visual abilities is underway in several studies currently being conducted.

Additionally, general principles of visual perception which were not familiar to the congenitally blind participants were demonstrated and taught using stimuli from the various classes. Such principles were (i) the conversion of 3- dimensional objects to two-dimensional images (and back) depending on viewpoint and on object position, (ii) the transparency of objects and the ability to see through parts of objects, and (iii) the occlusion of parts of objects. Other visual perception principles which required active sensing were demonstrated using the live-view training technique. These included principles such as (i) visual field-of-view, (ii) orienting their heads (on which the webcam was mounted, placed on sunglasses) to the objects at hand in order to scan a visual scene (iii) variation of apparent object size depending on distance, and (iv) the use of monocular depth cues such as occlusion between different objects and perspective to estimate the depth and distance of seen objects.

Other experimental methods used in the behavioral and neuroimaging experiments are described in full detail in the publications in the results section.

3. Results

3.1 'Visual' acuity of the congenitally blind using visual-to-auditory sensory substitution

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'Visual' Acuity of the Congenitally Blind Using Visual-to-Auditory Sensory Substitution

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Abstract

Sensory Substitution Devices (SSDs) convey visual information through sounds or touch, thus theoretically enabling a form of visual rehabilitation in the blind. However, for clinical use, these devices must provide fine-detailed visual information which was not yet shown for this or other means of visual restoration. To test the possible functional acuity conveyed by such devices, we used the Snellen acuity test conveyed through a high-resolution visual-to-auditory SSD (The vOICe). We show that congenitally fully blind adults can exceed the World Health Organization (WHO) blindness acuity threshold using SSDs, reaching the highest acuity reported yet with any visual rehabilitation approach. This demonstrates the potential capacity of SSDs as inexpensive, non-invasive visual rehabilitation aids, alone or when supplementing visual prostheses.

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Introduction

Blindness is a highly limiting disability, affecting tens of millions of individuals worldwide [1]. One of the current challenges in sight restoration and sensory aids for the blind pertains to the possible visual acuity and capacity which can be transmitted through various restoration approaches. For example, neuroprostheses [2,3] which offer great hope for restoring visual qualia suffer at the moment disadvantages such as invasiveness, their restricted applicability to particular etiologies, extremely high cost and poor resolution and visual field to date (e.g. maximal resolution of 60 electrodes and 20° visual field-of-view in chronic implantation clinical trials; Second Sight Inc., Sylmar, CA, USA; http://2-sight.eu/ee/benefits-of-argus-ii; and 1000–1500 electrodes and 11° visual field-of-view in development stages [4]; Retina Implant AG, Reutlingen, Germany). Moreover, the resulting acuity is lower than predicted given the number of pixels, because the translation from technical resolution to functional acuity is highly complex. For instance, the newest subretinal prosthesis under development technically has 1500 pixels, but provides a much lower than expected functional acuity, with a maximal measurable acuity of only 20/1000 [4]; thus the smallest letter implant patients can see at 20 feet could be seen by a normal eye at 1000 feet (i.e. they can discern only extremely large letters).

Visual rehabilitation may alternatively be achieved using Sensory Substitution Devices (SSDs [5]) which enable the blind to 'see' using their other senses. Initially these focused on tactile-to-visual SSDs [6], and interestingly, although their maximal technical resolution was only 144 pixels at the time, they enabled better acuity than the highest 1500-electrode technical resolution retinal implant under development today (20/860 vs. 20/1000 [4,7,8]), stressing the need to test for functional acuity beyond potential pixel resolution. However, this acuity was still functionally quite poor. For purposes of comparison, the blindness threshold of the World Health Organization (WHO) is set at best corrected sight of 20/400 acuity (and a 10° visual field; 10th revision of the WHO international classification of diseases, update 2007; note that other legal definitions may be applicable in various countries), and up to now retinal prostheses and tactile-to-visual SSDs remain far below such levels of acuity.

In contrast, auditory SSDs can offer, at least theoretically, extremely high resolution. While one such device used in research and in an effort to rehabilitate the blind, the PSVA (Prosthesis Substituting Vision with Audition; [9]) has a maximal theoretical resolution of only 124 pixels (although this too has been shown to enable some functional sight; [10]), "The vOICe" SSD [11] can in principle generate much higher resolution, up to 25,344 pixels (see **Figure 1A**). However, its actual functional visual acuity has never been tested to the best of our knowledge, and especially not in a blind users group systematically. It is thus important to determine the best possible visual acuity that can be achieved by blind individuals using such an auditory SSD, in order to understand the potential value of these devices. Moreover, as critical developmental periods [12,13,14] for perception of natural vision in adulthood may limit the medical means of sight restoration (for example, several rare accounts of sight restoration in adulthood resulted in only partially functional vision, likely due to such limitations; [15,16,17,18,19,20]), it is interesting to determine if early-onset and congenitally blind adults can learn to see fine "visual" details after many years of blindness using SSDs.

To clarify these questions we devised an adapted visual-to-auditory version of the Snellen E-chart visual acuity test used by

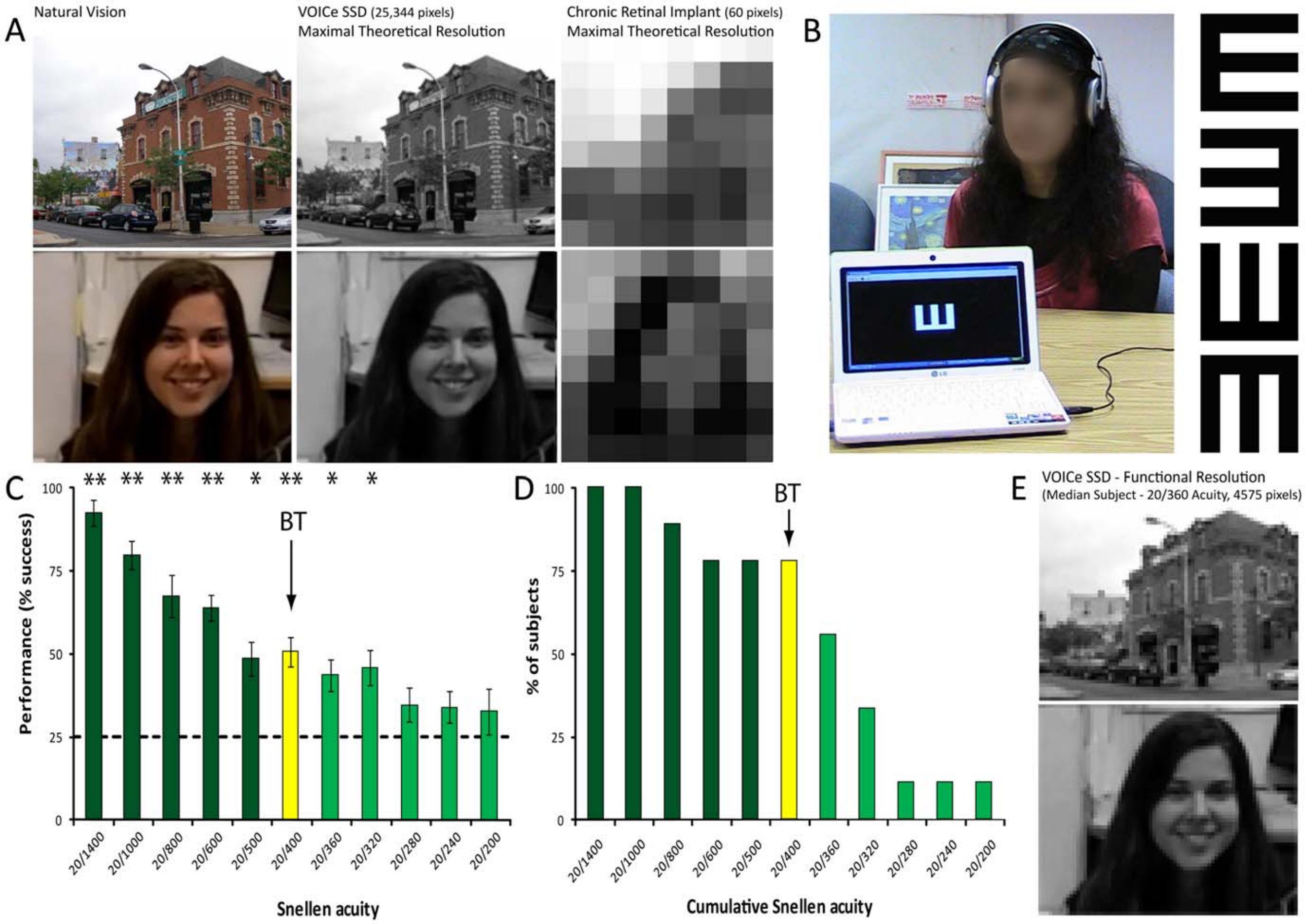

Figure 1. Visual Acuity of the congenitally blind using a visual-to-auditory SSD. A. Illustration of the typical theoretical resolution (in terms of number of pixels) provided by different current means of visual rehabilitation (the vOICe and implants provide only gray scale information). B. A blind participant during training, perceiving an image of a large Snellen E and identifying its direction (of the 4 possibilities). C. The group performance on the Snellen acuity test. * $p<0.01$, ** $p<0.001$. As an interesting reference point in relation to visual acuity in health and disease, we also display the World Health Organization (WHO) criterion for blindness, at an acuity of 20/400, in the results (yellow bar, BT – WHO Blindness Threshold). D. Cumulative frequency Snellen acuity of the individual participants; the percentage of subjects whose visual acuity threshold passed each acuity level. Most (5/9) participants performed above chance level even above the 20/400 WHO BT. E. The images in A are processed to reflect the functional resolution achieved in this experiment by the median participant (Snellen acuity of 20/360, below blindness threshold). This resolution enables identification of the scene and, at least in one of our subjects, emotional facial expression in a real life scenario (see **Movie S1, Figure S1**).
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ophthalmologists (See **Figure 1B**), and used it to test a group of eight congenitally and one early-onset fully blind individuals (see **Table 1**) who were given structured relatively short (tens of hours; see details in the experimental procedures) training in vOICe visual perception.

Methods

Participants

Eight congenitally and one early-onset fully-blind individuals participated in the experiment (see **Table 1**). All participants had normal hearing, and had no neurological or psychiatric conditions. The Hebrew University's ethics committee for research involving human subjects approved the experimental procedure and written informed consent was obtained from each participant.

Visual-to-auditory sensory substitution

The vOICe [11] is a visual-to-auditory sensory substitution device (SSD) which converts images into sounds, technically preserving visual detail at high resolution (up to 25,344 pixels, the resolution used here; see **Figure 1A**). In a clinical or everyday setting, users wear a video camera connected to a computer and stereo headphones; the images are converted into "soundscapes" using a predictable algorithm, allowing them to listen to and then interpret the visual information coming from a digital video camera. Remarkably, proficient users are able to differentiate the shapes of different objects, identify the actual objects, and also locate them in space [21,22,23]. The functional basis of this visuo-auditory transformation 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.

Training procedure

All the participants in this study were enrolled in a new unique training program in which they were taught how to effectively

Table 1. Characteristics of blind participants.

Subject	Age & Gender	Cause of blindness	Light perception	Handedness	Blindness onset	Training duration (hours)
1	27 F	Retinopathy of prematurity	None	Right	birth	55
2	23 F	Microphthalmia	None	Right	birth	65
3	23 F	Leber congenital amaurosis	Faint	Ambidextrous	birth	60
4	24 F	Retinopathy of prematurity	None	Right	birth	61
5	30 M	Retinopathy of prematurity	None	Right	birth	101
6	33 F	Enophthalmia	None	Left	birth	32.5
7	48 M	Retinopathy of prematurity	None	Right	birth	101
8	21 F	Retinopathy of prematurity	None	Right	birth	87
9	22 F	Microphthalmia, Retinal detachment	None	Left	birth	98

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extract and interpret high-resolution visual information from the complex soundscapes generated by the vOICe SSD. Each participant was trained for several months in a 2-hour weekly training session by a single trainer on a one-by-one basis. The training duration and progress rate varied across participants and were determined by the personal achievements and difficulties (the average training here was 73 hours, for detail of individual training durations see **Table 1**). The training program was composed of two main components: structured 2-dimensional training, in which the participants were taught how to process 2-dimensional still (static) images, and live-view training in which visual depth-perception and training in head-'eye' (camera installed on glasses)-hand coordination were taught, using a mobile kit of the vOICe SSD assembled in our lab. In the structured 2-dimensional training the participants were taught guiding principles of visual processing by learning to process hundreds of images of seven structured categories: geometrical shapes, Hebrew letters and digital numbers, body postures, everyday objects, textures (geometrical shapes placed over visual texture, used to teach object-background segregation), faces and houses, introduced in controlled and growing complexity and detail.

Experimental design

We conducted a Snellen tumbling-E test, which is used by ophthalmologists to measure visual acuity. The Snellen fractions are measures of the spatial acuity of sight (if vision is blurred in a given size, the orientations cannot be reported). The original ophthalmologists' Snellen tumbling-E test used to measure visual acuity contains rows of the letter E in various types of rotation (up, down, left or right), and the patient is asked to state where the limbs of the letter "E" are pointing. Depending on the smallest letter line (i.e. the smallest size) the patient can read or recognize the orientation, his visual acuity is defined. The Snellen fractions are measures of visual spatial discrimination, relating to the ability to identify small high-contrast letters at a specific distance. In "20/20 vision" (20 feet or 6/6 in the metric system) the numerator refers to the distance in feet (or meters) between the subject and the chart, the denominator is the distance at which the lines that make up the letters are separated by a visual angle of 1 arc minute (minute of angle), which is the level of discrimination achieved by an eye with no refractive errors, or with the errors corrected. To control for individual factors which could affect the performance of our participants other than pure perceptual acuity, we introduced the tumbling E stimuli of the Snellen acuity chart using static images of each differently oriented E separately (see in **Figure 1B**), similarly to previous testing of a visual-to-tactile SSD ([7]; with which an acuity of 20/860 was achieved). Stimuli were created by photographing a standard Snellen chart with a 66° field-of-view webcam (A4Tech, Montclair, CA, USA) from a distance of 1 meter, and calculating the Snellen fraction from this distance according to the standard reference scale. In this way we created a series of stimuli in different orientations and with different acuity scores (see **Table 2**), within a relatively wide field-of-view (thus not trading high acuity for a small field-of-view). Prior to testing, the subjects were trained for one hour on the Snellen acuity task, in order to familiarize them with the task and response buttons. Subjects were introduced to tumbling E's in all four directions at large sizes (larger than tested in the experiment) and were trained to identify the letter directions. The order of the stimuli in the training did not reflect that in the test, which was differently randomized per stimulus size.

During the experiment, soundscape stimuli were played using the Presentation software (Neurobehavioral Systems, CA, USA) in a pseudo-randomized order of E directions for each size, in decreasing order of size, similar to a conventional eye exam. Each size was presented four times in each of the four directions. Each soundscape was played until the subject responded regarding its position using a keyboard by pressing the arrow in the corresponding direction. No "zoom in" of the soundscapes was permitted, thus the field-of-view was fixed during the entire experiment to represent a 66° visual field (much more than the WHO blindness threshold for field of view, which is 10°). The answer and the reaction time were recorded, and no feedback was given to the subject during the experiment. Average reaction time per stimulus (across the stimuli sizes) was 9.16 ± 1.26 seconds, and no significant correlation was found between reaction time and acuity (in linear LogMAR units, see **Table 2**; [24]) or success rate (participants were not instructed to answer as quickly as possible, thus a speed-accuracy tradeoff was not necessarily expected).

Results

We analyzed the data both statistically at the group level (providing the raw accuracy scores of the group, **Figure 1C**) and at the single-subject level of individual acuity scores (**Figure 1D**).

Group performance differed statistically from chance level at all visual acuities up to 20/320 (one-way ANOVA; $p<0.01$; See **Figure 1C**), below the WHO blindness criterion (20/400). In addition, individual 'visual' acuity scores were determined by the

Table 2. Snellen stimuli sizes.

Snellen acuity (m)	letter size (mm)	LogMAR
20/2000	146	2
20/1800	131	1.954
20/1600	117	1.903
20/1400	102	1.845
20/1200	88.7	1.778
20/1000	73	1.699
20/800	58	1.602
20/600	44	1.477
20/500	36	1.398
20/400	29	1.301
20/360	26	1.255
20/320	23.5	1.204
20/280	20.4	1.146
20/240	17	1.079
20/200	15	1

Snellen original stimuli sizes are reported in Snellen fractions (distance from which the participant perceives the letter in meters in the numerator and the distance from which a normally sighted individual would perceive the same letter in the denominator), physical letter size (in mm) and logMar, a linear scale which expresses the logarithm of the minimal angle of resolution [24].

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smallest size at which a participant achieved over 60% correct responses, more than twice the chance level on this task (25% correct responses). The visual acuity of the individual participants varied between 20/200 and 20/600 (see **Figure 1D** for a cumulative acuity distribution). Therefore, all the participants performed better than reported using tactile SSD (20/860; [7,8]) and the highest-resolution retinal prostheses (20/1000; [4]). Interestingly, five of the nine participants (55%) had visual acuity that exceeded the visual acuity threshold for blindness as defined by the WHO.

Discussion

Our findings suggest that early and congenitally blind individuals using auditory SSDs can retrieve detailed visual information at a much higher resolution than previously demonstrated with any other sight rehabilitation approach. Most of our participants could even pass the WHO blindness threshold (also demonstrated statistically for the whole group) when using a SSD with a relatively wide field-of-view, capturing more than half of the binocular horizontal visual field in humans [25] (66°; it is important to note that no use of "zoom-in" was allowed in the experiment, which could enhance performance even further but at the expense of the field-of-view) and at least formally by the WHO criteria, be defined as low-vision sighted. For a demonstration of the possible detail conveyed at the resolution perceived by our median participant, see **Figure 1E** which roughly corresponds to extracting information from ~4500 of the ~25,000 pixels transmitted by The vOICe. This is by no means the upper bound as it may well be that further specific high-acuity training will yield better acuity results. These results show that high visual acuity can be restored to early-onset and congenitally blind individuals even after decades of (or life-long) blindness, suggesting there may be adult plasticity at the most important level – of actual "visual" perception in the adult congenitally blind. Retrieving high-acuity information from sounds may be more difficult and slower than real vision in more complex, natural settings. However, some capabilities demonstrated by our participants during training suggest this too may be possible. For example, our participants were able to identify and mimic the body posture of a person standing a few meters away, navigate in crowded corridors while avoiding obstacle, and recently, one of the participants in our study (participant #4, who achieved a 20/400 acuity score) was also able to identify live, 3-dimentional emotional facial expressions (see **Movie S1, Figure S1**).

Although our study did not inspect the SSD visual acuity of normally sighted or that of late-onset blind individuals, one may expect that they will show comparable performance, though possibly with some inferiority relative to early-onset blind, due to the latter's compensatory advantage in auditory processing [26,27,28]. While future studies should test this hypothesis more rigorously, we also trained in vOICe-use a few sighted individuals (though to a more limited extent), who had no difficulty in learning to apply the SSD transformation algorithm or in extracting high-detail information from soundscapes, supporting the usability of this system also for late-onset blind.

Therefore, SSDs may be beneficial in restoring high-resolution functional vision at very low cost (the vOICe software is free to blind users; the setup costs approximately $200 or much less if utilized through existing android cellphones). The factor of price may prove important to the vast majority of the world's visually impaired population, amounting to tens of millions of individuals worldwide, who reside in developing countries (about 90% of the world's visually impaired live in developing countries; [1]) and are unlikely to benefit in the near future from expensive medical equipment. In fact, even in developed countries not all types of blindness will be treatable in the coming years using prostheses, as these implants currently depend upon the existence of intact retinal ganglion cells, which characterize only some (such as age-related macular degeneration and retinitis pigmentosa) but not all blindness etiologies [3]. Moreover, SSDs may also be beneficially used as a complement to visual prostheses or other novel medical advances [2,4,29,30] in developed countries (and later in the rest of the world). SSDs may be used for instance before a retinal prosthesis implantation, to train the visual cortex to 'see' again after years or life-long blindness, by addressing and strengthening the preserved "visual" task selectivities of the occipital cortex of the blind; for instance we recently showed that SSD use activates the ventral and dorsal streams respectively [31] (see also [21,32,33,34,35,36,37,38]), and to teach visual processing principles (such as visual monocular depth cues [10]) that were not in use for extended periods prior to the operation. This training might be important not only for understanding high-acuity and holistic vision again based on a smaller number of pixels (as provided by retinal prostheses, at least currently), but also to awaken the 'visual' system to performing its original tasks [39,40]. SSDs can also be used post- surgically, to provide parallel explanatory "sensory interpreter" input to the visual signal arriving from the foreign invasive device (early-onset blind may otherwise find it difficult to interpret vision; [15,16]). At a later stage the SSD can be used to provide information beyond the maximal capabilities of the prostheses, increasing both the resolution (as shown here) and the visual field-of-view (which is also currently very limited in retinal prostheses). SSDs can additionally be used for visual perception enhancement for individuals who have impaired natural vision, either in terms of acuity (for example in cases of cataract) or reduced visual field (such as that affecting retinitis pigmentosa or glaucoma patients).

In discussing SSDs benefits, visual-to-auditory SSDs such as the one used here offer several advantages over current visual-to-tactile SSDs. For example, while the Tongue Display Unit (TDU) visual-to-tactile SSD offers a potentially wide field-of-view, and has since being last tested for acuity increased its pixel grid from 144 to 324 pixels , which is likely to result in increased functional acuity, current models are far from the functional acuity demonstrated here, which is equivalent to ~4500 pixels. Furthermore, beyond its relatively costly price, using the tongue to display visual information precludes its concurrent use for eating, drinking or talking, which will plausibly limit its use. Perhaps it may be more productive in the future to apply visual-to-tactile transformations to other skin surfaces, which may be less intrusive in every-day life. On the other hand visual-to-tactile SSDs offer better temporal resolution, improving detection of online motion and optic flow. Therefore, ultimately the optimal SSD will be one combining both auditory (e.g. through bone-conductance earphones, leaving the ears open) and tactile interfaces arriving from the same camera (see for instance a schematic diagram of such a proposed system in [40]).

These findings should thus also encourage the development of new SSDs with finer and additional visual detail, such as color (which is currently not provided in retinal prostheses) and direct depth cues. SSDs are also a unique research tool to study sensory and multisensory processing, developmental critical periods and adult plasticity, as well as cortical specialization in the blind visual cortex [31], especially for the processing of visual stimuli which require high-resolution 'vision', such as facial expressions and reading. Thus overall, our results suggest that auditory (and tactile) SSDs are both a valuable research tool and a potentially high resolution option in any clinical visual rehabilitation protocol.

Supporting Information

Movie S1 Utilization of high-resolution vision by a congenitally blind participant – identifying emotional facial expressions. The video depicts a vOICe training session of one congenitally blind subject in which she is requested to identify emotional facial expressions of two individuals, on live, 3-dimentional faces. She is able to distinguish between a smiling, surprised and angry facial expression, and to identify the same emotional expressions on a novel face, exhibiting learning generalization. See also **Figure S1** depicting her possible approximate functional acuity.
(AVI)

Figure S1 Deciphering facial expressions. Illustration of the detail which can be conveyed by different current means of visual rehabilitation and that conveyed at the functional resolution perceived by our median participant, for the aim of detecting an emotional facial expression. Facial expression is perceivable using the vOICe SSD used here (see **Movie S1** depicting a congenitally blind participant conducting this task), but not in other current means of sight restoration.
(TIF)

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Author Contributions

Conceived and designed the experiments: ESA AA. Performed the experiments: ESA MG. Analyzed the data: ESA MG. Wrote the paper: ESA MG AA.

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3.2 The large-scale organization of "visual" streams emerges without visual experience

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The large-Scale Organization of “Visual” Streams Emerges Without Visual Experience

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A key question in sensory perception is the role of experience in shaping the functional architecture of the sensory neural systems. Here we studied dependence on visual experience in shaping the most fundamental division of labor in vision, namely between the ventral “what” and the dorsal “where and how” processing streams. We scanned 11 fully congenitally blind (CB) and 9 sighted individuals performing location versus form identification tasks following brief training on a sensory substitution device used for artificial vision. We show that the dorsal/ventral visual pathway division of labor can be revealed in the adult CB when perceiving sounds that convey the relevant visual information. This suggests that the most important large-scale organization of the visual system into the 2 streams can develop even without any visual experience and can be attributed at least partially to innately determined constraints and later to cross-modal plasticity. These results support the view that the brain is organized into task-specific but sensory modality-independent operators.

Keywords: blindness, neuroimaging, plasticity, sight restoration, visual cortex

Introduction

Ever since the seminal work by Ungerleider and Mishkin (1982), it has been repeatedly shown that visual processing is carried out in 2 parallel pathways. The ventral occipitotemporal “what” pathway, or the “ventral stream,” has been linked with visual processing of form, object identity, and color. Its counterpart is considered to be the dorsal occipitoparietal “where/how” pathway, or the “dorsal stream,” which analyzes visuospatial information about object location and participates in visuomotor planning and visually guided movement (Goodale and Milner 1992; Goodale 2008).

This double dissociation between the processing of the 2 streams has been thoroughly validated by studies of localized lesions separately affecting visual object identity recognition (visual agnosia) and object visuomotor spatial manipulation (optic ataxia: for a review, see Goodale 2008) and numerous human imaging studies (e.g., Haxby et al. 1991; Shmuelof and Zohary 2005).The anatomical basis for this division has also been studied and shows a complex pattern of bottom-up connectivity, beginning with the primary visual cortex and creating 2 parallel (though not completely independent) anatomical connectivity streams, one of which leads dorsally, through the posterior parietal cortex toward the premotor cortex, thus creating a natural “path” toward preparation for motion and spatial processing, while the other leads through area V4, which is selective for the color and size of visual objects (Zeki 1983; Desimone and Schein 1987), to inferotemporal areas containing complex visual object representations (Desimone 1991; Tanaka 1997), and up to the prefrontal cortex (O’Scalaidhe et al. 1997). This hardwired bottom-up connectivity pattern creates a strong constraint toward the generation of these streams in the presence of normal visual input during development. However, the creation of 2 separate visual streams and their functional selectivities may not be so trivial in the absence of visual input, which deprives the streams of their natural input.

Thus, while years of specialized research have established visual cortex segregation into functional streams as one of most fundamental characteristics of the visual system, what remains unclear is the role of visual experience in shaping this functional architecture of the brain. Does this fundamental large-scale organizational principle depend on visual experience? Or are innately determined constraints sufficient for the emergence of the division of labor between the 2 streams, even in the absence of vision?

One way to study these questions is to investigate whether traces of the visual functional division of labor can be identified in fully CB individuals who have never had any visual experience, by using sensory substitution devices (SSDs). SSDs are noninvasive devices that provide visual information to the blind via their existing senses (mainly audition and touch, see Fig. 1*A*; Meijer 1992; Bach-y-Rita and Kercel 2003) which may thus provide a valuable test for the existence of critical (or sensitive) periods for developing this fundamental functional segregation between the 2 visual streams. If the CB show no such differentiation, then visual experience is necessary and stream formation may be restricted to the presence of visual input. Conversely, if there are indications of a functional “visual” segregation in the absence of visual experience, the streams may emerge at least partially from innate biases, connectivity patterns or functional differentiation of processing shape and location functions which are not necessarily intrinsically visual by nature, but reflect a task- or computational-selectivity that is independent of the sensory input modality (e.g., Reich et al. 2011) and may thus be flexible at later ages regardless of visual experience (see also Pascual-Leone and Hamilton 2001; Renier et al. 2005a, 2005b, 2010; Poirier, Collignon et al. 2006; Amedi et al. 2007; Beauchamp et al. 2007; Mahon et al. 2009, 2010; Ptito et al. 2009; Ricciardi et al. 2009; Matteau et al. 2010; Sani et al. 2010).

In addition to the important theoretical implications of such questions, answering them could also contribute to clinical rehabilitation of individuals suffering from peripheral blindness, who may regain some level of visual peripheral sensory input through novel cutting-edge medical approaches. Although these approaches can restore some visual information in the periphery, this does not guarantee that such information can be easily and adequately understood by the individual (e.g., Fine et al. 2003; Gregory 2003; Ostrovsky et al. 2006, 2009). Because the blind brain undergoes vast cross-modal plastic changes due

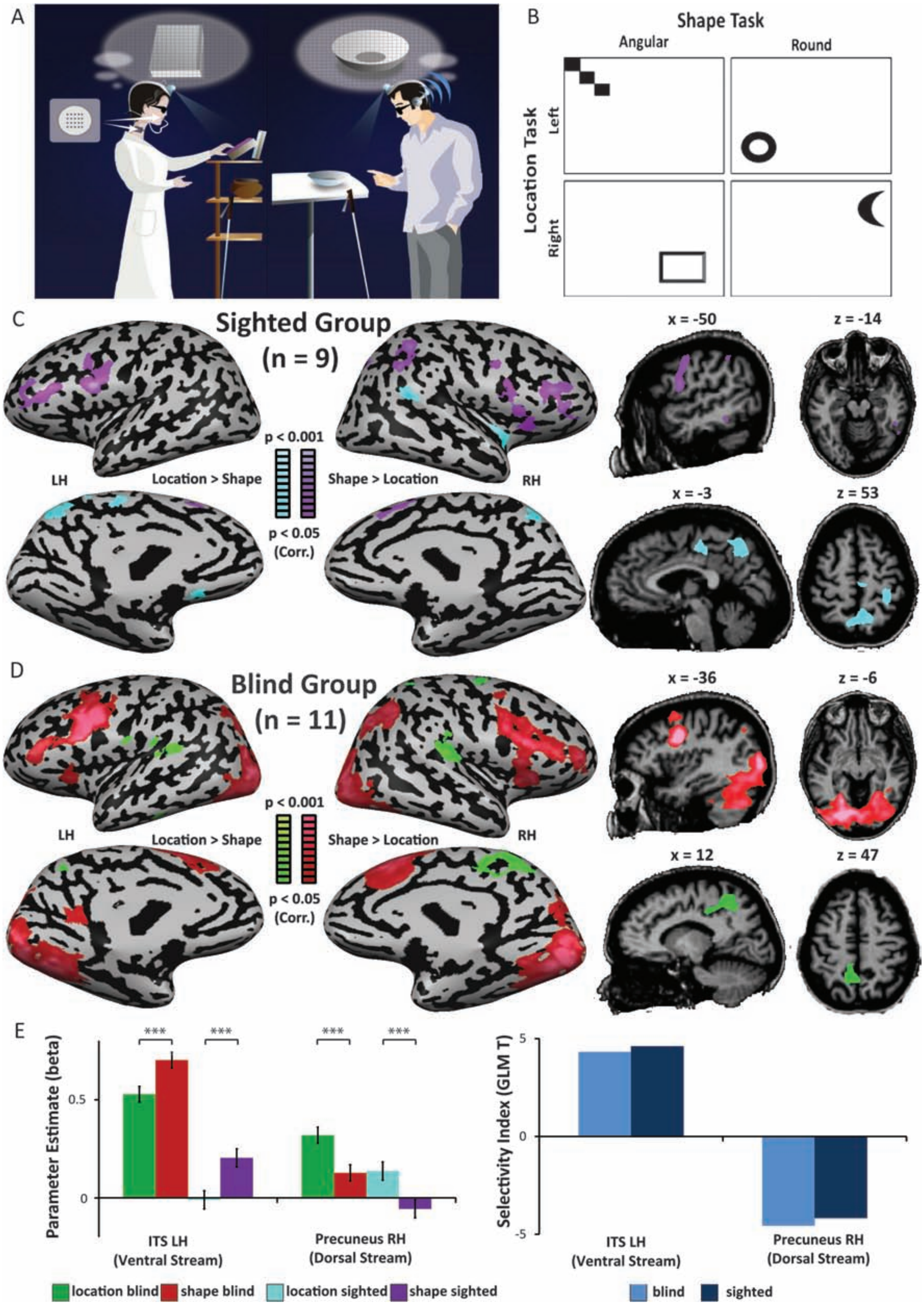

Figure 1. Task-specific activation generated by shape and location processing in sensory substitution. (*A*) Typical visual-to-auditory (such as the vOICe, used here) and visual-to-tactile user interfaces. SSDs typically include a visual capturing device (e.g., camera glasses), a computational device transforming the visual input into an alternative sense (audition or touch) using a simple known transformation algorithm and an output device (such as headphones or a tactile electrode array) transmitting the sensory-transformed information. (*B*) The experimental design included a shape task (identifying whether the shape was round or angular) and a location task (identifying whether the object was in the left or right of the image). Each stimulus was repeated once for each task (without feedback), thus on average, the stimuli were identical in both conditions. (*C*) Task-specific activation for shape (vs. location, in purple) and location (vs. shape, in cyan) in the sighted group. The statistical parametric maps show a differentiation of neural networks involved in the 2 tasks, including a dorsal (precuneus) activation preference for location and a ventral occipital activation observed in a ROI analysis (see part *E*, and volume view

to prolonged sensory deprivation (even to the extent of processing language and memory in the occipital cortex, especially in the ventral stream: Röder et al. 2001; Amedi et al. 2003; Bedny et al. 2011), it may have lost, or never developed, its ability to properly process vision and the functional neural architecture supporting it. Thus, it may be relevant also for clinical sight restoration to question whether the functional architecture of the visual cortex critically and exclusively depends on visual experience and whether congenital and longitudinal visual deprivation causes the visual streams to entirely lose their natural visual roles, which may prevent them from reverting to natural vision processing if peripheral input could be restored (and vice versa if residual stream specialization can be found).

Materials and Methods

Visual-To-Auditory Sensory Substitution

We used a visual-to-auditory SSD called “The vOICe” (Meijer 1992), which enables “seeing with sound” for highly trained users (seeing with sounds can also be achieved using other algorithms, e.g., PSVA see Renier and De Volder 2010). In a clinical or everyday setting, users wear a video camera connected to a computer and stereo headphones; the images are converted into “soundscapes” using a predictable algorithm, allowing them to listen to and then interpret the visual information coming from a digital video camera. Remarkably, proficient users are able to differentiate the shapes of different objects, identify the actual objects, and also locate them in space (Amedi et al. 2007; Auvray et al. 2007; Proulx et al. 2008). The functional basis of this visuoauditory transformation 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.

Participants

The study included a total of 20 subjects, 9 normally sighted individuals (sighted controls [SCs]), and 11 blind individuals. Our group of legally blind subjects was relatively homogeneous in terms of blindness in that all of them were congenitally blind (CB) and 9 of the blind subjects did not have any form of light perception. The remaining 2 had faint light perception but they were unable to localize light or recognize any shape or form. The age range of the subjects was wide, from 18 to 60, all had normal hearing, and had no neurological or psychiatric conditions. For a full description of the subjects, causes of blindness, etc. see Supplementary Table 1. Sighted subjects had normal vision (corrective lenses permitted) and hearing. The Tel-Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure, and written informed consent was obtained from each subject.

Training Procedures and Performance

All subjects had their first training session, which lasted between 1 and 1.5 h, on sensory substitution using the vOICe software immediately before the functional magnetic resonance imaging (fMRI) session reported here (i.e., the subjects were completely naïve to the principles of the vOICe before the training session). During the session, subjects were first taught the visual-to-auditory transformation rules and proceeded to practice the very simple shape and location perception of a standardized set of stimuli which is part of the training set of stimuli used in our laboratory to teach CB individuals to use the vOICe (including small lines, rectangles, and round objects presented at 4 possible locations on the screen; see Fig. 1*B*). Feedback on performance was given by showing the participants the sensory image that they had heard following each training trial, using vision for the sighted subjects, and haptic dimensional models of all the stimuli for the CB individuals. Critically, none of the stimuli delivered during training was repeated during the scan, in which they were introduced to completely new stimuli. Testing fully CB participants without any visual experience and using SSD enabled us to test the dependence of visual stream segregation on visual experience directly. Furthermore, given that such short training probably does not enable any long-term or extensive learning-induced plasticity (Pascual-Leone et al. 2005), this design also enabled us to isolate and research the baseline state of the visual system in CB in relation to form and location processing. In contrast to most previous studies using SSDs, we also collected the behavioral results from inside the scanner in order to ensure that subjects were deeply engaged in the shape and localization tasks (even if performance was not very high due to the brief training, prompted by our interest in the baseline—innate—state of the visual cortex prior to extensive training which may influence it). Performance was comparable (2-way analysis of variance [ANOVA], group effect, $F = 0.65$, $P < 0.56$) in the blind and sighted groups, which was a critical comparison in order to determine whether the blind also recruit shape and location centers and to allow comparison between groups. However, performance differed, on average, between the tasks, as the shape task was more difficult than the location task for both groups (2-way ANOVA, $F = 297$, $P < 0.05$, 47.5 ± 4.2% and 44.4 ± 4.4% for shape in the CB and SC, 83.5 ± 5.8% and 82.2 ± 4.3% for location in the CB and SC). No significant task ($F = 0.62$, $P < 0.57$), group ($F = 18.1$, $P < 0.15$), or interaction ($F = 0.05$, $P < 0.82$) effects were observed in a 2-way ANOVA for reaction time (10 ± 0.7 s and 10.1 ± 0.8 s for shape in the CB and SC, 9.9 ± 0.5 s and 10.2 ± 0.8 s for location in the CB and SC). It is worth noting that the activation pattern on the shape task in this study replicates to a large extent the pattern seen following 40 h of training in sighted subjects (Amedi et al. 2007), suggesting that subjects focused their attention on extracting shape.

Moreover, in order to address the potential influence of behavioral differences, we analyzed various subgroups that had both: 1) above chance performance in both tasks and 2) no significant difference between the 2 tasks. All the data from these subgroups were subjected to several converging analyses, including random-effect (RFX, see details below; Friston et al. 1999) analyses. The subgroups included a group of 5 briefly-trained participants with matched performance at the individual level (no more than 10% accuracy difference between the tasks; see details below), a group of 12 participants which included better-trained participants, and a critical group as regards our main research question; namely, a group of 7 CB participants subjected to an RFX analysis. First, we examined a subgroup of 5 briefly-trained subjects, 3 of whom were fully CB, who performed similarly on the 2 tasks (at an individual subject level) and exhibited higher than average performance on the shape task (student’s paired *t*-test $t_4 = 1.132$, $P < 0.29$, 62 ± 5.4% and 72 ± 8.2% for shape and location, respectively) in more detail. All these individual subjects (Supplementary Fig. 3), as well as the group analysis of this subgroup (Fig. 3*A*), showed similar effects to the ones reported for the main groups, suggesting that the task-specific activation did not result from general difficulty biases. To further control for the effect of performance in a larger group of subjects, we scanned again as many subjects as possible from our original cohort (an average of 11 months after the

presented at an uncorrected threshold to illustrative the cluster location). (*D*) Task-specific activation for shape (vs. location, in red) and location (vs. shape, in green) in the CB group reveals differentiation in the occipital cortex which does not depend on visual experience. In addition to the dorsal activation for location exhibited by the sighted, the CB group also shows robust ventral stream selectivity for shape. (*E*) Beta values (GLM-beta) and a selectivity indices (the difference between the T values of the 2 tasks, $T_{\text{shape}} - T_{\text{location}}$) were sampled from the second repetition of the experiment in ROIs defined by the peak shape and location activation in the first repetition of the experiment across the entire dataset ($n = 20$). The results of the independent ROI analysis are consistent with the statistical parametric maps, demonstrating the task specificity of the ventral stream (inferior temporal sulcus, ITS; blind $P < 0.00005$, sighted $P < 0.00001$) and dorsal stream (precuneus; blind $P < 0.000001$, sighted $P < 0.0001$) foci for shape and location respectively in each group separately. Error bars represent standard error of the mean. $^*P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$.

original scan) after being further trained for 40 additional hours on various tasks and visual stimuli using the vOICe SSD, enabling them to achieve better task performance. We thus inspected a mixed group of 12 participants (7 blind, 5 sighted) at both training levels, in which performance was matched between the tasks (2-way ANOVA, no effect of task—$F = 3.5$, $P < 0.31$, group—$F = 1.5$, $P < 0.44$ or interaction—$F = 1.16$, $P < 0.29$) and showed that they also manifested the double task dissociation between the visual streams, at the group level (using RFX analysis) (Fig. 3*B*), in a group of blind participants only (Fig. 4; $n = 7$, no behavioral task effect, $F = 3.75$, $P < 0.07$), and in all the individual subjects (Supplementary Fig. 3), regardless of their training.

General Experiment Design

Twenty novel simple visual stimuli were created using 2 different shape categories: round and angular shapes (e.g., a circle and a square; see Fig. 1*B*) and 2 different locations (left and right). The stimuli also varied in their vertical location (up and down), but this factor was irrelevant to the tasks required, enabling generalization of shape and location to various locations within the "visual" field. The use of novel stimuli is very demanding but also further enabled us to inspect the neural correlates of the online computation of discerning shapes and locations, as opposed to possible memory effects (in themselves activating the occipital cortex of the blind; Röder et al. 2001; Amedi et al. 2003). During each trial, subjects were presented with an auditory instruction: either "shape" or "location," which directed their attention to the task. They were then presented with a 1-s soundscape (SSD sound rendering of the visual stimulus) that was repeated 4 times (total presentation time—4 s), given 5 additional seconds to reconstruct the image in their mind and were then instructed, by an auditory cue, to respond using a response box. Subjects used a two-button response box to indicate the parameter specified (Is the shape round? Is it in the left of the picture?). Each stimulus was presented twice: once for the shape task and once for the location task (without feedback), in a pseudorandomized order, such that half the stimuli were first presented in the shape task and half in the location task. Therefore, the location condition and shape condition each repeated a total of 20 times, once for each of the different stimuli. Half of the stimuli (and thus also the trials) were round; similarly, half of the stimuli were on the right side of the visual field. Subjects were not allowed to see or touch the pictures that generated the vOICe stimuli used in the fMRI testing, and none of the stimuli presented during training were used for the scan. Sighted subjects wore blindfolds and had their eyes shut for the duration of the scan to control for the lack of visual information during the scan between the groups.

fMRI Recording Parameters

The blood oxygen level–dependent (BOLD) fMRI measurements were performed in a whole-body 3-T GE scanner. The pulse sequence used was the gradient-echo echo planar imaging sequence. We used 29 slices of 4 mm in thickness. The data in-plane matrix size was 64 × 64, field of view (FOV) 20 cm × 20 cm, time to repetition (TR) = 1500 ms, flip angle = 70°, and time to echo (TE) = 30 ms. Each experiment had 320 data points with 2 repetitions (runs), whose order of presentation was controlled for across individual subjects. The first 5 images (during the first baseline rest condition) were excluded from the analysis because of non-steady state magnetization. Separate 3D recordings were used for coregistration and surface reconstruction. High-resolution 3D anatomical volumes were collected using T_1-weighted images using a 3D turbo field echo T_1-weighted sequence (equivalent to magnetization prepared rapid gradient echo). Typical parameters were: FOV 23 cm (RL) × 23 cm (VD) × 17 cm (AP); fold over—axis: RL, data matrix: 160 × 160 × 144 zero filled to 256 in all directions (approximately 1-mm isovoxel native data), TR/TE = 9/6 ms, flip angle = 8°.

Data Analysis

Data analysis was performed using the Brain Voyager QX 1.10 software package (Brain Innovation, Maastricht, Netherlands) using standard preprocessing procedures. fMRI data preprocessing included head motion correction, slice scan time correction, and high-pass filtering (cutoff frequency: 3 cycles/scan) using temporal smoothing in the frequency domain to remove drifts and to improve the signal to noise ratio. No data included in the study exceeded motion of 2 mm in any given axis or had spike-like motion of more than 1 mm in any direction. Functional and anatomical data sets for each subject were aligned and fit to standardized Talairach space (Talairach and Tournoux 1988). Single-subject data were spatially smoothed with a minimal 3 dimensional 6-mm half-width Gaussian (2 functional voxels) in order to reduce intersubject anatomical variability and then grouped using a general linear model (GLM) in a hierarchical random effects analysis (RFX; Friston et al. 1999; see for instance implementation in Amedi et al. 2007). In addition to the main contrast, all GLM contrasts reported in this study also included a conjunction (or a mask) of the comparison of the main condition to baseline, to verify that only positive BOLD for the main predictor would be included in the analysis (e.g., in a contrast of location vs. shape, location was also contrasted with baseline, and the 2 contrasts were analyzed in conjunction, thus only voxels that showed significant RFX positive BOLD to location and also significantly higher activation to location vs. shape were highlighted in the maps). This also precluded misleading comparisons including the default mode network (DMN; Raichle et al. 2001; Raichle and Mintun 2006; Raichle and Snyder 2007) in areas showing deactivation to one condition and a larger deactivation to another (e.g., to preclude an area showing for instance deactivation to location and significantly more deactivation to shape from appearing on the map, to further demonstrate the dissociation of our findings from the DMN, see Supplementary Fig. 1). In order to directly compare the effects of blindness and task across the entire data set, a 2-way ANOVA was computed (Fig. 2), taking into account all the sighted subjects ($n = 9$), and, in order to control for group size and complete blindness, the 9 fully CB who did not have any form of light perception (although the remaining 2 CB had merely faint light perception and no ability to recognize visual shapes). Post hoc contrasts were further computed from the ANOVA design and presented within the statistically significant main effect statistical parametric maps. Similar ANOVA analyses were also computed for the performance-matched subgroups (Figs 3 and 4). The minimum significance level of all results presented in the study was set to $P < 0.05$ taking into account the probability of a false detection for any given cluster (Forman et al. 1995), thus correcting for multiple comparisons. This was done based on the Forman et al. (1995) Monte Carlo simulation approach, extended to 3D data sets using the threshold size plug-in Brain Voyager QX. We also conducted a complementary independent regions of interest (ROIs) analysis. ROIs (Fig. 1*E*) were derived from the occipital peaks for the shape versus location and location versus shape contrasts (in conjunction with positive activation for the main condition, i.e., shape and location accordingly) in the first run of the experiment on the entire ($n = 20$) group. Additionally, we sampled the peaks of activation in the ANOVA interaction statistical parametric map (sampled from the interaction effect on the first run of the experiment for both groups) in each of the groups (Fig. 2*D*). Activation peak beta and selectivity indices (contrast T values, the T value for the shape task minus that of the location task) were sampled from these ROIs at the group level of activation on the second run (repetition) of the experiment, thus making the ROI definition and parameter sampling independent of each other. Separate 3D recordings were used for surface reconstruction. Anatomical cortical reconstruction procedures included the segmentation of the white matter using a grow-region function embedded in the Brain Voyager QX 1.9.10 software package (Brain Innovation). The Talairach normalized cortical surface was then inflated, and the obtained activation maps were superimposed onto it.

Results

To test for the putative dorsal–ventral division of labor dissociation, we tested what happens when a group of CB and blindfolded sighted individuals are trained to extract shape and location information using a unique visual-to-auditory sensory substitution algorithm utilized for visual rehabilitation by embedding the visual information in sounds (soundscapes).

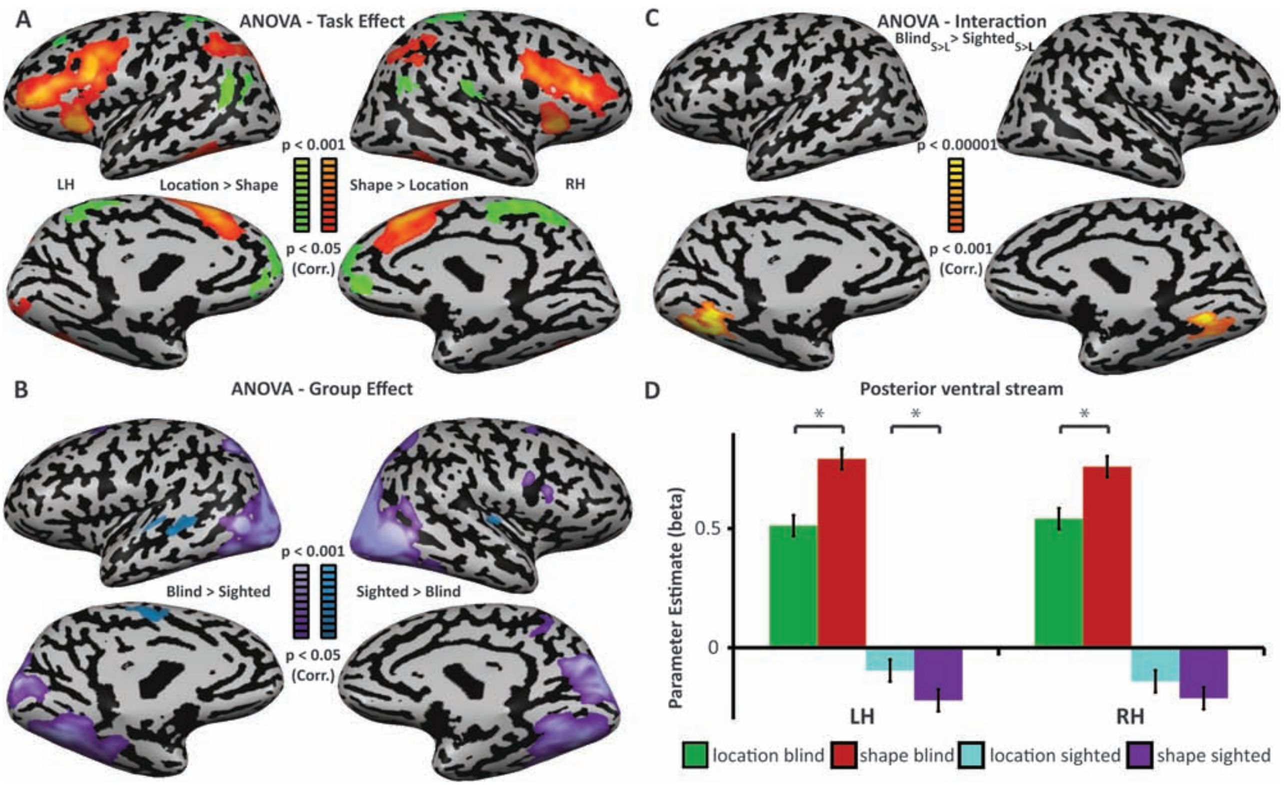

Figure 2. Effects of task and sight show increased involvement of the occipital cortex in the blind in a 2-way ANOVA. (*A*) ANOVA TASK effect was calculated across groups of 9 fully blind and 9 sighted subjects (for the main effect maps, see Supplementary Fig. 2). Within the statistically significant areas of the main TASK effect, the ANOVA TASK post-hoc contrasts are displayed (shape vs. location and location vs. shape in orange and green, respectively), replicating the visual stream segregation displayed in the GLM random-effect analysis of each group separately (Fig. 1). (*B*) ANOVA GROUP effect was calculated. Within the statistically significant areas of the main GROUP effect, the ANOVA GROUP post-hoc contrasts are displayed (CB vs. SC and SC vs. CB in purple and blue, respectively), demonstrating the increased involvement of the posterior occipital cortex of the CB for processing sensory substitution relative to the sighted. This increased activation of the visual cortex was accompanied by decreased reliance on the auditory cortex in the CB. (*C*) ANOVA interaction (TASK × GROUP) was calculated. Within the statistically significant areas of the interaction effect, contrasts of interaction were calculated, showing that the shape versus location contrast in the CB relative to the sighted was responsible for the observed interaction, supporting the increased involvement of the ventral posterior occipital cortex in shape processing in the blind group alone. (*D*) The peaks of activation for the interaction effect were sampled in both groups in the posterior ventral occipital cortex (Talairach coordinates −22, −65, −10 and 21, −54, −8 in the left and right hemispheres, respectively, corresponding to ventral Brodmann area 19). While the CB group shows preferential activation for shape, the sighted demonstrate significant deactivation for soundscape shape processing. $^*P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$.

We analyzed the data in our experiment using several complementary methods of analysis. First, we tested for task preference in each group independently using GLM RFX statistical parametric maps (Fig. 1*C*,*D*) and independent ROI analysis (Fig. 1*E*). Additionally, we conducted a 2-way ANOVA analysis that directly tested the TASK, GROUP, and interaction effects in the entire data set (Fig. 2). We also examined several subgroups of subjects with matched performance between the 2 tasks (Figs 3 and 4) including the critical group of fully CB individuals with controlled performance using RFX analysis (Fig. 4).

First, we examined task selectivity separately for the 2 participant groups (Fig. 1*C*,*D*, see map peaks coordinates in Supplementary Table 2). We found a clear differentiation between the dorsal and ventral pathways for the processing of location and shape of soundscapes, respectively. In addition to the network of multisensory areas (such as the intraparietal sulcus and inferior frontal sulcus; Amedi et al. 2005, 2007; Lacey and Campbell 2006; Naumer et al. 2008; Striem-Amit, Dakwar, et al. 2011), shape processing activated the ventral occipital inferior temporal sulcus (ITS) located in the midst of the ventral visual stream. In contrast, the localization task preferentially activated a network involving both auditory regions (such as the supramarginal gyrus in the inferior parietal lobe; Weeks et al. 1999) as well as the precuneus, corresponding to Brodmann area 7, a higher order part of the visual dorsal stream. Therefore, despite the identical perceptual auditory stimulation in the 2 tasks, we observed differential recruitment of the ventral versus dorsal stream for shape and location processing. Most critically, we found a division of labor for form and location in the visual system of CB (Fig. 1*C*). Thus, we find visual stream/task-specific selectivity in the CB in the same experiment and show that this division of labor is common to both groups (Fig. 1*C*,*D*). One clear difference in the magnitude and distribution between the 2 groups was found in the ventral visual stream. Whereas the SC group (Fig. 1*C*) showed a weaker soundscape activation limited to higher order object-related areas in the inferior temporal ventral cortex (significant in the ROI analysis; see Fig. 1*E* but not significant enough to pass the strict multiple comparison correction applied across the entire volume of the brain), the CB group (Fig. 1*D*) showed robust and vast ventral visual cortex preference for shape conveyed by sounds, demonstrating task-selective cross-modal plasticity (also see below, a direct examination of this effect using the interaction between GROUP and TASK effects in ANOVA, Fig. 2). This activation was even found within the early ventral stream areas, which corresponds to ventral retinotopic areas reaching as far as the calcarine sulcus (V1). Although activation

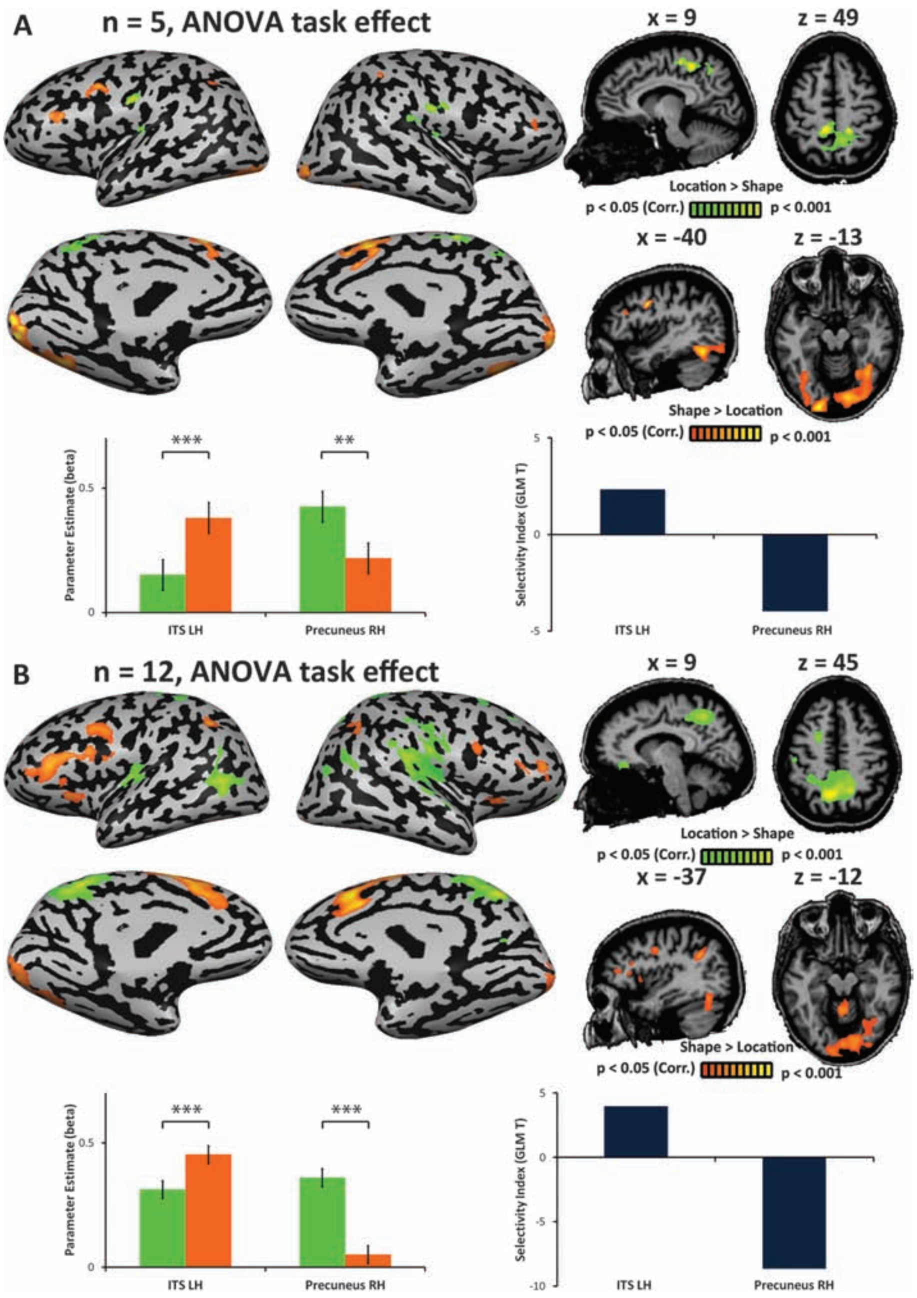

Figure 3. Task-specific activation in performance-matched control groups. (*A*) Task-specific activation for shape (vs. location, in orange) and location (vs. shape, in green) in a subgroup of 5 subjects (3 fully CB and 2 SC) who had similar performance on the shape and location tasks fully replicates the ventral–dorsal differentiation seen in the entire group, negating the possibility that the stream differentiation resulted from general task difficulty or performance bias. This is shown in the ANOVA analysis and independently in the ROI analysis (GLM-betas and selectivity indices, ITS: $P < 0.000001$, precuneus: $P < 0.005$) sampled from the peaks of the main group. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$. (*B*) Similar results were obtained in a random-effect (RFX) 2-way ANOVA of a larger group of participants ($n = 12$, 7 CB, and 5 SC) with matched performance and variable training (for detail, see Materials and Methods). ROI analysis (ITS: $P < 0.0005$, precuneus: $P < 0.000001$) and single-subject analysis of all the subjects (Supplementary Fig. 3) also supported these findings.

was stronger in the precuneus of the CB in the location task, no additional activation was found in this group in early areas corresponding to dorsal retinotopic areas or V1.

To further investigate task preference of the ventral and dorsal visual cortex through an additional independent method, we defined ROIs from the peaks of selective activation of the first run of the experiment in the entire group ($n = 20$, combined SC and CB group) for shape and location processing (Talairach coordinates: ITS LH −43, −60, −18, Precuneus RH 11, −52, 51) and examined the activation generated in the second run of the experiment in each group separately in these ROIs (Fig. 1*E*). The beta values of both the ITS and precuneus regions (ventral and dorsal stream peaks, respectively) showed a highly significant difference (Fig. 1*E*; at least $P < 0.0005$ for all contrasts) between the 2 tasks in both groups. Interestingly, activations in both peaks were higher in the CB group ($P < 0.05$).

To critically and directly investigate the separate effects and interaction between the task preference of the ventral and dorsal visual cortex and the group (with and without visual

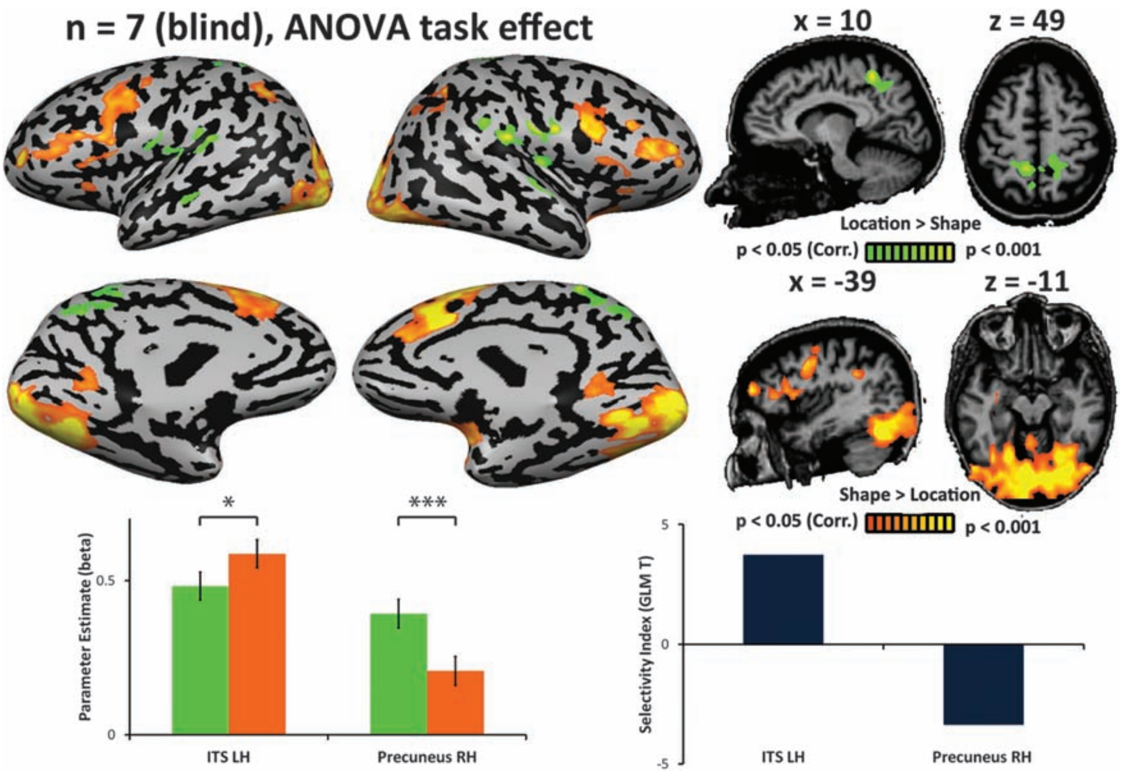

Figure 4. Task-specific activation in the performance-matched (RFX analyzed) CB group. Random effect (RFX) ANOVA analysis of a large group of 7 CB with matched performance between the tasks shows significant stream-specific task selectivities for shape in the ventral stream ITS and dorsal stream precuneus. The effect is evident in both ANOVA and independently in the ROI analysis sampled from the peaks of the main group (ITS: $P < 0.05$, precuneus: $P < 0.0005$), demonstrating that the main effect of the stream functional segregation is independent of visual experience. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$.

experience), we computed a two-way ANOVA (see Supplementary Fig. 2), with a TASK factor (shape and location) and a GROUP factor (SC and CB). In this analysis, we included all 9 SC participants and the 9 fully CB subjects (the 2 other CB were completely blind with minimal light perception and thus were omitted to fully control for both group size and for absolute blindness; results are similar when including these 2 blind subjects, data not shown). Performance in both groups was comparable (no significant group effect, $F = 0.02$, $P < 0.92$). Post hoc contrasts were computed within the significant statistical parametric maps of the main effects analysis. The TASK effect showed, as seen in the GLM analysis, a significant effect in the visual cortex (see Supplementary Fig. 2*A*). The post hoc TASK contrasts (Fig. 2*A*; see map peaks for the ANOVA in Supplementary Table 3) replicated the stream segregation seen between shape preference in the ventral stream and location preference in the precuneus in the dorsal stream, which were independent of the GROUP effect. Furthermore, this analysis suggests there was an additional region within the more posterior dorsal stream (Fig. 2*A*), in the bilateral lateral-occipito-parietal cortex (in the middle temporal gyrus/sulcus) showing preference for the location task across the groups. The GROUP effect indicated a main effect of long-term blindness in the posterior occipital cortex (see Supplementary Fig. 2*B*), in that an increased involvement of the posterior occipital cortex for processing soundscapes was identified in the CB relative to the SC (Fig. 2*B*). This increase was accompanied by a decrease in the activation of auditory cortices, which was similar to previously reported decreases in auditory cortex activation in CB for auditory localization (Weeks et al. 2000). Furthermore, the interaction of the 2 main effects (TASK × GROUP; Supplementary Fig. 2) was significant, indicating different task selectivity between the 2 groups. Post hoc contrasts revealed that this effect stems from differential preference for shape between the groups (Fig. 2*C*, other contrasts showed no significant activation). The posterior ventral cortex showed greater preference for shape in CB, even at a highly conservative threshold ($P < 0.001$ corrected for multiple comparisons; see Fig. 2*C*), which stretched all the way to the primary visual cortex (calcarine sulcus) at a more permissive yet significant threshold of $P < 0.05$ (corrected). In fact, areas more posterior to the inferior temporal cortex, in the retinotopic ventral posterior occipital cortex (ventral Brodmann area 19), showed a robust shape selective activation in the CB, in contrast to a significant deactivation in both tasks in the sighted ($P < 0.05$ for both groups; see GLM-beta values in Fig. 2*D*). These findings support the increased involvement of the ventral posterior occipital cortex in soundscape shape processing in the CB group alone (similarly, compare Fig. 1*C* and *D*).

Even though a general performance bias would not easily explain this complex task-specific stream-specific activation pattern or the similarity of the shape preference network to previous findings in highly trained sighted subjects who exhibited high performance (Amedi et al. 2007), the performance did differ between the tasks in both groups in favor of the easier localization task. We thus controlled for any general task performance biases and additionally inspected activation in several ways. We inspected several subgroups of participants that had higher and controlled performance across the tasks at both the single-subject level and the group level (including RFX analysis) and in independent ROI analyses for the peaks of activation derived from the main group effects.

Specifically, we first inspected a subgroup of 5 subjects (3 fully CB and 2 SC) who showed similar behavioral performance in both tasks at the individual level (student's paired *t*-test, $t_4 = 1.132$, $P < 0.29$ across the group, maximal difference of 10% performance in each subject), even after being very briefly trained. The results indicated a task-specific differentiation between visual streams in "all" single subjects in this subgroup (Supplementary Fig. 3; including 3 CB) and in the data pooled across them (Fig. 3*A*, fixed-effect ANOVA, map peaks are reported in Supplementary Table 4; for similar results using GLM analysis, see also Supplementary Fig. 4*A*), including a preference for the stream-matching task in the independent ROI analysis (Fig. 3*A*; $P < 0.005$), confirming that the ventral/dorsal division of labor could not stem from performance differences alone.

Moreover, to fully control for behavioral effects in a RFX analysis of a larger group, we further scanned participants who had trained for a longer period of time and achieved better and more matched performance between the 2 tasks (for details, see Materials and Methods). Both the whole group analysis ($n = 12$, random-effect ANOVA, Fig. 3*B*, see also map peaks in Supplementary Table 4; comparable GLM analysis in Supplementary Fig. 4*B*), the analysis of the blind group alone ($n = 7$, random-effect ANOVA; Fig. 4, map peaks in Supplementary Table 4; comparable GLM analysis in Supplementary Fig. 4*C*), the complementary independent ROI analyses (Figs 3*B* and 4), and the individual subject analysis level (of all the participants; Supplementary Fig. 3) confirmed that the stream dissociation does not result from performance differences. In all these types of independent analyses, for groups and individual subjects, we found a clear dissociation between the visual streams, regardless of task difficulty, including in RFX analyses in the CB. Therefore, the findings suggest that some aspects of large-scale dissociation between the ventral and dorsal streams are clearly independent of visual experience.

Discussion

Our study shows a double dissociation between the distinct activation of areas anatomically consistent with part of what is known to be visual ventral and dorsal streams in response to shape and location tasks using soundscape stimuli derived from visual origin in the same experiment. This pattern was seen across several independent analyses, in both groups (Fig. 2*A* and Fig. 1*C*,*D*) and most importantly, in the CB group separately (Figs 1*D* and 4). All the results in both groups and most critically in the CB group remain identical as well in the matched performance subgroups and analyses (Figs 3 and 4, Supplementary Fig. 3). The main regions showing task-specific activation across groups were the inferior temporal cortex for shape in the ventral stream and the precuneus and middle temporal sulcus/gyrus (Figs 1 and 2*A*) for location in the dorsal stream (e.g., Martinkauppi et al. 2000; Sestieri et al. 2006). Furthermore, the CB group also showed additional extensive recruitment of the posterior ventral stream for the soundscape shape task in ventral Brodmann area 19 (Figs 1*D* and 2*C*,*D*, Supplementary Fig. 2). The most crucial aspect of our findings suggests that despite life-long blindness, lack of visual experience and the use of novel stimuli with short training, a large extent of the ventral visual cortex in CB can be recruited to process visual-from-auditory shapes, while at least part of the dorsal stream processes visual-from-auditory location information. Therefore, life-long existence without vision does not render the 2 visual streams completely unresponsive to their classical division of labor.

The activation observed in the ventral stream is consistent with a previous study in sighted (as well as one late blind and one CB; Amedi et al. 2007) which showed that LOtv, a tactile-visual shape area, is activated for shape information conveyed using SSD soundscapes. However, that study, similar to other studies in sighted subjects (Renier et al. 2005a, 2005b; Poirier et al. 2006, 2007), could not entirely avoid the visual imagery confound, which may have contributed to any reported visual cortex activation. Moreover, most studies used a combination of only highly trained proficient SSD-users as participants (following as many as 40 h of training; Amedi et al. 2007) and familiar, well-practiced stimuli (Renier et al. 2005a, 2005b; Amedi et al. 2007; Ptito et al. 2009; Matteau et al. 2010; although sometimes as part of a training paradigm, Arno et al. 2001; Ptito et al. 2005; Kim and Zatorre 2011). All these might complicate the interpretation and strength of previous results. For instance, the brains of proficient users may have already undergone significant plastic changes due to the extensive use of SSDs (see, e.g., increased occipital cortex activation following SSD training; Ptito et al. 2005), and the use of familiar stimuli could generate activation due to memory rather than shape processing in the occipital cortex of the blind subjects (Röder et al. 2001; Amedi et al. 2003). More critically, since most of these studies focused only on one individual task (and did not contrast, e.g., shape and motion or shape and location), they were unable to directly test the double-dissociation division of labor of the visual cortex.

By circumventing these possible confounds, our study is the first to show the segregation between the ventral and dorsal streams in CB using an SSD in the same subjects, the same experimental setup and using novel stimuli. Thus, we are able to demonstrate the selective activation of visual areas by auditory stimuli in the absence of any experience that could support visual imagery. Interestingly, the activation and even task selectivity of the visual streams were more robust in the blind group than in the sighted group (Fig. 1*C*–*E* and Fig. 2*B*,*D*, Supplementary Fig. 2), particularly in the posterior occipital cortex (Figs 1 and 2*B*, Supplementary Fig. 2). While previous studies have reported increased activation in the occipital cortex of the blind (as compared with sighted) for various nonvisual tasks (Ptito et al. 2005, 2009; Matteau et al. 2010; Renier et al. 2010); in our study, we found a more complex interaction between plasticity in the blind and specific task preference in the posterior ventral occipital cortex (Fig. 2*C*,*D*). In the anterior ventral ITS, we found activation in both groups (though significantly stronger for the blind) while in the posterior ventral stream in retinotopic areas (BA 19; Fig. 2) we observed robust activation and preference for shape in blind and significant deactivation in the sighted (Fig. 2*D*). This stream- and task-specific cross-modal plasticity effect shows that not only is the ventral stream still selective for shape, this preference is enhanced (as compared with the sighted) when the shape is encoded through sound. Both results argue against a visual imagery explanation as the main basis for the ventral activation for shapes of auditory inputs which represent visual entities, suggesting instead that cross-modal plasticity biases

(Pascual-Leone and Hamilton 2001; Pascual-Leone et al. 2005) are a stronger factor in driving the visual ventral stream.

These findings have important theoretical implications, as they contribute further evidence supporting recent theories of brain organization which argue that the selectivity of the different functional cortical regions is not according to their input modality but rather according to task selectivity, which may be computed with various modalities (Amedi et al. 2001, 2007; Pascual-Leone and Hamilton 2001; Mahon and Caramazza 2009; Reich et al. 2011). The current results are consistent with several other studies demonstrating multisensory or task-dependent metamodal processing of specific brain areas within the visual system (e.g., LOtv; Amedi et al. 2002, 2007; James et al. 2002). Such studies showed recently that spatial processing of both simple auditory chords or vibrotactile stimulation selectively activate the middle occipital gyrus (MOG) of the blind (Renier et al. 2010; Collignon et al. 2011), suggesting a task-specific role for an additional unique area of the visual system. Our data are in line with this finding, as in addition to the robust task selectivity of the precuneus (which also showed multisensory properties in the sighted; Renier et al. 2009), we observed spatial selectivity in sensory substitution artificial vision input in an area in close proximity to the MOG, the posterior middle temporal sulcus/gyrus (Fig. 2*A*). Similarly, specificity for tool stimuli over other, non-manipulable objects was observed in 2 regions of the parietal cortex of the blind (Mahon et al. 2010), activation for Braille reading was found in the "visual word form area" (Reich et al. 2011), activation for kinesthetically guided hand movements was found in primary somatosensory cortex independent of the visual experience of participants (Fiehler et al. 2009), and activation of the human MT region was found for nonvisual motion in the blind (Poirier et al. 2006; Beauchamp et al. 2007; Ricciardi et al. 2007; Ptito et al. 2009; Matteau et al. 2010; Sani et al. 2010). All these suggest that the brain might be comprised of flexible task-selective but modality-independent operators (Reich et al. 2011). Another recent study that is particularly relevant to the conclusions drawn here looked beyond area-specific computation and showed that the larger scale animate/inanimate organization within the high-order anterior ventral visual cortex is independent of vision (in a group of sighted and 3 CB individuals; Mahon et al. 2009). Mahon et al. (2009) concluded from their results that modality dependence is secondary as a hierarchical organizational factor to the object domain (e.g., living vs. non-living, also see a review of conceptual object categories; Mahon and Caramazza 2009) in the ventral visual cortex. Our findings extend such concepts of a-modal innately determined developmental constraints to the more fundamental organizational principle of the segregation between the 2 processing streams. In doing so, it extends the findings beyond visual object conceptual categories to postulating that the whole brain may be task specific but sensory modality independent, if the relevant computation and task can be achieved from the sensory input (even if this is not an ecological way to do so, i.e., via SSD).

In this respect, sensory substitution is an ideal tool to study task-dependent operations as it teases apart the effect of the modality from the computation or task in question and also makes it possible to study tasks using untrained, novel, "modalities" and stimuli. The functional recruitment in the brain of CB following such a short training period makes it highly improbable that they reflect any extensive plastic changes (Pascual-Leone et al. 2005). Instead, it suggests that the division of labor between the ventral and dorsal streams for form and location in the visual cortex must already be present and the short training presumably "revealed" these innate preferences under our special experimental conditions. The life-long use of these areas for visual input more than for information originating in other senses (along with the usefulness of vision to decipher shape) makes the streams appear as though they are only or mostly visual. This study suggests this is not the case and that cross-modal plasticity can still result in their activation for their original visual tasks.

What are the developmental endogenous, or innate, constraints that might contribute to such a sensory-independent task-selective organization in the CB? We speculate that 2 factors, which are not mutually exclusive, could have taken part. The first are intrinsic modality-independent preferences for a particular (different) type of content or computation in each brain area (in our case, in the dorsal and ventral regions). For example, an area might specialize in computing motion due to computing subtractions of a motion coincidence detector regardless of sensory input. If this is true then all these areas were always multisensory, possibly with visual dominance since it is perhaps the most reliable sensory input in the sighted. Alternatively, the task specificity might stem from the different connectivity pattern of each area. In our case, the visual streams may differ in their connectivity pattern to other cortical areas, which together drive their task-selectivity organization (e.g., via top-down modulation). For example, it has been suggested that premotor–posteromedial parietal connections are likely to subserve abstract cognitive processes involving visuospatial information in the precuneus (Cavanna and Trimble 2006), while feedback connectivity from frontal and somatosensory cortices to the ventral (inferior temporal) occipital cortex may underlie its multisensory function for object recognition (Amedi et al. 2001, 2003; Deshpande et al. 2008). In addition to the preexisting connectivity, connectivity between the visual cortex and other sensory cortices may also be strengthened by sensory deprivation (e.g., between A1 and V1; Klinge et al. 2010). Thus, although the input in our case was auditory rather than visual, the preserved functional connectivity of each stream still dictates development toward processing shape or location, which may even be strengthened for the nonvisual modalities.

This type of top-down modulation based on the existing connectivity pattern might also originate from the corresponding auditory streams. Similar to the visual streams, auditory processing is also divided into what and where pathways, whose functional and anatomical segregation has been thoroughly validated in many species, including humans (Pandya and Vignolo 1969; Romanski et al. 1999; Kaas and Hackett 2000; Rauschecker and Tian 2000; Alain et al. 2001; Kubovy and Van Valkenburg 2001; Kraus and Nicol 2005; Lomber and Malhotra 2008; van der Zwaag et al. 2011). Some selective activation of these auditory streams is also seen in our contrasts in addition to the visual cortical streams. While our results do not clearly show the auditory division of labor between the rostral and caudal parts of the early-stage auditory areas on the supratemporal plane (which can better be depicted by ultra high-field 7-T scanners due to the relatively small size of the auditory areas and the integrated what and where processing of some of these regions; Griffiths and Warren 2002; van der Zwaag et al. 2011), we do, however, find evidence for the stream differentiation in the inferior parietal lobe (supramarginal gyrus and even post STG) and frontal lobe (between the inferior and superior what and where regions), in accordance with the auditory stream division. Therefore, it may be speculated that the same auditory connectivity may partially underlie the visual cortex differentiation and selectivities found in the current report. However, previous studies of purely auditory localization and object identification in the sighted or blind (as opposed to visual-to-auditory processing using an SSD) have not shown clear and consistent activation of the ITS (Amedi et al. 2002, 2007) or precuneus (Collignon et al. 2009, although the precuneus may sometimes be activated by nonvisual localization in sighted; Renier et al. 2009). An exception to this may be the MOG, which shows selective activation for auditory localization in the blind (Collignon et al. 2007; Renier et al. 2010). This suggests that the main occipital cortical regions shown here (ITS and precuneus) are less likely to partake in the auditory processing streams per se but rather with processing computations that resemble vision (e.g., object shape). Thus, their roles are less likely to develop as regular parts of the auditory streams.

Interestingly, one difference between the shape and location activation was the lack of more posterior recruitment of the dorsal stream even in the CB (Figs 1 and 2*B*–*D*). One possible explanation is that the location task was simply easier (possibly resulting in less activation for this task). However, the replication of the group results in our subgroup of 5 subjects, in the larger mixed group (n = 12) and critically, in the large group of the CB (n = 7, RFX analysis), who had similar performance on both tasks, as well as in all the individual subjects comprising these groups (Figs 3 and 4, Supplementary Fig. 3), rules out this explanation. Alternatively, these differences might be due to different developmental timelines of the 2 streams. Although both streams may be not only visual but task-specific and sensory-input independent to some extent, the dorsal stream matures earlier in development (Lewis and Maurer 2005), whereas it has been shown that the ventral stream may continue to develop until adolescence (Golarai et al. 2007). This suggests that the ventral stream may continue to be plastic later in life (e.g., have longer sensitive periods) relative to dorsal stream regions and thus be more likely to reorganize differently and adaptively (e.g., as seen in our study, to sounds). Supporting this notion, previous studies have shown robust changes of the ventral visual cortex to other nonvisual functions such as language and memory (Sadato et al. 1996; Cohen et al. 1997; Röder et al. 2001, 2002; Burton, Snyder, Conturo, et al. 2002; Burton, Snyder, Diamond, et al. 2002; Amedi et al. 2003; Pascual-Leone et al. 2005; Noppeney 2007; Bedny et al. 2011). Moreover, studies of sensory restoration after long-term visual deprivation (Fine et al. 2003; Gregory 2003; Ostrovsky et al. 2006, 2009) suggest that ventral stream visual functions may remain deficient after visual peripheral recovery even after months of training following the procedure (perhaps due to the aforementioned robust plastic cross-modal changes), whereas motion perception (a dorsal stream function, processed in the early-maturing MT; Lewis and Maurer 2005) appears to recover almost immediately following sensory restoration.

Does this condemn the critical ventral stream functions to remaining largely deficient following sight restoration? While previous studies (Fine et al. 2003; Gregory 2003; Ostrovsky et al. 2009) indeed show very serious deficits in object shape recognition and segregation from background that might hinder sight restoration efforts regardless of the exact clinical/technological approach, our results imply that the ventral stream could hypothetically be shifted back toward its original task preference. The preferential activation of the posterior ventral stream for shape in the CB (Figs 1 and 2, Supplementary Fig. 2) suggests that while visual deprivation may modify the role of these regions, the general stream preference remains and can be revealed after learning to extract the relevant information from other modalities (in our case audition). The adaptation of the blind to processing auditory information more than the sighted may even result in quicker recruitment of cross-modal visual shape processing transmitted by SSD. Although our subjects were not studied under a clinical sight restoration protocol (in the more conventional sense of restoration of visual qualia using, e.g., retinal prostheses; Dowling 2008), we feel it is important to discuss our results in the context of clinical settings and to speculate on their putative importance. For example, future work should examine whether this unique combination of sensory-input independent organization, baseline biases to shape and location, and longitudinal long-term plasticity enables the use of SSDs as neuro-rehabilitative aids to train the visual cortex to analyze visual information. Therefore, SSDs can theoretically support visual rehabilitation both before such procedures, for example, to help reprogram or awaken the hypothesized visual streams to selectivity process "vision" (rather than language and memory; Sadato et al. 1996; Cohen et al. 1997; Röder et al. 2001, 2002; Burton, Snyder, Conturo, et al. 2002; Burton, Snyder, Diamond, et al. 2002; Amedi et al. 2003; Pascual-Leone et al. 2005; Noppeney 2007; Bedny et al. 2011; Striem-Amit, Bubic, et al. 2011) and then by serving as a "sensory interpreter," providing explanatory input to the novel visual signal arriving from an alien invasive device when it is first introduced to the visually restored individual. Interestingly, in a recent study, the more intact and faster recovering dorsal stream functions (e.g., detecting moving stimuli) were successfully used to train the deficient ventral stream functions (visual parsing and object recognition) in blind individuals who regained sight through medical intervention using shape-from-motion training (Ostrovsky et al. 2009). SSDs could thus be used in a similar way to train the visual cortex via other modalities.

To conclude, this study shows that visual experience is not necessary in order for the dorsal–ventral division of labor within the visual system to emerge, at least to some extent. This suggests the operation of innately determined constraints on the emergence of the most important large-scale organization of the visual cortex. Our results favor the view that these preferences are determined, in part, by dimensions of domains of knowledge or task similarity that cannot be reduced to the visual experience of individuals (e.g., Mahon and Caramazza 2009; Renier et al. 2010, 2011). Finally, our results support the notion that large parts of the visual system are task-specific modality invariant in nature and can be accessed, via cross-modal mechanisms, by any sensory modality.

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Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes

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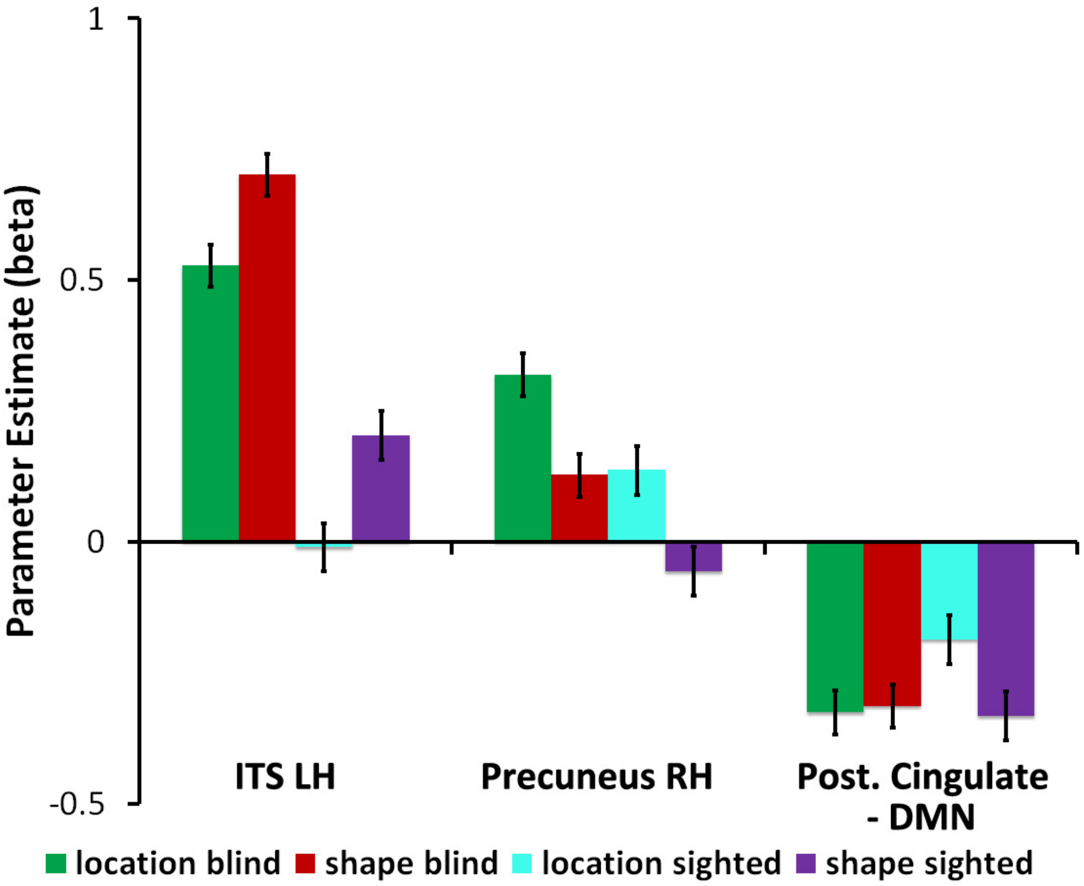
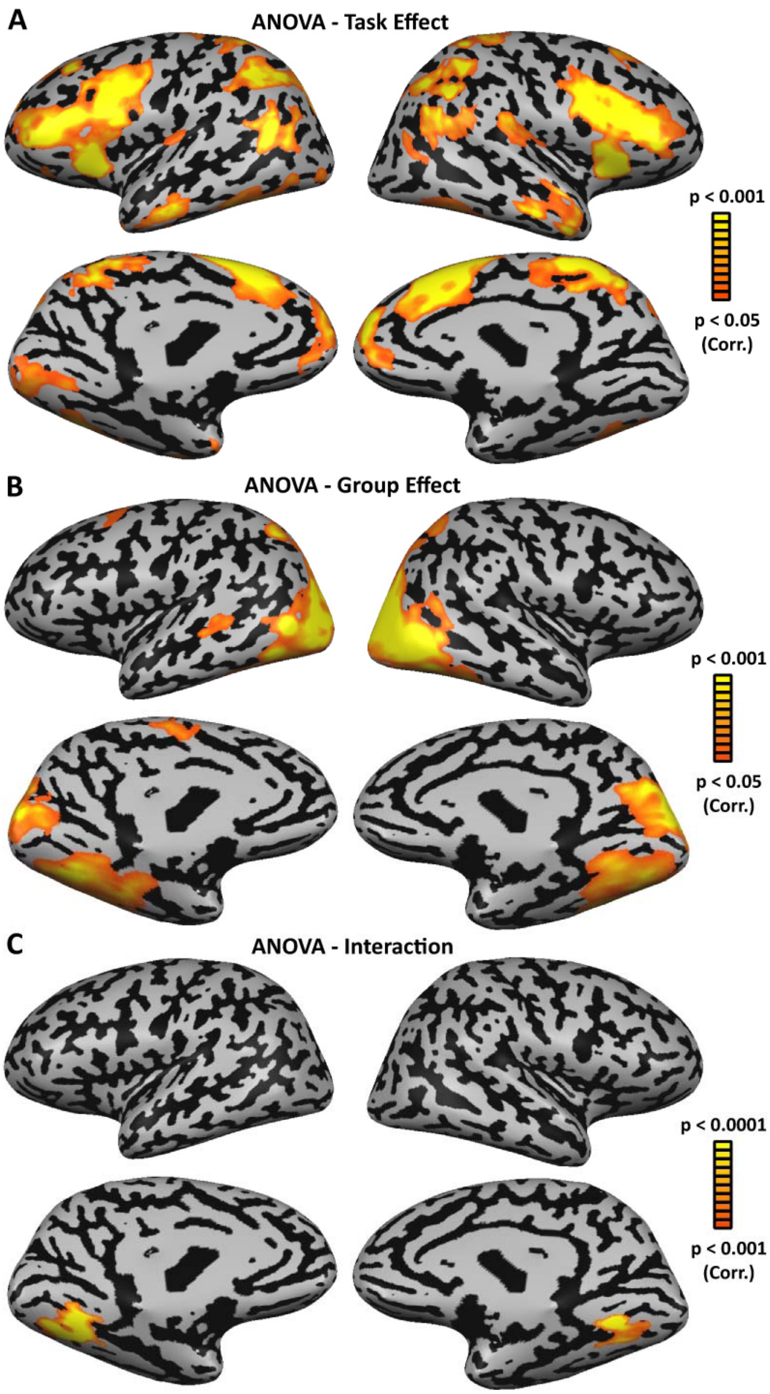
Supplementary Figure Legends



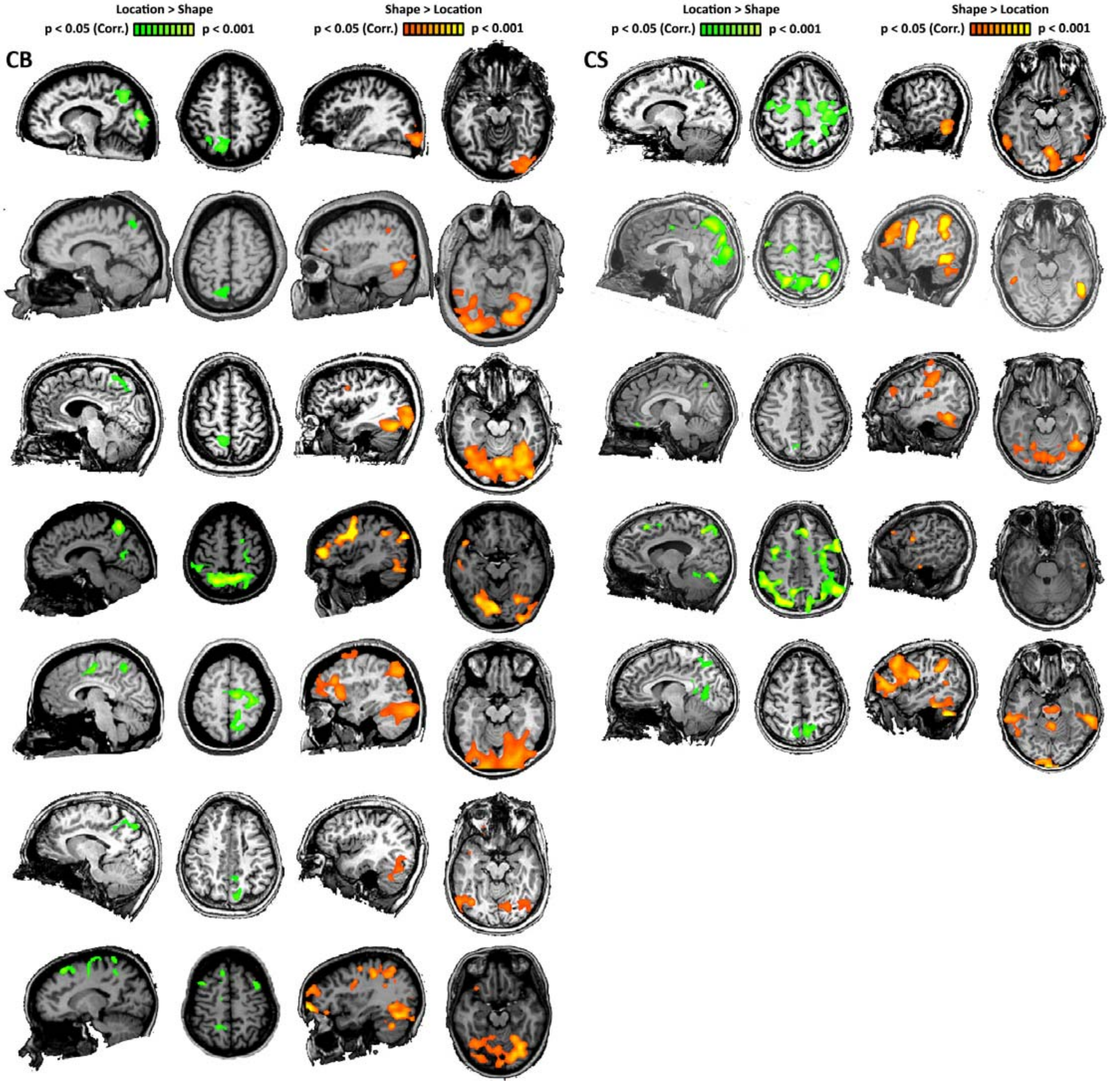
Supplementary Figure 1: Controlling for deactivations in our design.

In order to verify that our conjunction GLM analysis (see methods) successfully excluded misleading deactivation comparisons which include the default mode network (DMN; Raichle ME et al. 2001; Raichle ME and MA Mintun 2006; Raichle ME and AZ Snyder 2007), we further examined the DMN within our own data. We sampled the peak of the negative BOLD results for the contrast “all tasks vs. rest” in the posterior cingulate gyrus, which is the closest peak to our regions-of-interest (DMN peak: -6,-54,30, peak defined in the first repetition of the experiment and parameters sampled from the second repetition). This peak is clearly dissociated from our main regions-of-interest (i.e. ITS and precuneus) as presented in our results both in location (the precuneus peak is located some 20mm below it, at Talairach coordinates: 11,-52,51) and in functional preferences: while the DMN is characterized as a network of areas exhibiting de-activation during performance of externally oriented cognitive tasks, as can be seen in the parameter estimates of the posterior cingulate peak, our regions-of-interest show significantly positive BOLD.



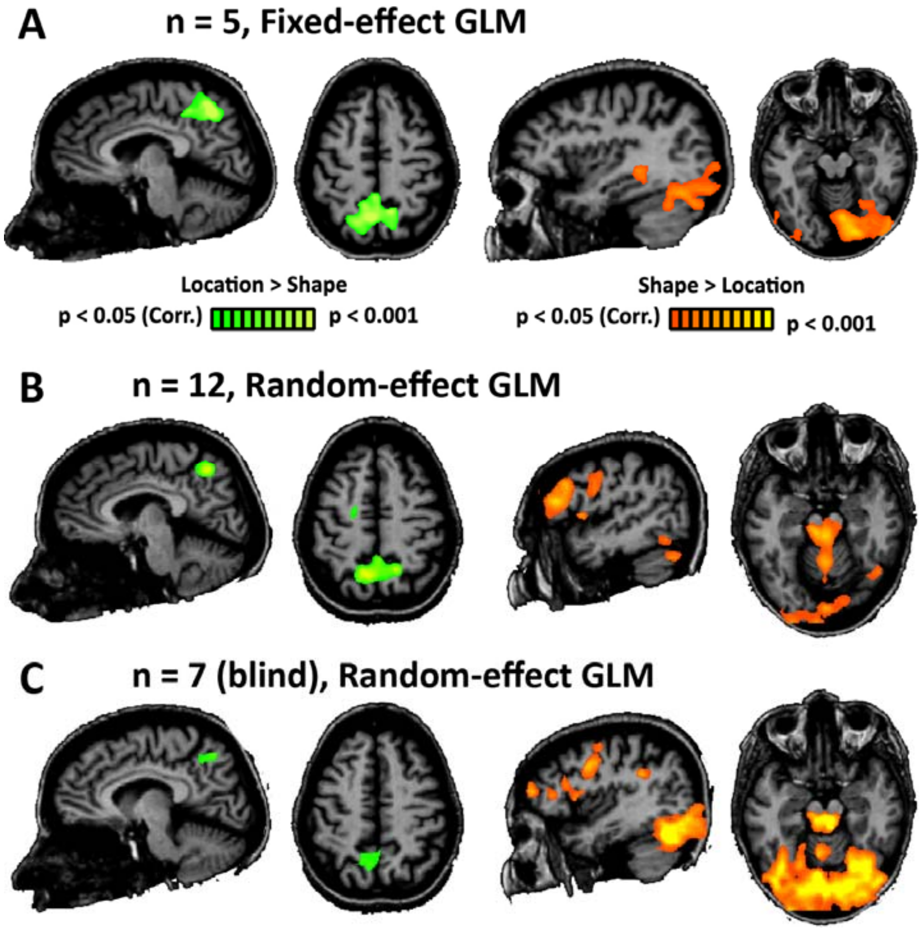
Supplementary Figure 2: ANOVA main TASK, GROUP AND TASK X GROUP effects.

- **A.** ANOVA TASK effect was calculated across groups of nine fully-blind and nine sighted, demonstrating that both ventral and dorsal stream regions were indeed selective for task. For post-hoc contrasts of this effect see **Fig.2A**.
- **B.** ANOVA GROUP effect showed a highly significant effect of sight on the activation of the visual cortex. For post-hoc contrasts of this effect see **Fig.2B**.
- **C.** ANOVA interaction (TASK X GROUP) effect showed an interaction between sight and visual task in the posterior ventral occipital cortex. For post-hoc contrast of this effect see **Fig.2C**.



Supplementary Figure 3: Task-specific activations in single subjects in which performance was matched across tasks.

The task specific activation is depicted for each of the twelve subjects in the performance-matched group, in sagittal and axial views of individual brains. Both the dorsal stream precuneus task preference and the ventral stream task preference can be observed in all single subjects. This suggests that the stream-segregation effect obtained independently of performance at the group level (see **Figs. 3, 4**) can be replicated in individual subjects as well. CB – congenitally blind, SC – sighted controls.


A
n = 5, Fixed-effect GLM
Location > Shape
p < 0.05 (Corr.)
p < 0.001
Shape > Location
p < 0.05 (Corr.)
p < 0.001
B
n = 12, Random-effect GLM
C
n = 7 (blind), Random-effect GLM

Supplementary Table 1: Characteristics of blind and sighted subjects

Subject	Age & Gender	Cause of blindness	Light perception	Handedness	Age of blindness onset
1	27 F	Microphthalmia	None	Right	0
2	27 F	Leber's congenital amaurosis	Faint	Ambidextrous	0
3	38 M	Retinopathy of prematurity	Faint	Right	0
4	35 M	Retinopathy of prematurity	None	Right	0
5	36 F	Rubella	None	Right	0
6	52 M	Retinopathy of prematurity	None	Right	0
7	56 F	Leber's congenital amaurosis	None	Right	0
8	31 F	Retinopathy of prematurity	None	Right	0
9	28 F	Retinopathy of prematurity	None	Right	0
10	21 F	Microphthalmia, Retinal detachment	None	Left	0
11	36 F	Enophthalmus	None	Left	0
12	32 F	Retinopathy of prematurity	None	Left	0
13	23 F	-	full	Right	sighted
14	23 F	-	full	Right	sighted
15	27 F	-	full	Right	sighted
16	24 M	-	full	Right	sighted
17	24 F	-	full	Right	sighted
18	23 F	-	full	Left	sighted
19	23 F	-	full	Left	sighted
20	22 M	-	full	Right	sighted
21	22 M	-	full	Right	sighted

Supplementary Table 2: Peaks of activation of GLM analysis (presented as statistical parametric maps in Fig. 1)

	X	Y	Z	T value	p value
Sighted Group (n=9)					
Shape > Location					
IFS post. LH	-46	1	21	4.9	0.005
IFS post. RH	41	10	15	3.6	0.01
IFS ant. LH	-46	49	18	4.6	0.005
IFS ant. RH	44	31	24	4.3	0.005
ant. Insula RH	35	22	9	3.4	0.01
Precentral G. RH	44	1	33	3.2	0.05
IPS RH	41	-53	42	4.4	0.005
SFG - medial	5	22	60	3.2	0.05
Location > Shape					
Precuneus LH	-13	-62	54	3.6	0.01
Precuneus RH	8	-71	48	3.6	0.01
Paracentral Lobule LH	-10	-23	48	4.3	0.005
Insula RH	38	-5	-3	5	0.005
STG RH	44	-47	24	3.2	0.05
Blind Group (n=11)					
Shape > Location					
IFS ant. LH	-46	34	21	3.7	0.005
IFS ant. RH	38	52	18	4.7	0.001
IFS post. LH	-40	1	33	8.4	0.0001
IFS post. RH	50	16	24	5.5	0.0005
ant. Insula LH	-28	19	6	3.5	0.01
ant. Insula RH	35	25	6	4.6	0.001
IPS LH	-19	-89	33	4.3	0.005
IPS RH	32	-74	42	6	0.0005
ITS LH	-28	-68	-12	4.8	0.001
ITS RH	32	-68	-18	4.3	0.005
Cuneus LH	-7	-80	-12	5.2	0.0005
Cuneus RH	11	-77	-12	7.5	0.0001
Parieto-Occipital S. LH	-6	-44	9	3.1	0.05
Parieto-Occipital S. RH	17	-74	18	3.7	0.005
Location > Shape					
Precuneus LH	0	-56	48	3	0.05
Precuneus RH	17	-53	54	4.1	0.005
Supramarginal G LH	-64	-41	18	3.9	0.005
Supramarginal G RH	44	-35	21	4.2	0.005
SFG RH	20	-11	54	5	0.001
SFG RH	20	-11	54	5	0.001
Central S. LH	-46	-2	6	3	0.05

Supplementary Table 3: Peaks of activation of the analysis of variance (ANOVA; presented as statistical parametric maps in Fig. 2)

	X	Y	Z	T value	p value
TASK effect -					
Shape > Location					
IFS ant. LH	-46	46	12	6.8	0.0001
IFS post. LH	-43	4	27	5.9	0.0001
IFS RH	44	28	27	5.6	0.0001
SFG	-4	19	48	5.8	0.0001
ant. Insula LH	-31	16	3	6.8	0.0001
ant. Insula RH	32	22	6	6.9	0.0001
IPS LH	-13	-74	30	4.4	0.0005
IPS RH	29	-68	33	3.9	0.005
ITS LH	-46	-53	-15	3.8	0.005
ITS RH	47	-53	-15	3.3	0.005
Lingual G LH	-13	-83	-12	2.7	0.05
Location > Shape					
Precuneus LH	-13	-53	51	3.8	0.005
Precuneus RH	8	-38	48	4.8	0.0005
SFG LH	-22	19	42	3.4	0.005
MTG RH	44	-59	21	3.2	0.005
MTG LH	-52	-71	24	4.2	0.005
Supramarginal G. RH	50	-35	27	3.3	0.005
Group effect -					
Sighted > Blind					
STG LH	-40	-32	6	6.4	0.0001
STG RH	38	-23	6	4.1	0.005
STS RH	65	-23	9	2.7	0.05
Blind > Sighted					
IPS LH	-22	-62	42	5.8	0.0001
IPS RH	29	-62	51	4	0.005
Lateral Occipital S. LH	-43	-71	3	6.8	0.0001
Lateral Occipital S. RH	41	-68	0	8.2	0.0001
Parieto-Occipital S.	5	-86	18	6.6	0.0001
IFS RH	50	7	24	4	0.005
SFS LH	-31	7	45	3.3	0.005
SFS RH	26	-5	51	3.5	0.005
Interaction					
Blind (shape) > Sighted (Shape)					
Collateral S. LH	-31	-62	-15	55.2	0.0001
Collateral S. RH	20	-59	-9	46.9	0.0001
Lateral Occipital S. LH	-31	-83	-3	39.8	0.0001

Cuneus RH	14	-86	9	33.2	0.0001
Other interaction contrasts showed no significant activation					

Supplementary Table 4: Peaks of activation of performance-matched groups (presented as statistical parametric maps in Figs. 3,4)

	X	Y	Z	T value	p value
<u>Briefly-trained participants (n=5)</u>					
Shape > Location					
IFS ant. LH	-46	28	24	4.4	0.05
IFS post. LH	-40	4	36	5.8	0.005
IFS ant. RH	41	37	15	3.2	0.05
IPS LH	-34	-56	30	7.2	0.005
IPS RH	47	-44	39	5.9	0.005
SFG LH	2	19	60	13.9	0.0005
SFG RH	5	16	60	14.2	0.0005
ITS LH	-40	-59	-18	5.2	0.01
ITS RH	35	-62	-18	4.8	0.01
Lingual G. LH	-16	-86	-6	12.3	0.0005
Lingual G. RH	11	-102	0	6.1	0.005
Location > Shape					
Central S. LH	-49	-14	24	7.1	0.005
Central S. RH	68	-12	18	5.4	0.01
Post. Insula LH	-34	-23	21	5.3	0.01
Post. Insula RH	38	-20	21	4.9	0.01
Lateral S. RH	50	-35	24	4.4	0.05
Precuneus LH	-16	-41	51	9.5	0.001
Paracentral Lobule RH	11	-38	51	9.8	0.001
Precuneus RH	14	-59	45	6.2	0.005
<u>Full matched-performance group (n=12)</u>					
Shape > Location					
IFS ant. LH	-46	31	15	3.8	0.005
IFS ant. RH	41	49	21	3.8	0.005
IFS post. LH	-46	1	36	3.5	0.005
IFS post. RH	41	4	24	2.9	0.05
ant. Insula LH	-46	31	15	3.8	0.005
ant. Insula RH	32	19	3	3.4	0.01
SFG LH	-7	-2	60	5.5	0.0005
SFG RH	8	16	39	5.3	0.0005
IPS LH	-34	-53	30	4.7	0.001
IPS RH	32	-53	33	3.7	0.005
ITS LH	-40	-62	-18	3.4	0.01

Lingual G. LH	-13	-92	-6	3.8	0.005
Lingual G. RH	-1	-89	-15	3.6	0.005
Location > Shape					
Precuneus LH	-19	-53	48	5.9	0.0005
Precuneus RH	8	-62	48	6.2	0.0001
Central S. LH	-28	-38	70	5.4	0.0005
Central S. RH	13	-44	57	5.2	0.0005
post. Insula LH	-37	-20	18	3.9	0.005
post. Insula/inf. Central S. RH	53	-32	24	4.5	0.001
SFG RH	23	4	45	4	0.005
MTS/MTG LH	-40	-59	9	4.2	0.005
MTS/MTG RH	44	-75	24	3.5	0.005
Parieto-Occipital S. RH	14	-58	17	2.8	0.05
Blind matched-performance group (n=7)					
Shape > Location					
IFS ant. LH	-37	55	15	9.6	0.0001
IFS post. LH	-31	1	39	12.1	0.0001
IFS ant. RH	38	45	18	9.3	0.0001
IFS post. RH	47	4	24	8	0.0005
ant. Insula LH	-43	19	6	5.4	0.005
ant. Insula RH	41	16	-3	4.6	0.005
SFG LH	1	22	53	6.6	0.001
SFG RH	5	19	36	14.8	0.0001
IPS LH	-28	-65	24	8.3	0.0005
IPS RH	32	-56	39	7	0.0005
ITS LH	-28	-62	-6	9.4	0.0001
ITS RH	37	-71	-17	5.6	0.005
Lingual G. LH	-13	-91	-6	6.7	0.001
Lingual G. RH	14	-92	-18	8.4	0.0005
ant. Calcarine S./ Parieto-Occipital S. LH	-19	-44	0	4.1	0.001
ant. Calcarine S./ Parieto-Occipital S. RH	17	-41	-5	4.2	0.01
Location > Shape					
Precuneus LH	-25	-38	60	5.8	0.005
Precuneus RH	14	-44	57	5.7	0.005
STS LH	-54	-21	-3	5.3	0.005
Central S. LH	-25	-38	60	5.8	0.005
post. Insula/Central S. LH	-46	-29	27	6.1	0.001
post. Insula/Central S. RH	65	-5	18	10.1	0.0001
Supramarginal RH	50	-32	30	8.3	0.0005

3.3 Reading with sounds: Sensory substitution selectively activates the visual word form area in the blind

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Reading with Sounds: Sensory Substitution Selectively Activates the Visual Word Form Area in the Blind

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SUMMARY

Using a visual-to-auditory sensory-substitution algorithm, congenitally fully blind adults were taught to read and recognize complex images using "soundscapes"—sounds topographically representing images. fMRI was used to examine key questions regarding the visual word form area (VWFA): its selectivity for letters over other visual categories without visual experience, its feature tolerance for reading in a novel sensory modality, and its plasticity for scripts learned in adulthood. The blind activated the VWFA specifically and selectively during the processing of letter soundscapes relative to both textures and visually complex object categories and relative to mental imagery and semantic-content controls. Further, VWFA recruitment for reading soundscapes emerged after 2 hr of training in a blind adult on a novel script. Therefore, the VWFA shows category selectivity regardless of input sensory modality, visual experience, and long-term familiarity or expertise with the script. The VWFA may perform a flexible task-specific rather than sensory-specific computation, possibly linking letter shapes to phonology.

INTRODUCTION

Reading, despite being a recent ability in evolutionary time scales, appears to relate to a partially dedicated neural network. This network includes, as a central node, a patch of left ventral visual cortex located lateral to the midportion of the left fusiform gyrus dubbed the "visual word form area" (VWFA; Cohen et al., 2000; Dehaene and Cohen, 2011; Schlaggar and McCandliss, 2007) or left ventral occipito-temporal cortex (vOT; Price, 2012; Price and Devlin, 2011; Wandell, 2011). Extensive research has demonstrated the specialization of this region for the visual representation of letters, its category selectivity manifested in its preference for letters over other types of visual objects (Cohen and Dehaene, 2004; Dehaene and Cohen, 2011; Dehaene et al., 2010; Szwed et al., 2011), its invariance to changes in visual scripts, fonts, or location in the visual field (Bolger et al., 2005; Dehaene et al., 2010), as well as its high intersubject anatomical and functional reproducibility (Cohen et al., 2002).

One key question is what causes the apparent selectivity of the VWFA for letters. This hotly debated issue (Price, 2012; Price and Devlin, 2011) was recently resolved to some extent by an integrative view suggesting that the selectivity of VWFA may arise from a conjunction of two properties that make it optimally appropriate for reading: (1) efficient reciprocal projections to language areas (Mahon and Caramazza, 2009; Pinel and Dehaene, 2010) and (2) a sensitivity to the visual features that characterize scripts, such as reliance on line junctions (Szwed et al., 2011), foveal position (Hasson et al., 2002), and high spatial frequencies (Woodhead et al., 2011).

How dependent is VWFA selectivity on such visual sensory features? It was recently shown (Rauschecker et al., 2011) that reading activates VWFA even when the shape of the letters is derived from atypical features such as the movement or the luminance of sets of dots. This suggests that within vision there is remarkable feature tolerance. Here we explored whether this tolerance of VWFA activation for reading can be generalized as far as to reading in a new nonvisual sensory modality, and further, when reading in this novel modality is learned in adulthood, well after reading skills are usually acquired. We took advantage of a unique setup to probe these questions and several other related key issues. We studied a group of congenitally fully blind adults trained to read through a visual-to-auditory sensory substitution device (SSD; Bach-y-Rita and W Kercel,

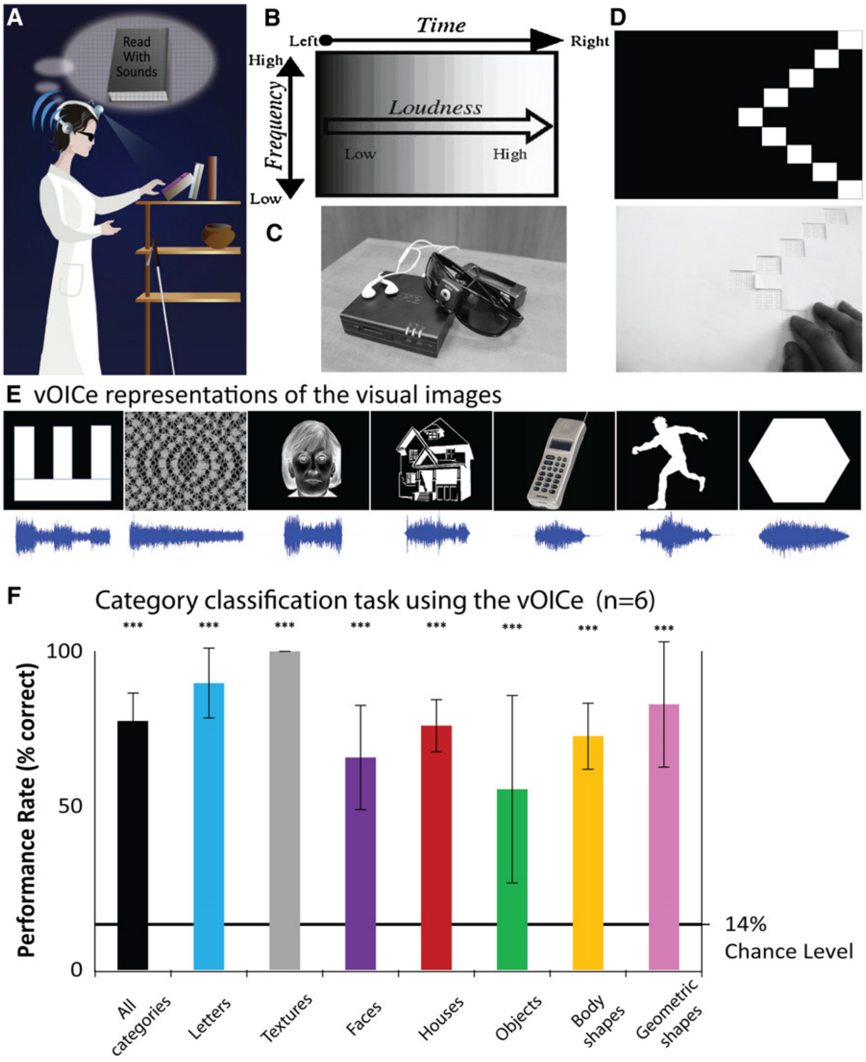

Figure 1. "Visual" Performance in Blind Users of "The vOICe" Sensory Substitution Device after Training

(A) Visual-to-auditory sensory substitution is used to convey visual information to the blind using their intact auditory modality.

(B) The transformation algorithm of the vOICe (Meijer, 1992): each image is scanned from left to right, such that time and stereo panning constitute the horizontal axis in its sound representation, tone frequency makes up the vertical axis, and loudness corresponds to pixel brightness (see also http://www.seeingwithsound.com).

(C) The mobile kit for SSD usage includes a lightweight inexpensive webcam worn on eyeglasses, a computing device (such as a netbook computer or smartphone), and earphones.

(D) Tangible image feedback (bottom), identical to that presented using the vOICe (top), was provided to the blind participants to help them further understand the images during training.

(E) The structured two-dimensional training program consisted of hundreds of stimuli organized in order of complexity and grouped into structured categories: Hebrew letters, textures, faces, houses, tools and everyday objects, body postures, and geometric shapes.

(F) Success in discriminating between object categories was assessed upon completion of the structured two-dimensional training (n = 6). Object discrimination differed significantly from chance (mean percent correct 78.1% ± 8.8% SD, $p < 0.00005$, Student's t test), and no difference was observed between performance in the letter category and any of the other object categories ($p > 0.05$, corrected for multiple comparisons). Error bars denote SD. Significance refers to difference from chance level: *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$.

2003), which converts visual images to auditory "soundscapes" using a predetermined consistent algorithm (The vOICe; Meijer, 1992). This enabled the blind to perceive high-resolution visual information (Striem-Amit et al., 2012b) and, in this case, to learn to read, with sounds topographically representing visual images of letters (see Figure 1).

Moreover, subjects also learned to recognize soundscapes of other visually complex object categories such as faces, houses, and body parts. This ability helped us test a fundamental question: can the "visual" category selectivity of the VWFA develop in the absence of any visual experience? In sighted subjects, the VWFA is characterized by increased responses to letters as compared to different visual object categories (such as faces, houses, and objects; Cohen and Dehaene, 2004; Dehaene and Cohen, 2011; Dehaene et al., 2010; Hasson et al., 2002; Puce et al., 1996; Szwed et al., 2011; Tsapkini and Rapp, 2010), similar to the preferential activation of the neighboring regions for faces, scenes, objects, and body shapes (Kanwisher, 2010). Can full category selectivity in the VWFA also emerge without visual experience and by using auditory sensory substitution, and if so, what is the basis for such a robust preference pattern?

Finally, another key question relates to the developmental origin of the VWFA (and the ventral stream more generally). Even assuming that the VWFA can develop specialization and selectivity for reading in nonvisual modalities, how dependent is such specialization on the age and amount of training? Reading in the visual modality is usually learned in childhood and improves over many years of practice (Aghababian and Nazir, 2000). Recent evidence shows that plasticity of the ventral visual cortex extends into adolescence and beyond (Dehaene et al., 2010; Golarai et al., 2007). However, does the VWFA show selectivity for script over other object categories when it is trained to read using an SSD in the fully developed adult brain and with quantitatively limited practice? This question is important both with regard to visual rehabilitation and in relation to the mechanisms of brain plasticity.

Thus, the unique capacity of congenitally blind adults to learn to read and to recognize objects using SSD enabled us to examine three key issues regarding brain organization and

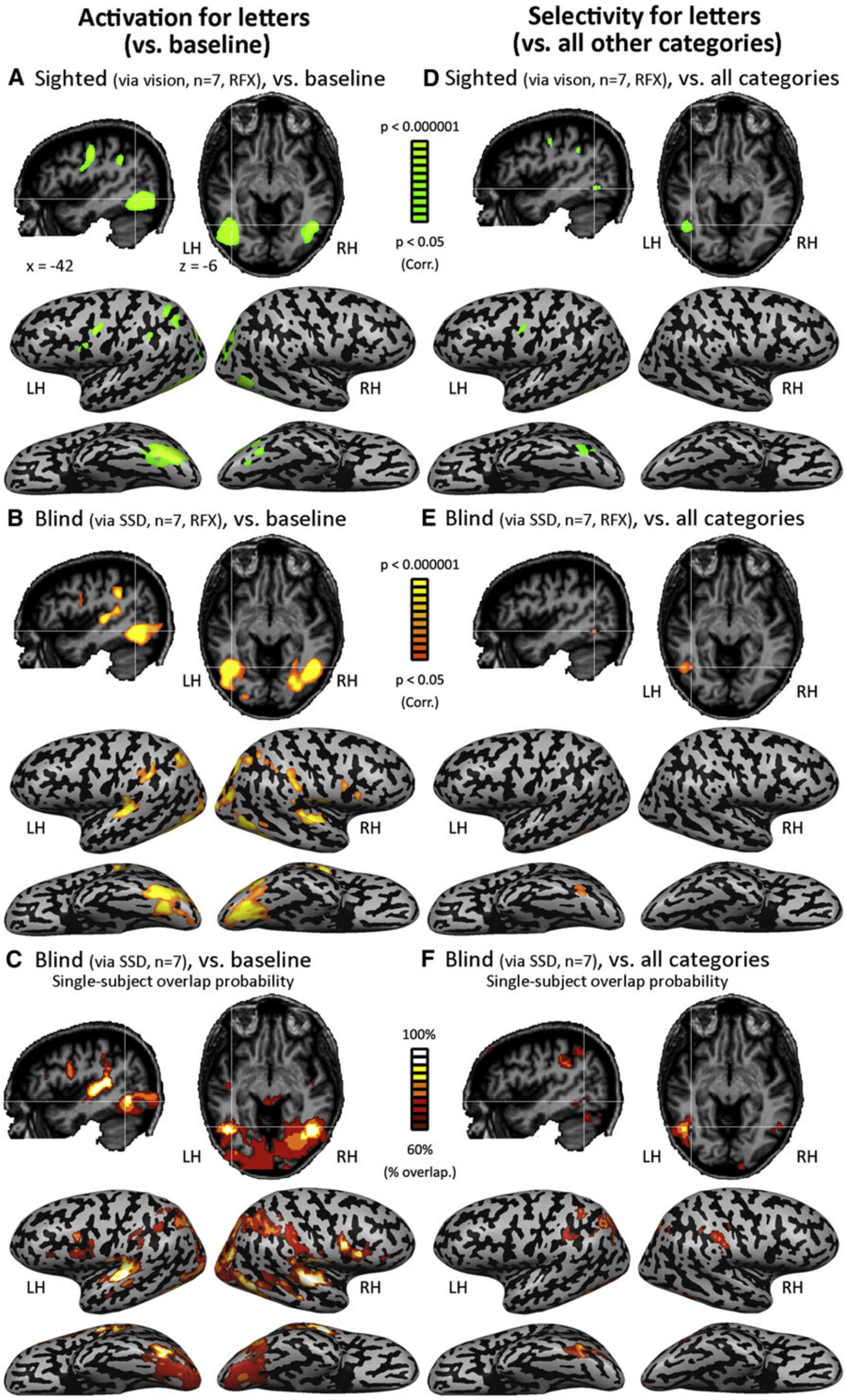

Figure 2. Comparable Selectivity in the VWFA of the Blind and Sighted

(A and B) Activation for letters versus baseline is shown in comparable experiments in the sighted controls (A; using vision) and in the congenitally blind (B; using SSD soundscapes), showing extensive bilateral ventral visual cortex activation, including at the location of the canonical peak of the VWFA in the sighted, which is marked by cross-hairs on the slice views.

(C) The reproducibility of the VWFA activation for letters in the blind is emphasized by the probability map showing overlap of activation for this contrast across the blind subjects.

(D–F) Letter selectivity (versus all other categories grouped together) in both groups (D and E), for sighted and blind groups, respectively, and across all (100%) single subjects in the blind (F) is focused to comparable locations in the approximate location of the VWFA (marked by cross-hairs).

function through the case of the VWFA. (1) Can VWFA feature tolerance be generalized to a new sensory transformation (“soundscapes”), thus expressing full independence from input modality? (2) Can the VWFA show category selectivity for letters as compared to other categories such as faces, houses, or objects, without any prior visual experience, suggesting a preference for a category and task (reading) rather than for a sensory (visual) modality? (3) Can the VWFA be recruited for a novel reading modality and script learned for the first time in the fully developed adult brain (adult brain plasticity)?

RESULTS

To test whether the VWFA could be activated by auditory SSD-based letters, we examined the activation induced by letters conveyed by sounds using a sensory substitution algorithm in a group of congenitally blind people (see details in Table S1 available online). Subjects had been trained to identify letters and other visual stimuli successfully using the vOICe SSD (see Figure 1F; see details of the training protocol in the Supplemental Experimental Procedures). We also conducted a visual version of this experiment in a group of normally sighted subjects, using the same visual stimuli and experimental design. We compared the SSD results in the blind to those obtained in the sighted in the visual modality, both at the whole-brain level and using the sighted data to define a VWFA region of interest (ROI). Similar to the activation in the sighted for letters relative to the baseline condition (see Figure 2A), the congenitally blind group showed bilateral extensive activation of the occipito-temporal cortex for SSD letters (see Figure 2B, as seen previously in blind adults reading Braille; Burton et al., 2002; Reich et al., 2011). We also found robust auditory cortex activation (including A1/Heschl’s gyrus) in the blind for this contrast, given the auditory nature of the stimuli. As the VWFA is characterized not only by activation to letters but mostly by its selectivity for letters and words, we compared the VWFA activation elicited by letters to that generated by other visual object categories. In the sighted group, as reported elsewhere (Dehaene and Cohen, 2011), selectivity toward letters as compared to all other categories was highly localized to the left ventral occipito-temporal cortex, at a location consistent with the VWFA (Figure 2D). The peak of letter selectivity of the sighted (Talairach coordinates −45, −58, −5) was only at a distance of 3.3 mm (~1 functional voxel) from the canonical VWFA coordinates (−42, −57, −6; Cohen et al., 2000; see cross-hairs marking this location in the slice views in Figure 2), well within the small spatial variability reported for the VWFA (SD of ~5 mm; Cohen et al., 2000). Importantly, a similar pattern of letter selectivity was observed in the blind group, which showed a left-lateralized selective focus in the occipito-temporal cortex (Figure 2E) greatly overlapping that of the sighted and encompassing the canonical location of the VWFA (see cross-hairs marking this location; note that this contrast shows no activation in the auditory cortex, which was equally activated by all categories).

In order to assess the intersubject consistency of this finding in the blind group, we computed these contrasts (letters versus baseline and letters versus all categories) in each of the single subjects and plotted the cross-subject overlap probability maps for each contrast. All the subjects (overlap probability of 100%) showed not only activation of the VWFA location for vOICe SSD letters (Figure 2C), but also selectivity for letters in this area (Figure 2F). Thus, the high anatomical consistency across subjects reported in the VWFA of the sighted (Cohen et al., 2000) can be extended to reading without visual experience using a novel sense learned in adulthood.

We next directly compared the activation generated by soundscape letters with those of each one of the other visual categories separately across the entire brain. All contrasts identified significant left ventral visual stream activations, whose intersection was restricted to the left ventral occipito-temporal cortex (peaking at Talairach coordinates −51, −58, −9; see Figure 3A) in a location close to the sighted canonical VWFA (extending also laterally, to the lateral inferotemporal multimodal area; Cohen et al., 2004). This area was the only one across the entire brain to show full overlap of selectivity for letters versus each of the other visual categories at the group level (for a list of other areas showing weaker selectivity overlap, see Table S2). These results show that the left ventral occipito-temporal cortex, alone across the entire brain, develops full functional specialization for letters over all other tested categories, despite an exclusively auditory input and the lack of visual experience, suggesting that there is a full sensory modality tolerance.

In order to verify our results in another independent manner, we also conducted an ROI analysis of the selectivity for letters of the blind in the canonical VWFA as identified in the sighted literature (Cohen et al., 2000; Talairach coordinates −42, −57, −6). The standard left-hemispheric VWFA showed highly significant activation for SSD letters in the blind as compared not only to the vOICe SSD transformation of visual textures, i.e., simple low-level visual stimuli ($p < 0.000001$, $t = 6.1$; Figure 3B), but also to each of the (visually) more complex categories separately ($t > 4.4$, $p < 0.0005$ for letters versus faces, objects, body, or textures; $t = 3$, $p < 0.005$ for letters versus houses, corrected for multiple comparisons, see Figure 3B). An analysis of the blind group data within the selectivity peak of the sighted (used as an external localizer) showed similar results (Figure S1A; $t > 3.8$, $p < 0.0005$ for all the contrasts). None of the other (nonletter) categories showed selectivity in the VWFA defined by either the canonical peak or the external sighted ROI, even at a more permissive contrast, in comparison with all the other categories grouped together ($t < 1.7$, $p > 0.09$).

Theoretically, the activation of the VWFA of the blind for vOICe SSD letters could arise either in a bottom-up manner or from top-down modulation by higher-order language areas involved in reading (Price, 2012). However, besides the contrast relative to the baseline condition (in which we found both temporal, parietal, and frontal cortex activation, see Figure 2B) no selective activation for letters was observed in the frontal cortex or in the left anterior temporal language areas (e.g., auditory word form area; DeWitt and Rauschecker, 2012) of the blind in any of the other tested contrasts: letters versus all other categories, letters versus each specific category contrast, or the probability map (see Figures 2E and Figures 3A). Although this is a null finding, and therefore must be taken with caution, it tentatively suggests that the selective activation of the VWFA was not driven by top-down modulation due to higher-order language processing (see also the semantic control condition in the next control experiment).

Although no subject reported such an experience, conceivably, some of the activation of the VWFA for letters (although likely not its selectivity, see above) might arise from imagining Braille letters (as Braille reading activates the VWFA more than a sensorimotor control; Reich et al., 2011), due to linking the two types of different-shaped letters during learning to read with sounds. To test this hypothesis as well as to control for the pure semantic content of referring to the letter names (e.g., by covertly naming them), we conducted an additional experiment on perception and mental imagery of letters in the congenitally blind. We found that the canonical VWFA showed significantly more activation for the perception of vOICe SSD letters than for hearing the same letter names (which controls for semantic content without assigning letter shapes; Figure 3C; $t = 12.3$, $p < 0.000001$). Moreover, vOICe letter perception generated significantly higher activation relative to imagining the letters in Braille script (see Figure 3C; $t = 7.7$, $p < 0.000001$) and also relative to vOICe script mental imagery ($t = 7.9$, $p < 0.000001$). Similar results were found in the VWFA as defined from the external localizer in the sighted ($t > 4.5$ $p < 0.00001$ for all comparison with the control conditions). These results rule out the possibility that the robust VWFA activation in response to SSD letters was solely due to top-down imagery processes.

Interestingly, although Braille imagery activated the VWFA significantly less than vOICe SSD letters, it did generate widespread activations as compared to passively hearing the letter names (which controls for both auditory stimulation and semantic content; see Figure S1B). One area of activation is of particular interest given theories on mental imagery originally framed in the context of vision (Kosslyn et al., 1999): we found robust activation to Braille imagery as compared to the semantic control in the hand area of S1 (Figure S1C; $t = 6.5$, $p < 0.000001$). This mental imagery reactivation was specific to the relevant

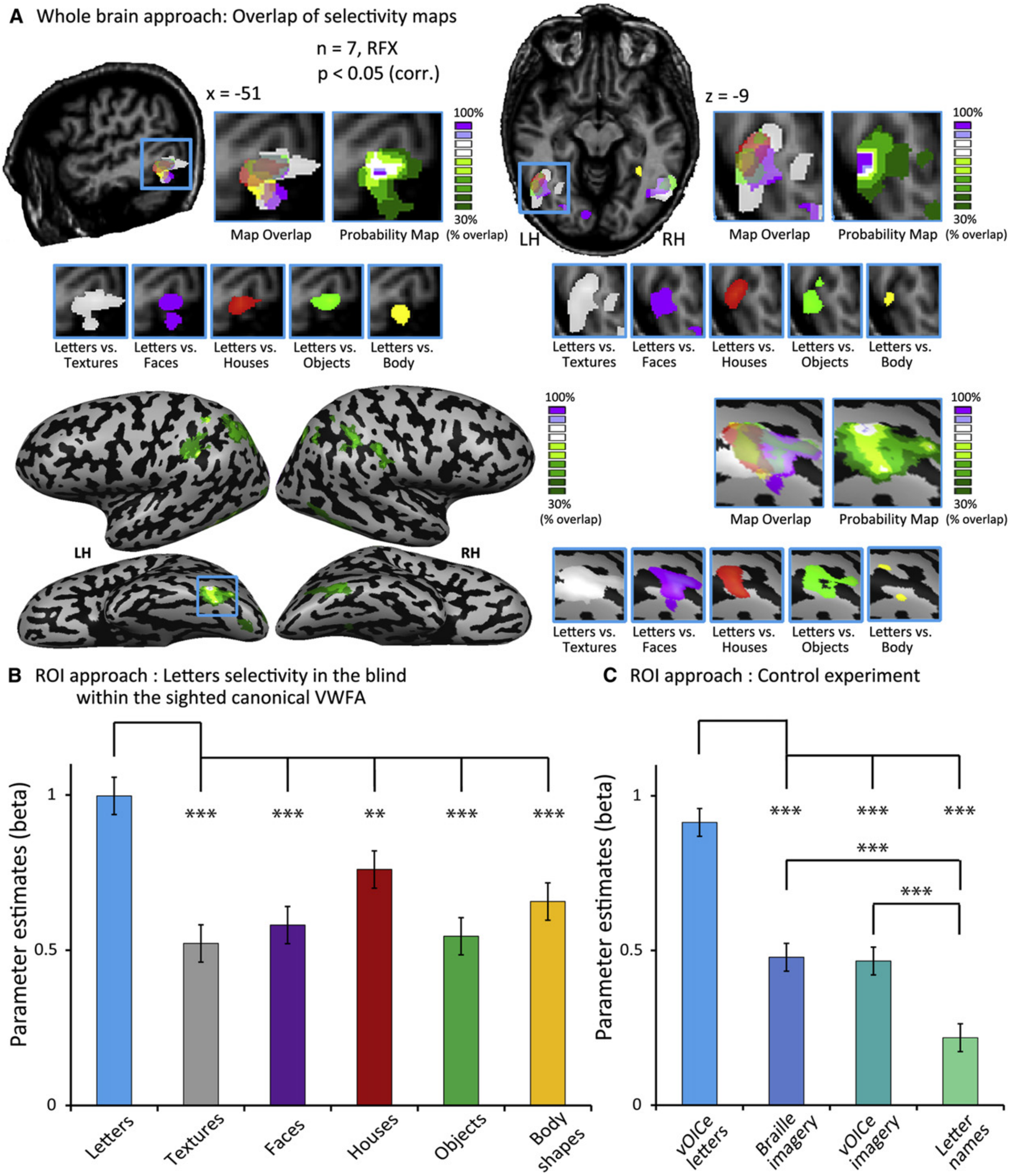

Figure 3. Selectivity to Soundscape Letters in the VWFA of the Blind

(A) The robust letter selectivity is unique to the left ventral occipito-temporal cortex across the entire brain: the left vOT is the only region showing full selectivity for letters over all other categories in a location close to the sighted VWFA (Talairach coordinates −51, −58, −9). Each map is a random-effect GLM contrast between letters and one of the other visual categories at $p < 0.05$, corrected for multiple comparisons. Also shown (see inflated cortical surface and magnification of slice views) is the probability map of the overlap between these contrast maps, which peaks in the vicinity of the sighted VWFA.

(B) Parameter estimate values (GLM-beta) sampled from the canonical peak of the VWFA in the sighted (used as an independent region of interest) show remarkable selectivity for soundscape letters in the blind as compared to multiple other categories of "visual objects" translated by the visual-to-auditory sensory substitution device. Error bars denote SE. *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$ (corrected for multiple comparisons).

(C) The canonical sighted VWFA is significantly more activated by vOICe letter perception than by imagining the same letters in Braille or vOICe scripts, or hearing the letter names, suggesting bottom-up rather than top-down activation.

part of the somatosensory homunculus, as we found no such effect in the S1 foot area ($p < 0.36$). Moreover, we also found Braille imagery activation in the left vOT (Figure S1B; $t = 4.6$, $p < 0.000005$; see also Figure 3C, showing a similar effect for vOICe imagery). Thus, our results demonstrate that imagery in the blind generates a pattern of activation similar to that seen when comparing visual perception and visual mental imagery in the sighted. Ventral visual cortex activation for imagery in the blind, as in the sighted, (1) is specific to the stimulus-selective cortical location (O'Craven and Kanwisher, 2000), in our case in the VWFA, and (2) is significantly less intense than bottom-up perception of the same stimuli (Amedi et al., 2005; O'Craven and Kanwisher, 2000). Moreover, as in sighted subjects, imagery in the blind can generate activation in the primary sensory cortex related to the stimulus modality and location—in our case in the hand area of S1 (Kosslyn et al., 1999).

Finally, we investigated a rather unique case of a single congenitally blind subject, T.B., who was highly literate in Braille but was completely unfamiliar with the shapes of the sighted alphabet in her native language (Hebrew). This allowed us to test whether the VWFA could be recruited for reading using an SSD (i.e., in a novel modality) in a new script in the adult brain after a brief 2 hr training period (e.g., without enabling long-term plasticity). We taught T.B. to identify complex geometric shapes by using the vOICe SSD (see details in the Supplemental Experimental Procedures) but refrained from teaching her the shapes of letters. We then scanned subject T.B. twice in a single day, before and after a single 2 hr session of learning to read several letters of the regular alphabet using vOICe. We compared the activation for reading in the tactile and auditory modalities with modality-matched nonreading controls to look for reading-selective activations both in an ROI located at the VWFA and across the entire brain. Braille reading (BR; contrasted with its modality-matched control, Braille control, BC, homogenous Braille dots) activated a left-vOT/VWFA peak identically in both scanning sessions (Figure 4A). Reading the same letters using the vOICe SSD (vOICe reading, VR) was contrasted with its modality-matched control, vOICe control (VC), soundscape representations of letters that were not learned during the training session and were not recognized as letters by T.B. Immediately after training, this contrast activated the left ventral occipito-temporal cortex extensively (including the left VWFA; Figure 4A). The extension of these activations beyond the VWFA to a broader ventral network is consistent with studies in vision showing higher or more extensive ventral visual activation in sighted adults reading relatively untrained scripts (artificial or foreign scripts; Bitan et al., 2005; Hashimoto and Sakai, 2004; Xue et al., 2006; Xue and Poldrack, 2007), in exilliterate adults (Dehaene et al., 2010), in effortful reading (e.g., reading a degraded text; Cohen et al., 2008), and in children when initially learning to read (Brem et al., 2010). The same contrast (VR versus VC) caused no activation prior to training, when the shapes of the letters were perceivable but not yet associated to phonology. Importantly, the increased activation of the left vOT/VWFA after training for the vOICe reading condition did not result solely from a repetition of the same stimuli a second time, as there was no similar effect of session in the VC condition in which other vOICe representations of letters were heard twice without being taught between the scans (see Figures S2A and S2B; see also the lack of session effect in VC in the VWFA ROI in Figure 4B below). Therefore, the recruitment of the VWFA in subject T.B. in the case of the vOICe reading condition resulted from learning to identify the letters and linking their shapes to their phonological representations.

To statistically assess the effect of training on selectivity for reading, we identified the vOT activation for tactile reading (BR versus BC) in T.B.'s first scan (Talairach coordinates -37, -60, -15) and used it as a within-subject VWFA localizer. This reading-selective ROI also showed selectivity for Braille in the second scan (Figure 4B; $p < 0.00001$, $t = 6.29$), confirming the accuracy and consistency of the localizer. Critically, T.B.'s VWFA showed a specific increase in activation after training only in the vOICe reading condition (Figure 4B; $p < 0.00001$, $t = 4.39$ for VR; $p < 0.50$, $p < 0.36$, and $p < 0.20$ for BR, BC, and VC, respectively). Moreover, this ROI was activated for vOICe reading more than for its modality-matched control (which represented untrained vOICe letters) only after the training session (Figure 4B; $p < 0.00001$, $t = 5.35$). In brief, this analysis also supported the flexible recruitment of the VWFA for reading in a novel modality and script, after only brief training.

DISCUSSION

By studying congenitally blind individuals reading through visual-to-auditory sensory substitution (Figure 1), we demonstrate that the ventral visual cortex contains a region that is selective to letters over all other tested stimuli, including the SSD transforms of both low-level textures and visually complex objects, regardless of sensory modality, visual experience, long-term familiarity, or expertise with the script (Figures 2, 3, and 4). This suggests a strong feature tolerance in this area, which generalizes even beyond sensory input modality and early sensory experience, while maintaining the relative category selectivity implied by the term "visual word form area." Moreover, this area shows remarkable adult plasticity, such that it can be recruited in an adult blind individual reading in a novel sensory modality after as little as 2 hr of training (Figure 4). After ~70 hr of training in a group of subjects, this area already displayed full category selectivity (Figure 2).

These findings impact several of the major issues regarding the function and developmental origin of the VWFA, as well as the balance between plasticity and conserved cortical functions resulting from sensory deprivation. Specifically, they suggest that the VWFA performs a highly flexible task-specific reading-related operation that can be sensory modality independent (Reich et al., 2012). We suggest that this operation is the learned link between letter shapes and their associated phonological content. This category and task selectivity is maintained in the congenital absence of vision, despite otherwise extreme plasticity for other functions and input types shown previously in the blind brain (see reviews in Frasnelli et al., 2011; Merabet and Pascual-Leone, 2010; Striem-Amit et al., 2011). This implies the presence of innately determined constraints (Striem-Amit et al., 2012a) on the emergence of VWFA selectivity for reading. Furthermore, in the context of visual rehabilitation, this study also shows that the recognition of many complex visual stimulus

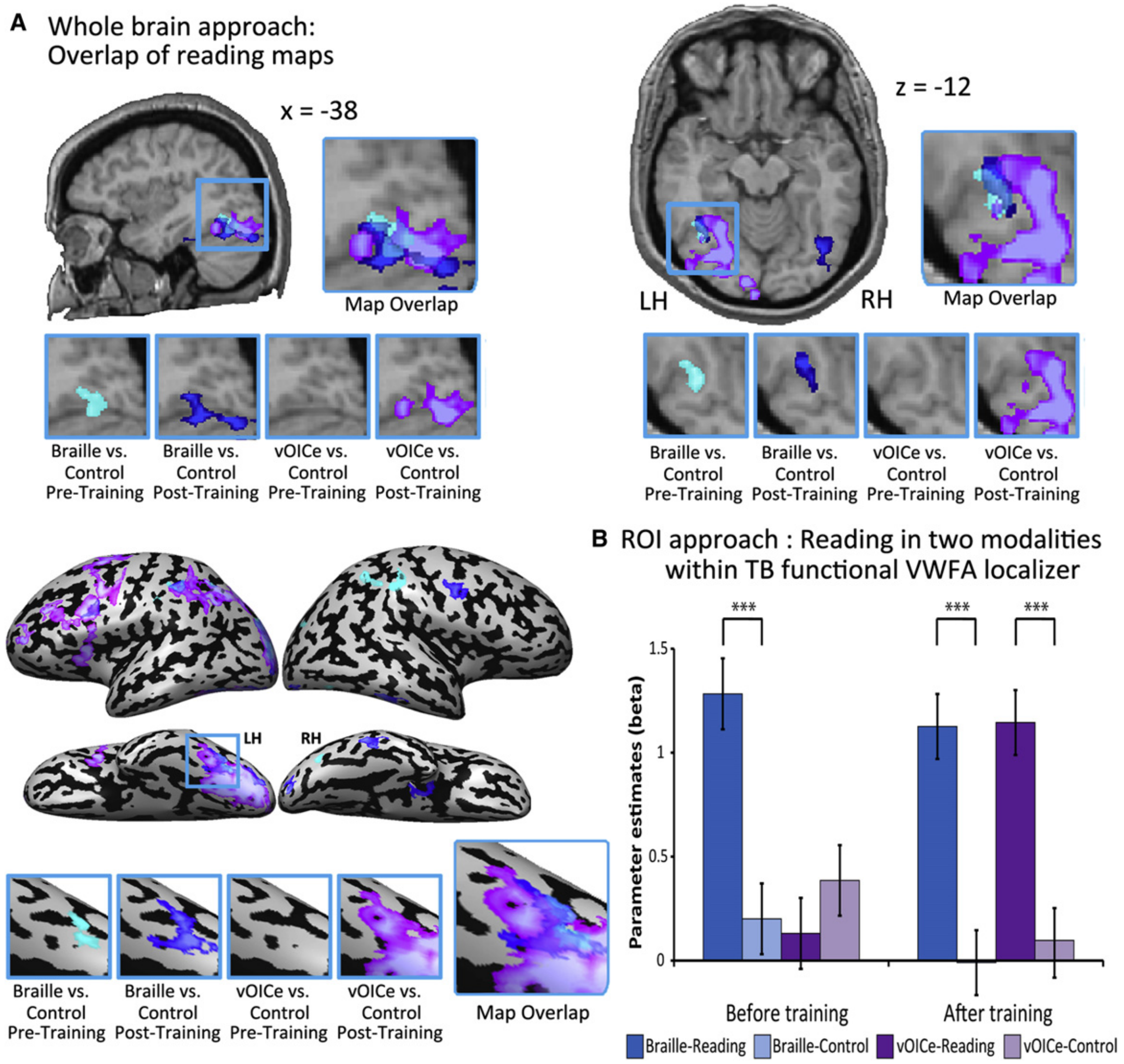

Figure 4. Rapid Adult Plasticity in the VWFA in a Single Case Study of Learning to Read Using Sounds

(A) Activation of the ventral visual cortex, particularly in the vOT/VWFA, is evident in subject T.B. for Braille reading (contrasted with a same-modality control, Braille control; homogenous Braille dots) in both scans (cyan and blue for pre- and posttraining contrasts) and in the vOICe reading condition (contrasted with a same-modality control, vOICe control; untrained soundscape representations of letters) only after a 2 hr session in which she learned to read the sighted script using soundscapes (marked in purple).

(B) ROI analysis of the selectivity cluster for Braille reading (versus Braille control) in the ventral stream (aka functional VWFA) in the first scan shows that this area is also selective for reading using sensory substitution but only after training in extracting the phonological values of the vOICe letters. Error bars denote SE. *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$.

categories can be learned using SSDs, including detailed images of faces and houses (see Movies S1 and S2). We describe how such training was implemented on computer and in natural three-dimensional (3D) environments, details of which may be of interest to those specializing in visual rehabilitation (see Supplemental Experimental Procedures). In the next sections, we address all these topics in more depth.

“Visual” Category Selectivity for Reading in the Absence of Visual Experience

In the visual modality, the VWFA has proved to be selective for letters over other complex visual stimuli such as drawings of objects, faces, and houses (Cohen and Dehaene, 2004; Dehaene and Cohen, 2011; Dehaene et al., 2010; Hasson et al., 2002; Puce et al., 1996; Szwed et al., 2011; Tsapkini and Rapp, 2010), thus justifying its “visual word form area” label. Note that the VWFA, like other specialized ventral areas (Kanwisher, 2010), is also partially responsive to stimuli from nonpreferred categories and that its preference for alphabetic stimuli may be missed under some experimental conditions (reviewed in Price, 2012; Price and Devlin, 2011). The results of our sighted control group (Figure 2D) clearly replicate the VWFA letter-string selectivity, in accordance with the major body of previous works.

Several studies have shown recruitment of the visual cortex of the blind for various tasks that mimic the visual tasks of the same regions in the sighted (e.g., Striem-Amit et al., 2012a; see review in Reich et al., 2012). This includes recruitment of the VWFA by tactile stimuli during a reading task (Reich et al., 2011). However, few studies have shown selectivity to one task over another and fewer yet have investigated the existence in the blind of a critical feature of the ventral visual cortex, namely, its regional selectivity for perceptual categories (see Pietrini et al., 2004; Mahon et al., 2009, who explored large-scale preference patterns). The current study now shows same category selectivity for a specific visual category (letters), as seen in the sighted, in the absence of visual experience. This finding was replicated across several independent analyses. We show letter selectivity over all other SSD categories both at the group level (Figures 2E and Figures 3) and across all congenitally blind subjects (Figure 2F). Moreover, this finding is so robust that even when compared to each category separately, selectivity for letters exists only in the left vOT (Figure 3). This result was further confirmed in an independent ROI analysis both when testing in the literature-based location of the VWFA in the sighted (Figure 3B) and when using the visual localizer scan, which we conducted using identical stimuli and design in the sighted controls (Figure S1A). Furthermore, we showed that mental imagery is not the driving force behind this activation (Figure 3C), a confound that is rarely controlled for in studies of sensory substitution and may contribute to at least some of the activation to SSD stimuli reported in the visual cortex of the blind. Therefore, our results clearly show that there is spatial specificity (limited to the VWFA) and high selectivity (relative to many types of visual images) for a "visual" category in the congenitally blind.

Sensory Modality Invariance in the VWFA

The activation of the VWFA has been shown to be invariant to changes in a variety of visual dimensions, including uppercase/lowercase (Dehaene et al., 2001), printed/handwriting style (Qiao et al., 2010), location in the visual field (Cohen et al., 2002; but also see Rauschecker et al., 2012, who recently challenged this to some extent), or type of shape-defining visual feature (Rauschecker et al., 2011). A key finding in the present study is that this feature tolerance extends beyond the visual domain, even as far as to an atypical reading sensory modality, audition (Figures 2 and 3).

The VWFA was repeatedly shown not to be typically activated in a bottom-up fashion by auditory words (e.g., spoken language; Cohen et al., 2004; Dehaene et al., 2002; Tsapkini and Rapp, 2010), giving rise to the hypothesis that its function is limited to vision (Cohen et al., 2004; see also Figure 3C replicating this result in the blind). Although our previous study (Reich et al., 2011) showed recruitment of the VWFA for touch, the inability to activate the VWFA using auditory words suggested that the VWFA was still sensitive to the modality of input. However, auditory words differ from visually written words not only in their input sensory modality, but also in the type of information that they convey. In written words, information is encoded as geometric shapes featuring line junctions, angles, etc., which are commonly actualized as contours in the visual space (or geometric haptic patterns in Braille; Reich et al., 2011). As we show here using the vOICe SSD, the geometric shapes of letters may also be translated into the auditory time-frequency space, and once such auditory input conveys geometric letter shapes, the VWFA may be recruited. Therefore, using SSD allowed us to tease apart the effects of stimulus type and input modality. Supporting this dissociation, we found no activation for SSD letters in the auditory parallel of the VWFA, the auditory word form area in the left anterior STG (DeWitt and Rauschecker, 2012; see Figures 2E, 2F, and 3; but functional connectivity between these two areas was found, see below), although vOICe letters are conveyed through audition. Furthermore, our results cannot be readily explained as a top-down modulation of the VWFA (which is occasionally seen in the VWFA for spoken language; Cohen et al., 2004; Dehaene et al., 2010; Yoncheva et al., 2010). Neither frontal nor temporal higher-order language areas showed selective activation for letters versus the other categories tested here (see Figures 2E and Figures 3A). Furthermore, activation of the VWFA in a top-down manner due to mental imagery or the semantic content of identifying the stimuli as letters and covertly naming them was also tested (Figure 3C). This hypothesis was refuted as a main source of activation, as vOICe letter perception generated significantly stronger activation than imagining letters or hearing their names.

Note that although our SSD transformation conserves the shape of the letters, it is unlikely that any specific low-level sensory shape processing mimicking vision drives the activation or selectivity observed in our results, since the physical dimensions on which it is based differ greatly from those characterizing both visual and tactile letters (Kubovy and Van Valkenburg, 2001). Specifically, visual features that have been proposed to drive the VWFA selectivity for letters, such as high-frequency vision (Woodhead et al., 2011) and foveal position (Hasson et al., 2002), are conveyed by completely different auditory cues in the vOICe SSD (fast auditory temporal processing and early/later temporal distinction). Therefore, at least in the blind, the tuning of the VWFA to reading may not depend on any vision-specific features. Instead, we suggest that the VWFA is selective to the type of information or computation rather than to the input sensory modality.

Development of a Task-Specific Operator in the VWFA and Adult Brain Plasticity

In addition to letter-stimulus selectivity and invariance to sensory modality, another key aspect of the current study is that the VWFA showed such selectivity although this mapping of symbol shapes into the soundscapes (i.e., audition) was learned in adulthood and was taught and trained for a very short duration. We have shown previously that the VWFA can be attuned to reading in a nonvisual modality in individuals who learned Braille from around the age of 6 (Reich et al., 2011). Nevertheless, such adaptation to an unusual modality might have been limited only to the one sense that is used to acquire reading in childhood. One major finding of the present study is that the recruitment of the VWFA for reading may take a surprisingly short time even in the adult brain for a new sensory modality. We show selectivity for letters after no more than 10 hr of reading training (of a total SSD training duration of ~70 hr) in a novel modality and in relatively unfamiliar script (Figures 2 and 3). In subject T.B., who learned to read Braille at the age of 6 but learned the shape of the sighted Hebrew letters only via the SSD in adulthood, SSD reading training was actually limited to as little as 2 hr and was still sufficient to activate the VWFA by a novel script and in a novel sensory modality (Figure 4). This rapid functional plasticity is likely to initially be accomplished by flexible, short-term modulation of existing pathways (Pascual-Leone et al., 2005), potentially aided by top-down modulation or imagery. Such changes may possibly later manifest in more stable, longer-term structural changes. Future studies of the anatomical basis for such plasticity in the blind would help clarify this issue. This result does not in any way contradict the evidence that the VWFA's selectivity for letters increases over months and years as a result of schooling and reading practice (Ben-Shachar et al., 2011; Brem et al., 2010; Dehaene et al., 2010; Schlaggar and McCandliss, 2007; Turkeltaub et al., 2003). In fact, in agreement with the present findings, Brem et al. (2010) also showed that preschoolers may develop a VWFA response for visual letters after less than 4 hr of training with a reading computer game. Furthermore, the blind subjects tested here were by no means illiterate but were already proficient Braille readers. Once the VWFA has specialized in converting signs to phonemes and words during the early acquisition of literacy (Brem et al., 2010), the brain may be relatively quickly reconfigured to map a novel set of symbols to the same set of phonemes, similar to learning a novel script via vision in a literate person (Hashimoto and Sakai, 2004; Maurer et al., 2010; Xue et al., 2006). Bayesian learning principles (Ernst and Bulthoff, 2004; Tenenbaum et al., 2011) enable the extraction of abstract schemas behind superficially different inputs, including sensory modalities. By learning to extract the abstract interpretation of a sound input as a two-dimensional (2D) shape using the vOICe algorithm, our participants were able to apply the same type of amodal (or metamodal; Pascual-Leone and Hamilton, 2001) shape processing even with newly learned artificial sensory inputs. Therefore, our results suggest that the processing of letters in the VWFA is highly flexible with regard to sensory modality, even in the adult brain.

How can such a modality-invariant functional selectivity for mapping topographical shapes onto phonemes and spoken language develop in the congenitally blind? A critical component of the development of such circuitry is probably reciprocal anatomical and functional connectivity with higher-order cortical regions involved in the processing of language (Ben-Shachar et al., 2007; Mahon and Caramazza, 2011; Pinel and Dehaene, 2010). In order to examine the underlying functional connectivity in the blind, we investigated the intrinsic (rest state; Biswal et al., 1995) functional connectivity in the blind from a small seed region focused on the canonical VWFA (for details see Supplemental Experimental Procedures). We found that the VWFA of the blind showed highly significant functional connectivity to a location consistent with the auditory word form area in the left anterior STG (DeWitt and Rauschecker, 2012; Talairach coordinates −56, −16, −2; statistics from this ROI; $t = 11.2$, $p < 0.000001$; see Figure S3), as well as to more posterior areas in the auditory ventral stream (Rauschecker and Scott, 2009), which may correspond to the phoneme-processing network (DeWitt and Rauschecker, 2012). The VWFA of the blind also showed functional connectivity to the left inferior frontal cortex (peaking at the inferior frontal sulcus; Talairach coordinates −43, −2, 18; $t = 10.7$, $p < 0.000001$). Such functional connectivity (which probably follows anatomical, albeit not necessarily monosynaptic, connectivity; Vincent et al., 2007) may be speculated to affect cortical organization during development even in the absence of bottom-up visual information, perhaps in conjunction with somatosensory shape input, which is processed in the nearby general shape multisensory operator in the LOC (which also shows functional connectivity to the blind's VWFA in our data; $t = 40.8$, $p < 0.000001$), jointly driving the organization of the left vOT to processing grapheme shapes. These results do not, however, exclude that visual features may be relevant to the emergence of the VWFA in sighted subjects (Hasson et al., 2002; Szwed et al., 2011; Woodhead et al., 2011). Bottom-up and top-down factors may together mold the developing cortex.

Category Specialization in the Blind and Relevance to Visual Rehabilitation and Critical Periods

It is especially noteworthy that by providing adequate training, the VWFA shows its usual category selectivity in the congenitally blind, despite the vast reorganization that the visual cortex undergoes after visual deprivation. The scope of this reorganization is such that the visual cortex of the blind "switches tasks" and processes nonvisual functions that differ considerably from those typical of the sighted brain, such as memory and language in the primary visual cortex (Amedi et al., 2003; Bedny et al., 2011; see reviews in Frasnelli et al., 2011; Merabet and Pascual-Leone, 2010; Striem-Amit et al., 2011). Here we show that when relevant stimuli and tasks are introduced, the ventral visual cortex displays its normal category-specific function, even with stimulation from an unusual sensory modality. Our finding of preserved functional category selectivity for letters in the VWFA is in line with previous results showing preserved task selectivity in the blind (Reich et al., 2012) for general shape recognition in the LOC, for motion detection in area MT, for location identification in the MOG, and even for the general segregation between the ventral and dorsal visual processing streams (Striem-Amit et al., 2012a; for relevant findings in deafness, see Lomber et al., 2010). This suggests that at least some regions may, despite their bottom-up deafferentation, be sufficiently driven by other innately determined constraints (Mahon and Caramazza, 2011) to develop typical functional selectivity. It remains to be tested whether such task-selective and sensory-modality independence (Reich et al., 2012) characterizes the entire cortex or if it is limited to only a subset of higher-order associative areas.

The present results may have clinical relevance for the rehabilitation of the visually impaired and have theoretical implications as regards the concept of critical/sensitive periods. Until recently, it was thought that the visual cortex of congenitally and early blind individuals would not be able to properly process vision if visual input were restored medically in adulthood. This claim was supported by early studies of a critical period for developing normal sight in animals (Wiesel and Hubel, 1963) and humans (Lewis and Maurer, 2005). It was also supported by the poor functional outcomes observed after rare cases of sight restoration in humans, especially in ventral stream tasks

(Ackroyd et al., 1974; Fine et al., 2003; Ostrovsky et al., 2009). In the congenitally blind, this may be especially true due to the aforementioned task switching (e.g., for language and memory) that may possibly disturb the visual cortex's original functions and interfere with attempts to restore vision (Striem-Amit et al., 2011). Therefore, even if visual information later becomes available to their brain (via devices such as retinal prostheses), it may be less efficient at analyzing and interpreting this information and may require more elaborate explicit training to develop fully functional vision. Some support for the effectiveness of adult training in overcoming developmental visual impairments comes from recent studies of amblyopia, in which deficits were considered permanent unless treated by the age of 7. Recent studies show that combined treatment that includes visual training (along with patching of the nonamblyopic eye) can trigger adult plasticity and greatly improve the perceptual outcome, thus reopening the sensitive period for plasticity (Maurer and Hensch, 2012; see also Bavelier et al., 2010). We suggest that in cases of more profound blindness, such rehabilitation may involve, for example, learning to process complex images using SSDs, as done here, or using the SSD as a stand-alone sensory aid. Alternatively, SSDs may be used as ''sensory interpreters'' that provide high-resolution (Striem-Amit et al., 2012b) supportive synchronous input to the visual signal arriving from an external invasive device (Reich et al., 2012; Striem-Amit et al., 2011). It is yet unclear whether crossmodal plasticity in SSD use, albeit task and category selective, will aid in reversing the functional reconfiguration of the visual cortex or will in fact interfere with visual recovery. Furthermore, fMRI does not allow for causal inference and thus cannot attest to the functional role of the selectivity in VWFA for reading task performance, which will be further examined in the future. Nevertheless, our results show that the visual cortex has, or at least can develop, functional specialization after SSD training in congenital blindness (and probably more so in late-onset blindness). This can be achieved even for atypical crossmodal information (visual-to-auditory transformation) learned in adulthood, making it conceivable to restore visual input and to ''awaken'' the visual cortex also to vision.

EXPERIMENTAL PROCEDURES

Participants

The study included eight congenitally blind participants and seven sighted controls. The main study group was composed of seven fully congenitally blind native Hebrew speakers. An eighth participant (fully congenitally blind), T.B., only participated in the specially tailored case study described below. All the blind participants learned to read Braille around the age of 6 (average age 5.8 ± 1.5 years). For a full description of all blind participants, causes of blindness, etc., see Table S1 and Supplemental Experimental Procedures. The external visual localizer was conducted on a group of seven normally sighted healthy control subjects (no age difference between the groups; $p < 0.89$). The Tel-Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject.

Visual-to-Auditory Sensory Substitution

We used a visual-to-auditory SSD called ''The vOICe'' (Meijer, 1992), which enables ''seeing with sound'' for highly trained users with relatively high resolution (Striem-Amit et al., 2012b). In a clinical or everyday setting, users wear a miniature video camera connected to a computer/smartphone and stereo earphones; the images are converted into ''soundscapes'' using a predictable algorithm (see Figure 1B for details), allowing the users to listen to and interpret the high-resolution visual information coming from a digital video camera (Figures 1A–1C).

Training Procedure and Performance

The blind participants in this study were enrolled in a novel training program in which they were taught how to effectively extract and interpret high-resolution visual information from the complex soundscapes generated by the vOICe SSD. The average training duration of participants here was 73 hr, with up to 10 hr devoted to learning to read using the SSD. As part of the training program, the participants were taught (using verbal explanations and palpable images; see Figure 1D and Supplemental Experimental Procedures) how to process 2D still (static) images, including hundreds of images of seven structured categories: geometric shapes, Hebrew letters and digital numbers, body postures, everyday objects, textures (sometimes with geometric shapes placed over visual texture, used to teach object-background segregation), faces, and houses (see Figure 1E; see Movie S1 for a demo of the visual stimuli and their soundscape representations). For full details on the training technique and protocol, see the Supplemental Experimental Procedures. After the structured training, participants could tell upon hearing a soundscape which category it represented. This required Gestalt object perception and generalization of the category principles and shape perception to novel stimuli. They could also determine multiple features of the stimulus, enabling them to differentiate between objects within categories. For an example, see Movie S2, depicting one congenitally blind participant reading a three-letter word and another participant recognizing emotional facial expressions. In order to assess the efficiency of training in terms of visual recognition, six of the participants in the training protocol underwent a psychophysical evaluation of their ability to identify different object categories. They were required to categorize 35 visual images (in pseudorandomized order) as belonging to the seven object categories. Each stimulus was displayed using headphones for four repetitions (totaling 8 s), followed by a verbal response. The average rate of object classification success in the blind was 78.1% (±8.8% SD), significantly better than chance (14%; see Figure 1F, t test $p < 0.00005$). Letter category recognition did not differ from that of the other object categories (all $p > 0.05$, corrected for multiple comparisons). In order to minimize sensory-motor artifacts, no recording of performance was conducted during the fMRI scan. Prior to each scan, we verified that the subjects were able to easily recognize learned stimuli from the tested categories (see more detail in Supplemental Experimental Procedures).

General Experiment Design

The main study included six experimental conditions presented in a block design paradigm. Each condition included ten novel soundscapes representing unfamiliar images from the trained object categories: letters, faces, houses, body shapes, everyday objects, and textures. Each condition was repeated five times, in a pseudorandom order. In each epoch, three different stimuli of the same category were displayed, each for 4 s (two repetitions of a 2 s stimulus). For instance, in each letter epoch, the subject was presented with a novel meaningless three-consonant letter string. The subjects were instructed to covertly classify and identify the displayed objects. We used letters instead of words as it diminished the semantic content of the letter condition as compared to the other categories, preventing VWFA preferential activation due to semantics (as the ventral stream of the blind is activated by semantics; Bedny et al., 2011). All epochs lasted 12 s and were followed by a 12 s rest interval. Digital auditory soundscapes were generated on a PC, played on a stereo system, and transferred binaurally to the subjects through a pneumatic device and silicone tubes into commercially available noise shielding headphones.

External Visual Localizer

In order to compare the letter category selectivity via vision versus via soundscapes and in order to localize the VWFA using an external localizer, we conducted a visual localizer experiment on a normally sighted group, using the same images and block design parameters (epoch and rest interval durations, number of condition repetitions) used in the main experiment. Twelve images from the same category were presented in each epoch; each image was presented for 800 ms and was followed by a 200 ms blank screen (similar to standard visual localizer experiments; e.g., Hasson et al., 2003). A central red fixation point was present throughout the experiment. The subjects were instructed to covertly classify and identify the displayed objects, as in the main experiment.

Imagery Control Experiment

We conducted a control experiment testing the role of top-down modulation on the VWFA of the blind in mental imagery, auditory word perception, and referring to the letter names. Four experimental conditions were presented in a block design paradigm identical to that of the main experiment except for the addition of a 1 s instruction at the beginning of each epoch (stating the task: e.g., "imagine Braille") and a 0.5 s stop instruction at its end (resulting in 13.5 s epochs). In the vOICe letter condition, the subjects heard vOICe letter strings in a manner identical to the letter condition in the main experiment. In the Braille imagery and vOICe imagery conditions, the subject heard letter names of the same letters presented in the vOICe letter condition, at the same rate of presentation of different letters in vOICe letters (i.e., three different letter names were presented, each for 0.5 s followed by 3.5 s imagery time) and were instructed to actively imagine the letters in Braille or in vOICe script. In an auditory- and semantic-content control condition, the subjects heard the same letter names but were instructed to remain passive. Six of the original seven congenitally blind subjects participated in the experiment.

Case Study of Learning to Read a New Script Using Sensory Substitution

A single case study was conducted on a unique congenitally blind individual, T.B. (age 35), who was highly literate in Braille reading (reading since the age of 6) but completely unfamiliar with the shapes of any other alphabet, specifically the regular "sighted" Hebrew alphabet. We applied a repeated-measures design comparing activations (using the same sensory stimuli) before and immediately after brief, less than 2 hr, training in learning to read five new script letters (Hebrew) through the SSD (see details of T.B.'s training in the Supplemental Experimental Procedures). Each fMRI session included four experimental conditions (each repeated five times in a pseudorandom order) in a block design paradigm. All epochs lasted 12 s and were followed by a 9 s rest interval. T.B. was requested to attempt to read the stimuli presented in all the conditions. In the Braille reading (BR) condition, T.B. read five- and six-letter-long letter strings using her dominant left hand. In the homogenous Braille (Braille control; BC) condition, she palpated strings of homogenous Braille dot matrices, which do not represent letters, controlling for the tactile and motor aspects of BR. In the vOICe reading condition (VR), she was presented with the same letter strings as in the BR, via soundscapes. In the vOICe control (VC) condition, soundscape representations of letters that were not learned during training were presented, composing letter strings of similar lengths.

Data Analysis and MRI Acquisition

The BOLD fMRI measurements were performed in a whole-body 3-T GE scanner. For full details on recording parameters and preprocessing steps, see Supplemental Experimental Procedures. Data analysis was performed using the Brain Voyager QX 2.2 software package (Brain Innovation) using standard preprocessing procedures, which included head-motion correction, slice scan-time correction, high-pass filtering, Talairach spatial normalization (Talairach and Tournoux, 1988), and spatial smoothing (with a three-dimensional 8 mm full-width at half-maximum Gaussian). Group analyses were conducted for the main experiment and visual localizer experiment using a general linear model (GLM) in a hierarchical random-effects analysis (Friston et al., 1999). For the imagery control experiment and the case study, the data were grouped using GLM in a fixed-effects analysis. All GLM contrasts between two conditions included comparison of the first term of the subtraction to baseline (rest times between the epochs), to verify that only positive BOLD changes would be included in the analysis. The minimum significance level of all results presented in the study was set to $p < 0.05$ corrected for multiple comparisons, using the spatial extent method based on the theory of Gaussian random fields (Forman et al., 1995; Friston et al., 1993). This method takes the data contiguity of neighboring voxels directly into account and corrects for the false-positive rate of continuous clusters (a set-level statistical inference correction). This was done based on the Monte Carlo stimulation approach, extended to 3D data sets using the threshold size plugin for BrainVoyager QX. Overlap probability maps across subjects (Figures 2C and 2F) were derived from single-subject activation contrast maps at a restrictive threshold of beta = 1 (similar to the group level activation in the VWFA). We also conducted a complementary ROI analysis. The ROI for the main experiment consisted of the literature peak voxel referred to as the sighted VWFA (Cohen et al., 2000; Talairach coordinates −42, −57, −6). Activation parameter estimates (beta, for each experimental condition) and t values were sampled from this ROI in a group-level random-effects analysis. Similarly, we sampled the blind group data from the peak of selectivity for letters (versus all other categories; Talairach coordinates −45, −58, −5) in the visual localizer control experiment. An additional, individual-level functional ROI was derived from the left vOT activation cluster for the Braille reading versus Braille control contrast (in conjunction with positive activation for Braille reading; Talairach −37, −60, −15) in T.B. in the first scan (hence, its selectivity for Braille reading in the second scan could independently verify its validity). Activation parameter estimates and t values were sampled from this ROI in both T.B. scans to assess the effect of learning on vOICe reading activation. In the ROI analyses, p values were corrected for multiple comparisons by dividing the alpha by the numbers of statistical comparisons made in that ROI, applying a strict Bonferroni correction.

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures, two tables, Supplemental Experimental Procedures, and two movies and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2012.08.026.

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Supplemental Information

Reading with Sounds:

Sensory Substitution Selectively Activates the Visual Word Form Area in the Blind

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Supplemental Figures

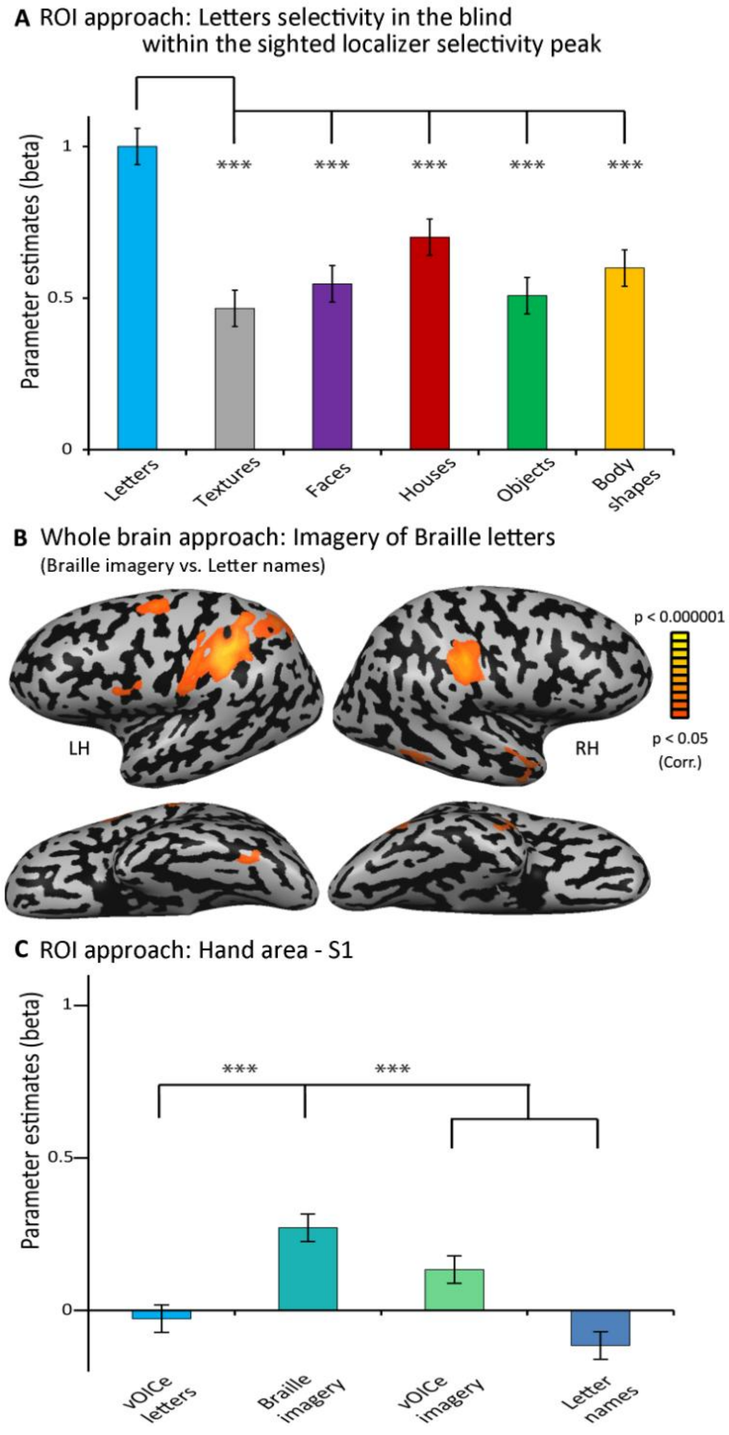

Figure S1, **related to Figure 3**

A. Parameter estimate values (GLM-beta) sampled in the blind group from the VWFA external visual localizer (peak of letters selectivity in the sighted group) show remarkable selectivity for letters in the blind as compared to all other visual categories translated by the visual-to-auditory sensory substitution device. * $p<0.05$, ** $p<0.005$, *** $p<0.0005$ (corrected for multiple comparisons). **B.** Braille imagery activated the left vOT as well as the inferior parietal and superior frontal lobe more than an auditory- and semantic-content- control (passively hearing the letter names). Activation can be seen in the bilateral somatosensory cortex, possibly in part since most blind people read Braille using both hands. **B.** Braille imagery additionally activated the hand area in the left primary somatosensory cortex, sampled from an external localizer (see **Supplementary Experimental Procedures** for details). No significant activation for Braille imagery was found in the S1 foot area (parameter estimate value = -0.04, t = -0.92, p < 0.36)

A vOICe Reading - Training Effect (post- vs. pre-training)

B vOICe Control - Training Effect (post- vs. pre-training)

Figure S2. The role of learning-to-read in activating the VWFA, related to Figure 4

The training effect (contrast between post-training and pre-training scans) is displayed for **A.** vOICe-reading (VR) and **B.** vOICe-control (VC; SSD representations of letters that were not trained between the scans) showing that the VWFA was more activated in the post-train scan only for letters trained between the scans, and was not merely driven by repetition of the same stimuli. Therefore, the recruitment of the VWFA in the case of the vOICe-reading condition resulted from learning to identify the letters and linking their shape to their phonological representations. T.B.'s functional VWFA localizer, peak of BR vs. BC in the first scan, is marked by a blue asterisk.

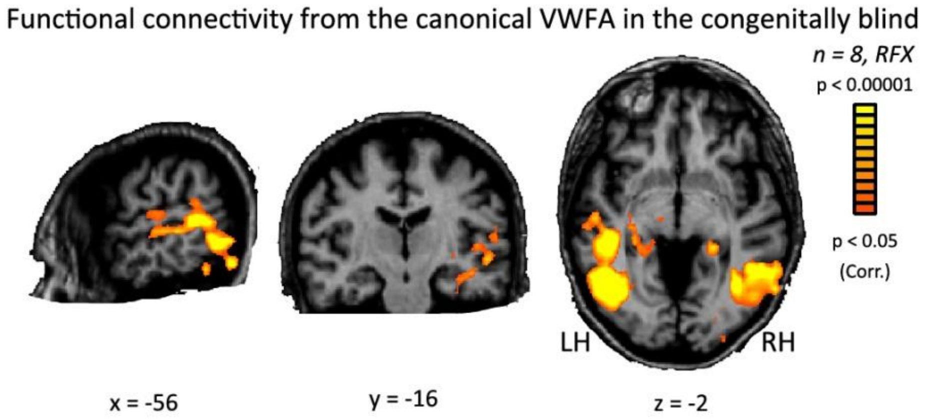

Figure S3. Functional connectivity between the VWFA and auditory language areas in the congenitally blind, related to Figure 2

Functional connectivity was computed from a seed in the canonical VWFA coordinates of the sighted (Cohen et al., 2000) in a group of congenitally blind subjects (for details see **Supplementary Experimental Procedures**), revealing robust functional connectivity to a location consistent with the auditory word-form area in the left anterior STG (DeWitt and Rauschecker, 2012; Talairach coordinates -56, -16, -2; statistical values from this region; t = 11.2, $p < 0.000001$), as well as to more posterior areas in the auditory ventral language-processing hierarchy which correspond to the phoneme-processing network (DeWitt and Rauschecker, 2012).

Supplemental Tables

Table S1. Characteristics of the blind participants, related to Figure 1

Subject	Age & Gender	Cause of blindness	Light perception	Handedness	Age at blindness onset
F.M.	23 F	Microphthalmia	None	Right	0
F.N.	23 F	Leber congenital amaurosis	Faint	Ambidextrous	0
I.S.	24 F	Retinopathy of prematurity	None	Right	0
P.C.	30 M	Retinopathy of prematurity	None	Right	0
P.H.	33 F	Enophthalmus	None	Left	0
T.T.	48 M	Retinopathy of prematurity	None	Right	0
H.B.	22 F	Microphthalmia, Retinal detachment	None	Left	0
T.B.	35 F	Retinopathy of prematurity	None	Left	0

The study included 8 congenitally blind participants. Seven of the blind subjects did not have any form of light perception. The remaining one had faint light perception but was unable to localize light or recognize any shape or form. The age of the subjects ranged from 22 to 48, all had normal hearing, and had no neurological or psychiatric conditions. All of them learned to read Braille around the age of six (average age 5.8 ± 1.5 years). The eighth participant (fully congenitally blind), T.B., only participated in the specially tailored case study.

Table S2. Selectivity for visual-to-auditory sensory substituted letters in the congenitally blind, related to Figure 3.

	X	Y	Z	Probability at peak (%)	p value
Fusiform Gyrus/ Inf. Temporal Sulcus, LH	-51	-58	-9	100	0.00001
Ant. Intaparietal Sulcus, LH	-40	-37	33	80	0.00001
Post. Intaparietal Sulcus, LH	-22	-69	39	80	0.00001
Inf. Temporal Gyrus, RH	53	-55	-8	60	0.00001
Ant. Intaparietal Sulcus, RH	34	-38	39	80	0.00001
Post. Intaparietal Sulcus, RH	29	-71	39	80	0.00001

(clusters meeting 50% selectivity overlap criterion; uncorrected)

Supplemental Experimental Procedures

Participants: The study included 8 congenitally blind participants and 7 sighted controls. The main study group was composed of seven fully congenitally blind native Hebrew speakers. Six of the blind subjects did not have any form of light perception. The remaining one had faint light perception but was unable to localize light or recognize any shape or form. The age of the subjects ranged from 22 to 48, all had normal hearing, and had no neurological or psychiatric conditions. All of them learned to read Braille around the age of six (average age 5.8 ± 1.5 years). An eighth participant (fully congenitally blind), T.B., only participated in the specially tailored case study described below. For a full description of all blind participants, causes of blindness etc., see **Table S1**. The external visual localizer was conducted on a group of seven normally sighted healthy control subjects (no age difference between the groups; $p<0.89$). The Tel-Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject.

SSD training procedure: All participants in this study (n=7), as well as two others who could not be scanned due to MR-incompatible implants, were enrolled in a novel unique training program in which they were taught how to effectively extract and interpret high-resolution visual information from the complex soundscapes generated by the vOICe SSD. Each participant was trained for several months in a 2-hour weekly individual training session by a single trainer. The training duration and progress rate varied between participants and were determined by the personal achievements and difficulties (the average training of the participants here was 73 hours, up to 10 of which devoted to learning to read using the SSD). The training program was composed of two main components: Structured 2-dimensional training, in which the participants were taught how to process 2- dimensional still (static) images, and live-view training in which visual depth-perception and training in head-eye-hand coordination were taught, using a mobile kit of the vOICe SSD (similar to that in **Fig. 1C**). The structured 2- dimensional training involved learning to process hundreds of images of seven structured categories: geometric shapes, Hebrew letters and digital numbers, body postures, everyday objects, textures (sometimes with geometric shapes placed over a visual texture, used to teach object-background segregation), faces and houses (see **Fig. 1E**; see also **Movie S1** showing images from all the categories and their SSD transformation to sounds), introduced with increasing complexity and detail. Thus, for teaching letters, we first introduced vertical, horizontal, diagonal and curved lines, and then built the letters from these elements (for a demo in English see http://doc.org.il/voice.ppsx). Some blind subjects, who were accustomed mostly to Braille letters, had to be reminded and trained on the shape of unfamiliar letters. The eighth participant, T.B., who had never learned the shapes of the letters, was taught separately as part of a case study and was scanned before and after this specially tailored training session (detailed below). Prior to the scan she was only given the structured 2-dimensional training for geometric shapes, and in between the two scans reported here, she underwent a short (<2 hour) training on the shape of 5 Hebrew letters. During this training session, T.B. was first introduced to the shapes of the "sighted" alphabet via the vOICe SSD. After each newly-presented soundscape, T.B. described its shape, received feedback regarding her description (both verbally: "yes, this is the shape" or "no, the line on the left is shorter than on the right", and using haptic two -dimensional models), and was told which letter this shape represented. T.B. successfully learned the shapes of the 5 trained letters, reaching a level of 100% recognition before the second scan. All the other participants in the study who completed the entire structured 2-dimensional training were taught the entire Hebrew alphabet, and also taught how to read whole words (up to 5 letters) in a single soundscape (for a demonstration of a blind participant reading a 3-letter word see **Movie S2**), which could be further sequenced to form longer words. The main consideration for choosing these particular categories for training was their functional importance in daily life. Additionally, these categories are known to be processed by distinct specialized brain areas in sighted individuals (Kanwisher, 2010). During the training sessions the participants heard each soundscape, tried to describe what it contained, and were directed through the trainers' questions to a detailed full description of the image. Additionally, whenever possible, we provided the blind subjects with haptic feedback by presenting them with palpable images identical to those they perceived through the SSD (**Fig. 1D**; e.g. for all 2D stimuli and some of the 3D stimuli). Following the structured 2-D training, participants could tell upon hearing a soundscape which category it represented. This required Gestalt object perception and generalization of the category principles and shape perception to novel stimuli. They could also determine multiple features of the stimulus (such as hairstyle in a face image, number of floors and windows in a house image, and body posture in a body-shape image), enabling them to differentiate between objects within categories. A demonstration of a blind participant recognizing emotional facial expressions from soundscapes can be found in **Movie S2**.

Additionally, general principles of visual perception which were not familiar to the congenitally blind participants were demonstrated and taught using stimuli from the various classes. Such principles were (i) the conversion of 3- dimensional objects to two-dimensional images (and back) depending on viewpoint and on object position, (ii) the transparency of objects and the ability to see through parts of objects, and (iii) the occlusion of parts of objects. Other visual perception principles which required active sensing were demonstrated using the live-view training technique. These included principles such as (i) visual field-of-view, (ii) orienting their heads (on which the webcam was mounted, placed on sunglasses) to the objects at hand in order to scan a visual scene (iii) variation of apparent object size depending on distance, and (iv) the use of monocular depth cues such as occlusion between different objects and perspective to estimate the depth and distance of seen objects. The scan was conducted following the completion of the structural 2-dimensional training (although most participants continued their live-view training further).

In order to minimize sensory-motor artifacts, no recording of performance was conducted during the fMRI scan. Prior to each scan we verified the subjects were able to easily recognize learned stimuli from the tested categories. In a complementary experiment within the scanner on the same day (not reported here) the subjects were instructed to decide whether a presented letter was one of 3 pre-specified target letters (3 target letters out of 10 different letters presented; each presented 3 times), and performed at 77.5% (±6.4% standard deviation), significantly better than chance (t-test $p<0.0005$).

Case study of learning to read a new script using sensory substitution: A single case study was conducted on a unique congenitally blind individual, T.B. (age 35), who was highly literate in Braille reading (reading since the age of 6), but completely unfamiliar with the shapes of any other alphabet, specifically the regular “sighted” Hebrew alphabet. This allowed us to apply a repeated-measures design comparing activations (using the same sensory stimuli) before and immediately after learning to read new script letters through the SSD. Prior to the scan, T.B. had been trained for 15 hours at deciphering visual images of various complex geometric shapes transmitted via the vOICe SSD, but was not taught other stimulus categories from the training program and remained completely naïve to the shapes of letters. Then, T.B. underwent a first fMRI session, followed by a single training session with letters (which lasted less than two hours; see **Supplementary Experimental Procedures** for details), followed by a second identical fMRI session, all on the same day. During the training session, T.B. successfully learned the shapes of the 5 trained letters, reaching a level of 100% recognition before the second scan. Each fMRI session included four different experimental conditions (each repeated five times in a pseudorandom order) in a block design paradigm. All epochs lasted 12 seconds and were followed by a 9s rest interval. A short (~1 s) auditory instruction was given before the beginning (“palpate” or “listen”) and at the end of each epoch. T.B. was requested to attempt to read the stimuli presented in all the conditions. In the Braille reading condition (BR) T.B. read 5- and 6- letter long letter strings using her dominant left hand. In the Homogenous Braille (Braille control; BC) condition, she palpated strings of 5- and 6-long homogenous Braille dots matrices, which do not represent letters, that were used as a control for the tactile and motor aspects of BR (as in Reich et al., 2011). In the vOICe reading condition (VR) she was presented with the same letter strings as in the BR, but via soundscapes. In the vOICe control (VC) condition, soundscape representations of letters which were not learned during training were presented, composing letter-strings of similar lengths.

MRI acquisition and Data analysis: The BOLD fMRI measurements were performed in a whole-body 3-T GE scanner. The pulse sequence used was the gradient-echo echo planar imaging EPI. We used 29 slices of 4mm thickness. The data in-plane matrix size was 64x64, field of view (FOV) 20cm x 20cm, time to repetition (TR) = 1500ms, flip angle = 70˚ and time to echo (TE) = 30ms. The main experiment and the visual localizer had 500 whole-brain images each collected in one functional scan, and the imagery control experiment had 360 whole-brain images collected in one functional scan. The case study experiment had 308 whole-brain images collected in each of the two repetitions (before and after training). The first five images of each scan (during the first baseline rest condition) were excluded from the analysis because of non-steady state magnetization. Separate 3D recordings were used for co-registration and surface reconstruction. High resolution 3D anatomical volumes were collected using T1-weighted images using a 3D-turbo field echo (TFE) T1-weighted sequence (equivalent to MP-RAGE). Typical parameters were: Field of View (FOV) 23cm (RL) x 23cm (VD) x 17cm (AP); Foldover- axis: RL, data matrix: 160x160x144 zero-filled to 256 in all directions (approximately 1mm isovoxel native data), TR/TE=9ms/6ms, flip angle = 8°.

Data analysis was performed using the Brain Voyager QX 2.2 software package (Brain Innovation, Maastricht, Netherlands) using standard preprocessing procedures. Functional MRI data preprocessing included head motion correction, slice scan time correction and high-pass filtering (cutoff frequency: 3 cycles/scan) using temporal smoothing in the frequency domain to remove drifts and to improve the signal to noise ratio. No data included in the study showed translational motion exceeding 2 mm in any given axis, or had spike-like motion of more than 1 mm in any direction. Functional and anatomical datasets for each subject were aligned and fit to standardized Talairach space (Talairach and Tournoux, 1988). For the main experiment and visual localizer experiment, single subject data were spatially smoothed with a three-dimensional 8 mm full-width at half- maximum Gaussian in order to reduce inter-subject anatomical variability, and then grouped using a general linear model (GLM) in a hierarchical random effects analysis (Friston et al., 1999). For the imagery control experiment the data were similarly smoothed and grouped using general linear model (GLM) in a fixed effects analysis. For the case-study analysis, the data from the two scans were grouped using general linear model (GLM) in a fixed effects analysis , and displayed at a threshold of $p < 0.05$, corrected for multiple comparisons using the false discovery rate (FDR) correction (Genovese et al., 2002).

Separate 3D recordings were used for surface reconstruction. Anatomical cortical reconstruction procedures included the segmentation of the white matter using a grow-region function embedded in the Brain Voyager QX 1.9.10 software package (Brain Innovation, Maastricht, Netherlands). The Talairach normalized cortical surface was then inflated and the obtained activation maps were superimposed onto it.

Functional connectivity data analysis and MRI acquisition: A dataset of spontaneous BOLD fluctuations for the investigation of intrinsic (rest state; Biswal et al., 1995) functional connectivity was collected while the subjects lay supine in the scanner without any external stimulation or task. Functional connectivity MRI (fcMRI) uses slow (<0.1 Hz) spontaneous (not task-related, e.g. during rest) fluctuations in the BOLD signal which were discovered nearly two decades ago (Biswal et al., 1995), and which have since been convincingly and repeatedly shown to correlate between areas that are parts of the same functional network (Smith et al., 2009; see review in: Auer, 2008; Deco et al., 2011; Fox and Raichle, 2007), closely mimicking anatomical (although not necessarily monosynaptic; Vincent et al., 2007) connectivity. Eight congenitally blind subjects (the group that participated in the main experiment and an additional congenitally blind woman, age 35) participated in this experiment. Data in-plane matrix size was 64x64, field of view (FOV) 24cm x 24cm, time to repetition (TR) = 3000ms, flip angle = 90˚ and time to echo (TE) = 30ms. 29 – 46 slices of 4mm thickness were used to obtain full coverage of the subjects' brain, and 182 whole-brain images were collected in one functional scan. The first two images of each scan were excluded from the analysis because of non-steady state magnetization. Ventricles and white matter signal was sampled using a grow-region function embedded in the Brain Voyager from a seed in each individual brain. Using MATLAB (MathWorks, Natick, MA) ventricle and white matter time-courses were regressed out of the data and the resulting time-course was filtered to the frequency band-width of 0.1-0.01 Hz (in which typical spontaneous BOLD fluctuations occur). The resulting data were then imported back onto Brain Voyager for group analyses. Single subject data were spatially smoothed with a three-dimensional 6 mm full-width at half-maximum Gaussian in order to reduce inter-subject anatomical variability. Seed region-of-interest (ROI) was defined by a spatial extent of 3 voxels centered on the canonical VWFA coordinates of the sighted (see details in the experimental procedures section of the main text). Individual time-courses from this seed ROI were sampled from each of the participants, z-normalized and used as individual predictors in a group analysis using a general linear model (GLM) in a hierarchical random effects analysis (Friston et al., 1999). The minimum significance level of the results was set to $p<0.05$ corrected for multiple comparisons, using the spatial extent method (see details in the experimental procedures section of the main text). T and P values were sampled at the group level of activation from several ROIs: *(1)* The literature peak voxel of the auditory word-form area (in the left anterior STG; DeWitt and Rauschecker, 2012); Talairach coordinates -56, -16, -2. *(2)* The peak of functional connectivity from the inferior frontal cortex located at the inferior frontal sulcus; Talairach coordinates -43, -2, 18. *(3)* The peak of the lateral occipital visuo-tactile object selective area (LOtv; contrast visual objects > visual textures AND tactile objects > tactile textures); experiment detailed in Amedi et al., 2002; peak Talairach coordinates -37, -63, -4.

Somatosensory localizer data analysis and MRI acquisition: In this experiment the body surface was stimulated by brushing the subjects' skin surface in a block design paradigm. In each block, the subject's right body was brushed at one of the following locations: lips, palm, shoulder, waist, knee and foot. A stimulation block lasted 9 seconds, followed by a 9 second rest baseline. Each body part stimulation was repeated 4 times, in a pseudo randomized order. 8 normally sighted subjects participated in this experiment. Subjects wore blindfolds and had their eyes shut for the duration of the scan and were asked to concentrate on the tactile sensation. The BOLD fMRI measurements were obtained in a whole-body, 3–T Magnetom Trio scanner (Siemens, Germany). The fMRI protocols were based on multi-slice gradient echoplanar imaging (EPI) and a standard head coil. The functional data were collected under the following timing parameters: TR = 1.5 s, TE = 30 ms, FA = 70°, imaging matrix = 80 x 80, FOV = 24 x 24 cm (i.e. in-plane resolution of 3 mm). 22-23 slices with slice thickness = 4.5-4.9 mm and 0.5-0.7 mm gap were oriented in the axial position, for complete coverage of the whole cortex, the thalamus and most of the cerebellum. Preprocessing steps and analysis was done similarly to the main experiment (see details in the experimental procedures section of the main text) and included head motion correction, slice scan time correction and high-pass filtering (cutoff frequency: 3 cycles/scan), transformation to Talairach space, a three-dimensional 8 mm full-width at half- maximum Gaussian spatial smoothing and grouping using a random effects GLM analysis. The peak of the hand selective activation (contrast stimulation of hand vs. stimulation of all other body parts, t=8, p<0.000005, corrected for multiple comparisons, peak Talairach coordinates -43, -26, 45) was defined as a primary somatosensory hand area localizer, and used to examine activation (sample parameter estimates, T and P values at the group level of activation) for Braille imagery in the blind in **Fig. S1C**. Similarly, activation was sampled from the peak of selective foot activation (contrast stimulation of foot vs. stimulation of all other body parts, t=6, p<0.0005, corrected for multiple comparisons, peak Talairach coordinates -7, -32, 60).

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4. Discussion and conclusions

4.1 Summary of the findings

In the works presented here, by studying congenitally blind individuals viewing visual information through visual-to-auditory sensory substitution we provided evidence that SSDs can become functional rehabilitative aids if appropriate training is provided. Following the dedicated training we developed (see methodology section; also detailed to a lesser extent in the supplementary material in section 3.3; Striem-Amit et al., 2012b) blind people were able to use the vOICe SSD for high-acuity visual perception beyond what was previously shown possible (results section 3.1), to the extent of surpassing the WHO blindness threshold, and also were able to perform various visual tasks, such as binding of features of complex objects, complex image category classification (results section 3.3), and more anecdotally (though rigorous scientific investigation of such abilities is underway), reading words, processing body posture and even identifying emotional facial expressions in natural ecological setting (see supplementary movie 2 in Striem-Amit et al., 2012b).

Furthermore, we have shown here that the processing of visual-through-auditory information may activate the visual cortex of congenitally fully blind adults, which shows not only mere extensive overall activation but rather selective activation which is specific to the type of tasks (shape identification vs. localization; results section 3.2) and stimuli (category of letters; results section 3.3; similar preliminary results for additional ventral visual cortex areas were also found; Striem-Amit et al., 2012a) which also characterize the same areas in the normally developed visual cortex of sighted people. Such activation was found despite the fact that the blind people were taught to process the visual-to-auditory transformation and stimuli only in adulthood. Furthermore, some selective activation such as the ventral-dorsal division of labor (results section 3.2) and the activation of the VWFA for letters in the case study (results section 3.3) may be found following relatively brief training of only up to two hours with the SSD algorithm, suggesting an impressive level of plasticity or tolerance with regard to sensory modality. Even in the case of the selectivity of the VWFA for letters over other visual categories, which is seen after somewhat longer training, the entire training protocol contained merely tens of hours of training.

Therefore, our findings show that several specific functional selectivities of the visual cortex may be found regardless of sensory modality, visual experience, or long-term familiarity or expertise with the novel sensory transformation. This suggests that at least certain parts of the visual cortex show a strong invariance beyond sensory input modality and early sensory experience, while maintaining the relative functional specialization of both the large-scale organizational principle of the two processing streams and parts of the ventral visual cortex.

Beyond the relevance of these findings for visual rehabilitation, these findings impact several of the major issues regarding the function and developmental origin of the visual cortex, as well as the balance between plasticity and conserved cortical functions resulting from sensory deprivation. Specifically, they suggest that the visual cortex regions perform highly flexible task-specific operations which can be sensory modality-independent. These category- and task-selectivities are maintained in the congenital absence of vision, despite otherwise extreme plasticity for other functions and input types shown previously in the blind brain (as discussed in section 1.2.2). This implies the presence of innately-determined constraints on the emergence of visual cortex selectivities. In the next sections I will address all these topics in more depth.

4.2 Task-selective operators in the visual cortex

In traditional neuroscience, the common view is that the human brain is divided into the ‘visual cortex’, the ‘auditory cortex’ and so on according to the sensory modality which elicits it, and into higher-order multisensory areas integrating information from these unimodal cortices (the sensory division-of-labor principle; Zeki, 1978b). Thus for example, the early visual cortex areas (V1, V2 etc.) were thought to process low-level visual features such as lines in different orientations and in different places in the visual field, and other low level increasingly complex visual features, area MT processes visual motion whereas multisensory areas for example in the frontal lobe integrate information from vision, audition and touch. However, in recent years there has been growing evidence that even the early stations in the visual cortex hierarchy may be less dependent on specific visual features in the processing of images than was previously thought. A general notion is emerging that although some percepts may be unimodal by nature (for example, the perception of hue, but see further discussion in section 4.3 below), most of our experiences are a combination of multisensory sensations, which can readily be linked and even translated from one sensory-modality to another. For example, we may perceive the shape of an object by touching it and identify it and even imagine it, visually, in a seemingly effortless process. In the last decade the study of the neural basis of such effects has shown that the specific visual sensory features of the stimuli may be less crucial for processing in several visual cortex areas. For example, the VWFA was originally thought to encode letters and words due to a combination of several low-level visual features, including a foveal location, high spatial frequencies and the availability of contours and line junctions (Szwed et al., 2011). Recently, it was shown that even word stimuli whose shape was defined using atypical features; namely dots which carried word information by spatially varying dot luminance or dot motion direction, rather than by composing line contours, could also engage the VWFA (Rauschecker et al., 2011).

Furthermore, there is evidence that the occipital visual cortex is not purely visual, in that it may also be activated by non-visual stimuli in normally sighted people. One such thoroughly investigated example is the occipito-temporal Lateral Occipital Complex (LOC), which is preferentially activated by visual objects compared to scrambled images or textures. As the visual objects' characteristic three-dimensional shape can also be perceived haptically, it was investigated whether the LOC region would also encode object information derived by touch. Using fMRI it was shown that the LOC region contained a sub-region which was activated by haptic perception of objects more than by the perception of haptic textures (Amedi et al., 2001), suggesting that it is also tuned to object perception via touch. Another experiment extended these findings using an fMRI adaptation design, which has the added advantage of measuring responses of neural subpopulations within standard fMRI voxels (Grill-Spector and Sayres, 2008). In this case the fMRI adaptation was used to study the cross-modal transformation of object shapes across the visual and tactile modalities. This study (Tal and Amedi, 2009) showed that LOC adaptation can be found across modalities (e.g. a haptic object presented after a visual one generates decreased activation), confirming that the same neuronal population is engaged in processing both vision and haptics, as opposed to the inter-digitation of unisensory neurons receiving information from either visual or haptic input. Thus, these studies show that the neuronal population in the occipito-temporal cortex may constitute a multimodal object-related network. The nature of the sensory inputs which may engage the LOC was also investigated. Specifically, for a time it was thought that LOC, while not being purely visual, could still be limited to the visual and haptic modalities, as it was not found to be activated by the auditory perception of objects' natural environmental characteristic sounds (Amedi et al., 2002). However, it was later shown that the LOC may be more flexible with regard to the input sensory modality, as long as the shape of the object is encoded in the input. Employing the same SSD used here, Amedi and colleagues (Amedi et al., 2007) showed that when auditory information is made to convey shape information, the LOC can indeed be activated in sighted people.

Like the multisensory activation of the LOC, several other areas in the visual cortex have also been shown to be activated by non-visual modalities in sighted people, for example in the MST, part of the motion perception network (Beauchamp et al., 2007), the body-shape preferential Extrastriate Body Area (EBA; Costantini et al., 2011; Kitada et al., 2009), the face-selective Fusiform Face Area (FFA; Kilgour et al., 2005) and the larger-scale animate-inanimate axis of selectivity within the ventral visual cortex (Mahon et al., 2009).

Although suffering from the potential confound of the involvement of visual imagery (activation of the visual cortex by touch or sound due to the visual imagery of the same objects in normally sighted people), the conjunction of such findings (along with several findings in the blind, see the next section) gave rise to the hypothesis that the visual cortex may process non-visual inputs and that the brain may be in fact composed of task-selective rather than visual, sensory-modality-selective operators (Amedi et al., 2001; also referred to as metamodal operators; Pascual-Leone and Hamilton, 2001). These operators are local neural networks defined by a given computation that is applied regardless of the sensory input received. This does not mean that there are not preferred sensory modalities for specific computations (and hence operators). Indeed, this is the case and the reason that the cortex gives the illusion of being organized around sensory modalities rather than operators. This may be because certain types of computations are usually most effective, or most typically approached, by using specific sensory inputs. Three-dimensional shape information of objects is normally perceived by vision, as audition normally does not provide shape information of objects to humans (as opposed to bats, who use sonar), and touch provides information only for a subset of the objects in our environments – those we actively explore haptically (as opposed to whiskered animals, such as rats and mice who depend more on haptic perception), and is specifically limited to objects within reach. This gives rise to the appearance of the existence of a “visual object area”, since vision is the most prevalent input providing such information. A further bias for the organization of these operators in their “sensory cortices” is that of a-priori structure, or connectivity (Mahon and Caramazza, 2009; Pascual-Leone and Hamilton, 2001). Because the structural properties of different brain regions differ (e.g. different patterns of neural connectivity), different brain regions are best at performing particular types of functions. A rather extreme example is motion processing. A computation of motion may be structurally derived by an asymmetric neural connection which thus computes the time difference between brightness patterns of the retinal image as sensed by the two-dimensional array of photoreceptors. Such a computation can be mediated by the specific direction of connectivity between neurons of retinally proximal preferences (Borst and Egelhaaf, 1989). More generally, the occipital cortex may initially be a region of the brain with structural and functional qualities that enable it to excel at tasks which require high-acuity processing of spatial information, which are properties best supplied by vision. It has been suggested that subsequently, in a process of competition between brain regions for the ability to perform a set of tasks, the learning of the patterns present in the environment and the reinforcement of winning networks by adjusting connectivity strengths, the role of the expert operators is determined (Pascual-Leone and Hamilton, 2001). Thus, because the occipital cortex was the best a-priori in spatial information processing, it continues to outplay other expert networks for the input of vision, performs spatial decoding more and more accurately, hence reinforcing visual input while increasingly suppressing inputs from other sensory modalities. Eventually, the occipital cortex may become so specialized for vision that it appears to be a ‘visual’ cortex, designed only for the specific task of further subdividing and processing visual information.

4.3 Brain organization in the absence of visual experience

The considerable impact of bottom-up connectivity on the organization of such metamodal operators makes the congenital absence of one of the sensory inputs an interesting and perhaps the most extreme test-case for the metamodal organization hypothesis, while also controlling for visual imagery. Theoretically, if some features of the development of metamodal operators are derived from the way neurons and areas are connected to input from the eyes, the congenital absence of such inputs should result in a distinctly different organization pattern of the brain. In fact, many studies have highlighted the different non-visual tasks that activate the visual cortex of the congenitally blind (see detailed in section 1.2.2), among them tasks such as verbal memory retrieval (Amedi et al., 2003; Raz et al., 2005) and semantic processing (Bedny et al., 2011a; Bedny et al., 2011b; Burton et al., 2003; Burton et al., 2002b), which are uncharacteristic of the normally developed visual cortex. However, in many cases the activation observed in the blind for other sensory modalities was not compared between tasks or stimuli, and thus merely demonstrated that the visual cortex of the blind is activated by the auditory or haptic modalities, but without determining the preferred computation or operation of the region. In contrast, our studies focused on the comparison of different tasks and stimuli, which enabled an estimation of preferential activation and task selectivity.

Our findings were thus the first to show the segregation between the ventral and dorsal streams in the congenitally blind (results section 3.2) using the same sensory stimuli, when the only difference between the conditions was the required task. This experiment indicated that the concept of task-selective organization can be applied without visual experience or inputs, even for the most fundamental organizational principle of the segregation between the two processing streams. Our second study (results section 3.3) pointed to the metamodal operation of a specific region, but in a more strict manner than previously by demonstrating that as in the normally sighted, the VWFA of the congenitally blind is characterized by full category selectivity that exhibits a preference for letters over all the other visual objects tested, similar to the definition and demonstration of category selectivity in the sighted. In both cases, the characteristic task- and category- preferences were observed in the full absence of visual experience and input during development.

Our studies confirm several other works conducted in recent years indicating that visual cortex processing in the blind matches the computations conducted visually by the same areas in normally sighted people (see review in Reich et al., 2012; Ricciardi et al., 2013). Such findings have been demonstrated for specific brain areas within the visual system: Area LOC, which as detailed above was shown to have multisensory properties in object processing in the sighted, was also shown to be activated for general shape processing in the blind for both haptic and auditory shape processing (Amedi et al., 2010; Arnott et al., 2013; Ptito et al., 2012), and the spatial processing of both simple auditory chords or vibrotactile stimulation selectively activate the middle occipital gyrus (MOG) of the blind (Collignon et al., 2011; Renier et al., 2010). Both these areas demonstrated a clear task-selectivity in the blind in our findings, thus revealing for the first time the double dissociation between the two regions according to their supposed processing streams (results section 3.2). Additional task-selective properties that were previously reported for the human MT (middle temporal) area, which normally specialized in processing motion, but have also been found for non-visual motion in the blind (Beauchamp et al., 2007; Matteau et al., 2010; Poirier et al., 2006a; Ptito et al., 2009; Ricciardi et al., 2007; Sani et al., 2010), and activation for Braille reading (as compared to other language tasks and low-level sensory-motor controls) was found in the VWFA (Reich et al., 2011). Several studies have also investigated object selectivity including the specificity for tool stimuli over other, non-manipulable objects which was observed in two regions of the parietal (Mahon et al., 2010) and occipitotemporal (Peelen et al., 2013) cortex of the blind. A recent study looked beyond area-specific computation, and showed that in a group of sighted and three congenitally blind individuals the larger-scale animate/inanimate organization within the high-order anterior ventral visual cortex is independent of vision (Mahon et al., 2009). In additional to fMRI studies, the involvement of some of these regions for these tasks in congenitally blind people was demonstrated using TMS interference, such that stimulation of area MT in the congenitally blind interfered with their motion processing (Kupers et al., 2009), and stimulation of the right dorsal extrastriate occipital cortex, supposedly near the MOG region, interfered with a sound localization task (Collignon et al., 2009a). Comparable metamodal findings were discovered in the auditory cortex of congenitally deaf cats, who also exhibited cross-modal plasticity causally linked to behavior (Lomber et al., 2010; Malhotra et al., 2008). In the deaf cats, reversible deactivation of posterior auditory cortex (usually involved in auditory localization in hearing cats) selectively eliminated superior visual localization abilities, whereas deactivation of the dorsal auditory cortex (area DZ, normally involved in sound source localization and duration coding) eliminated superior visual motion detection.

Therefore, there is a growing body of evidence, including our recent findings, that supports the task-selective/ metamodal hypothesis, suggesting further that brain operators may be task oriented (and in the case of the ventral visual cortex, domain-specific; Mahon and Caramazza, 2009, 2011) and highly flexible with regard to their sensory preferences (extending to non-ecological, newly learned SSD transformations) even in extreme cases of sensory deprivation and plasticity.

Mahon and colleagues (Mahon et al., 2009) concluded from their results that modality dependence is secondary as a hierarchical organizational factor to the object domain (e.g. living vs. non-living, also see a review of conceptual object categories; Mahon and Caramazza, 2009) in the ventral visual cortex. Our findings extend such concepts of a-modal innately-determined developmental constraints to the more fundamental organizational principle of the segregation between the two processing streams. In so doing, it extends the findings beyond visual object conceptual categories to postulating that the whole brain may be task specific but sensory modality-independent if the relevant computation and task can be derived from the sensory input.

It is important to note that our findings of task-selectivity were obtained when characteristic task- and category- preferences were observed for stimuli and tasks learned in adulthood, and were taught using an a-typical modality on participants trained to a limited extent. Nevertheless these effects do not necessarily reflect adult plasticity for a new modality transformation (SSD). Specifically, the functional recruitment in the brain of congenitally blind subsequent to a short training period makes it highly improbable that they reflect any extensive plastic changes (Pascual-Leone et al., 2005). Instead, it suggests that the division-of-labor between the ventral and dorsal streams for form and location in the ‘visual’ cortex must already be present and the short training presumably “reveals” these innate preferences for the newly learned sensory transformation of the SSD. Similarly, the blind subjects tested for category selectivity were by no means illiterate, but already proficient Braille readers. Once the VWFA has specialized in converting signs to phonemes and words during the early acquisition of literacy (Brem et al., 2010), which in the blind may be generated using haptic Braille script (Reich et al., 2011), the brain may be relatively quickly reconfigured to map a novel set of symbols to the same set of phonemes, similar to learning a novel script via vision in a literate person (Hashimoto and Sakai, 2004; Maurer et al., 2010; Xue et al., 2006). Thus, the apparent adult plasticity, at least in the case of these findings, is likely to reflect an a-priori modality invariance, which can plastically be applied regardless of learning to process the required computation using a new sensory input. Bayesian learning principles (Ernst and Bulthoff, 2004; Tenenbaum et al., 2011) may enable the extraction of abstract schemas behind superficially different inputs, including sensory modalities. By learning to extract the abstract interpretation of a sound input as a 2-D shape using the vOICe algorithm, our participants were able to apply the same type of amodal shape, location and reading-category processing even with newly learned artificial sensory inputs. Therefore, our results suggest that the processing of letters in the VWFA is highly flexible with regard to sensory modality, even in the adult brain.

4.4 How can "visual" task-selectivity arise in the blind brain?

What are the developmentally endogenous or innate constraints that might contribute to such a sensory-independent task-selective organization in the congenitally blind? We speculate that similar to the task-selective organization in the normally developing brain, two factors, which are not mutually exclusive, could take part. The first is the intrinsic modality-independent preferences for a particular (different) type of content or computation in each brain area. For example MT might specialize in computing motion due to computing subtractions of a motion coincidence detector regardless of sensory input, and not in a manner dependent on comparing retinally-derived inputs. The second factor is the connectivity pattern to higher-level processing areas in the brain whose organization towards their tasks is (generally) unaffected by the missing visual inputs; i.e. a-modal higher-order areas, as well as areas in the non-visual sensory cortices. While it is probably the case that in the normally developing (not visually-deprived) cortex, organization is affected by both bottom-up and top-down factors, in the case of a missing bottom-up input the top-down influences may suffice, and perhaps be even more dominant in determining the task selectivity of the visual cortex operators (but see also reservations detailed below). In the case of the visual streams, it has been suggested that premotor-posteromedial parietal connections are likely to subserve abstract cognitive processes involving visuo-spatial information in the precuneus (Cavanna and Trimble, 2006), whereas feedback connectivity from frontal and somatosensory cortices to the ventral (inferior-temporal) occipital cortex, which normally allows for its non-visual object processing in sighted, may underlie its multisensory function for object recognition (Amedi et al., 2001; Amedi et al., 2003; Deshpande et al., 2008; Striem-Amit et al., 2011b). A different balance between the bottom-up and top-down connectivity in driving the visual cortex organization in the blind may also explain why there is a back-propagation of the cross-modal task-selectivities in the blind towards the earlier visual cortex, as reported in results section 3.2, Figs. 1-2, in which shape-preference was observed in the blind in areas more posterior than those found in the sighted. In the case of the VWFA, the connectivity driving the organization of this region may be reciprocal anatomical and functional connectivity with higher-order cortical regions involved in the processing of language (Ben-Shachar et al., 2007; Mahon and Caramazza, 2011; Pinel and Dehaene, 2010). We tested this hypothesis in the blind adult participants, and showed that their VWFA is indeed functionally connected to the frontal and temporal areas engaged in processing language (the left inferior frontal cortex and auditory word-form area in the left anterior superior temporal gyrus), as well as to the nearby general shape multisensory operator in the LOC (see results section 4.3). Naturally, this hypothesis requires further examination in blind children as they learn to read, in order to verify that this connectivity is present prior to reading acquisition, and to track the way in which the reading-operator is created. Furthermore, fMRI does not allow for causal inference and thus cannot attest to the functional role of the selectivity in VWFA for reading task performance, which will be further examined in the future.

In addition to the connectivity of the visual cortex which is present in the normally sighted, connectivity between the visual cortex and other sensory cortices and subcortical nuclei has also been speculated to be strengthened by sensory deprivation. Such a strengthening of cortico-cortical connectivity was argued to underlie much of the cross-modal activation found in the blind. Generally, cross-modal plasticity in blind humans has been ascribed to cortico-cortical modulations of the occipital lobe via parietal, frontal or associative auditory inputs (Amedi et al., 2003; Bavelier and Neville, 2002; Buchel, 2003; Noppeney, 2007; Pascual-Leone et al., 2005), as well as from primary sensory cortices (Klinge et al., 2010; Kupers et al., 2011; Merabet and Pascual-Leone, 2010; Ricciardi and Pietrini, 2011). Interestingly, so far the use of neuroimaging to probe such enhanced connectivity patterns has generated conflicting results, as several studies measuring intrinsic functional connectivity (iFC) found significantly reduced cortico-cortical connectivity in the blind (Fujii et al., 2009; Liu et al., 2007; Yu et al., 2008). These studies reported that visual deprivation leads to extensive reduction in functional connectivity of many areas in the visual cortex with multiple cortical sites (Liu et al., 2007; Yu et al., 2008), including the auditory, motor, somatosensory and prefrontal cortices. Liu and colleagues compared the correlation coefficients of visual cortex and non-visual cortex areas in the blind, and found that 55 pairs of brain regions involving the visual cortex showed decreased iFC as compared to sighted controls (Liu et al., 2007). Decreased iFC was found between the visual cortex and the auditory, somatosensory and motor cortex, whereas connectivity to some prefrontal regions was increased. This is extremely counterintuitive since such an overall decrease in connectivity is consistent with the general loss hypothesis, which emphasizes the absence of the visual modality; however it is less appropriate to explaining the increased processing of non-visual information in the visual cortex.

In contrast to studies in blind humans, animal models of congenital blindness (Bronchti et al., 2002; Izraeli et al., 2002; Kahn and Krubitzer, 2002; Laemle et al., 2006; Piche et al., 2007; Piche et al., 2004; Rauschecker and Korte, 1993) have focused on the role of subcortical regions in driving visual cortex plasticity. Specifically, aberrant increased connectivity between the visual cortex or lateral geniculate nucleus and the auditory and somatosensory subcortical nuclei is thought to underlie such reorganization (Asanuma and Stanfield, 1990; Doron and Wollberg, 1994; Izraeli et al., 2002; Karlen et al., 2006; Kingsbury et al., 2002; Laemle et al., 2006; Piche et al., 2004), leading to non-visual functional recruitment of the visual cortex (Piche et al., 2007; Rauschecker and Korte, 1993; Yaka et al., 2000; Yaka et al., 1999). Such cross-modal recruitment is further strengthened by non-visually enriched environments (Piche et al., 2004). This abnormal connectivity pattern is speculated to result from developmental exuberance; namely, developmentally-normal transient cross-modal projections (Dehay et al., 1984; Innocenti et al., 1988; Kennedy et al., 1989; see review Innocenti and Price, 2005)which are poorly pruned in the absence of competition from visual input (Bavelier and Neville, 2002; Rauschecker, 1995). As exuberant production of both neurons and synaptic connections between neurons is also characteristic of human brain development (Buss et al., 2006; Rabinowicz et al., 1996), and there is evidence for transient cross-modal connections during development in primates (Kennedy et al., 1989), the existence of transient cross-modal projections may be speculated to exist in humans as well. However, despite several studies which have explored anatomical pathways in blind humans (Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008; Shimony et al., 2006;

Shu et al., 2009; Yu et al., 2007), and numerous others which showed cross-modal activation in the blind, no evidence for subcortical plasticity in blind humans has been reported to date.

An alternative for new or increased cross-modal connectivity in the blind may be that the connectivity patterns are similar to those seen in sighted, but that in the sighted such non-visual inputs are masked by the concurrent visual input and thus affect the observed activation to a lesser extent. Supporting evidence for such a model comes from experiments in which normally sighted people underwent a short period of blindfolding, while their brain activation was monitored several times. Although such experiments are rare, one such experiment (Merabet et al., 2008) showed that 5 days of full visual deprivation may suffice to show an increase in the fMRI BOLD signal within the occipital cortex in response to tactile stimulation, which disappeared 24 hours after the blindfold was removed. Furthermore, the visual cortex was functionally engaged in the tactile processing, in that a reversible disruption of occipital cortex function on the fifth day (by TMS) impaired Braille character recognition ability in the blindfolded group but not in the non-blindfolded controls. These findings suggest that even a very short complete visual deprivation in normally sighted individuals can lead to profound, but rapidly reversible, neuroplastic changes by which the occipital cortex becomes engaged in processing non-visual information. The speed and dynamic nature of the observed changes suggests that normally inhibited or masked functions in the sighted are revealed by visual loss. The unmasking of pre-existing connections and shifts in connectivity represent rapid, early plastic changes, which presumably can lead, if sustained and reinforced, to slower developing but more permanent structural changes (Merabet et al., 2008; Pascual-Leone and Hamilton, 2001). While such changes may be more profound they do not necessarily need to differ from those found in the sighted, which would help explain the puzzling findings or increased functional recruitment without, to date, evidence of increased functional or anatomical connectivity in blind humans.

4.5 Limitations and open questions regarding the task-selective model

Although the metamodal task-selectivity model seems an appealing explanation to many of the findings concerning brain organization in the blind, it is important to also acknowledge its current limitations. Specifically, a set of specific findings on the task-preferences of the primary visual cortex cannot be fully accounted for by this model. Several studies have shown that the primary visual cortex plays a role that is highly distinct from its standard role in simple visual processing, and engages in the processing of language and memory (Amedi et al., 2003; Bedny et al., 2011a; Bedny et al., 2011b; Burton et al., 2003; Burton et al., 2002b; Raz et al., 2005). In this case, the task-preferences of V1 have been compared between tasks, and it was found that a semantic task activates V1 more than a lower-level phonological task (Burton et al., 2003), verb generation and memory retrieval activated it more than Braille reading (Amedi et al., 2003), and the BOLD signal was modulated by phonological information, lexical semantic information, and sentence-level combinatorial structure (Bedny et al., 2011a). Furthermore, the activation level of the primary visual cortex correlated to the memory performance in individual subjects (Amedi et al., 2003; Raz et al., 2005), and TMS interference to the occipital pole of congenitally blind people caused interruptions to a verb-generation task (Amedi et al., 2004), suggesting a causal link between early visual cortex activity and successful performance on such tasks. The surprising “task switching” of the primary visual cortex has been suggested to result from the organizational-driving balance between the bottom-up and top-down connectivity in the absence of vision, a model termed the "inverted hierarchy model" (Amedi et al., 2003; Buchel, 2003). In the congenitally blind, visual thalamic connections to the primary visual cortex undergo partial atrophy (Noppeney et al., 2005; Shimony et al., 2006) due to the lack of visual input. In contrast, temporal and parietal lobe function feedback connectivity can have a greater effect on the organization of areas which are normally driven by bottom-up processing, and occupy the functional 'void' left in the visual cortex. This does not imply that the anatomical architecture of cortico-cortical connections (Felleman and Van Essen, 1991) is changed (in terms of inverted layer connectivity). Rather, it amplifies the importance of the existing feedback connections (from temporal-occipital regions; Rockland and Van Hoesen, 1994, and perhaps also frontal regions; Noppeney et al., 2003) in determining the functional role of the posterior occipital cortex. While this hypothesis has not yet been thoroughly tested, both the theory and the findings it attempts to explain pose an important question to the consistency of task-retention in extreme cases of abnormal brain development. In this context, it may also be that training to “see” using

SSDs may also modify the roles of these areas, and their preference for higher cognitive tasks. It will be interesting for future studies to test whether the heavy usage of SSDs and the potential plasticity it may elicit could affect the early visual cortex's responsiveness and selectively for such high order functions, and its accompanying behavioral compensatory abilities (e.g. visual training may in fact harm the superior memory abilities of the blind).

An additional question pertains to the ability to extrapolate the computation of certain visual operators to other modalities. Do all the visual properties have parallels in other modalities, or are some unique to vision and constitute what we perceive as visual qualia? For example, is there an auditory or haptic computation which in any way resembles hue perception? And if not, what does the "hue perception module" do in the absence of vision? In other words, what happens when a congenitally blind person learns to discriminate between colors when he never had a visual experience of color? Although these question may appear more philosophical than practical, it may be that the way to test them will soon become available through new SSDs that also convey color information (Levy-Tzedek et al., 2012), which may enable the study of the brains of congenitally blind people as they perceive color through a SSD.

Therefore, while our findings and those of other groups surveyed above support preserved task selectivity in the blind, it remains unclear whether such task-selective and sensory-modality independence characterizes the entire cortex or if it is limited to only a subset of higher order associative areas, whose tasks are more readily replicable using the non-visual modalities.

4.6 Implications for visual rehabilitation using SSDs

Our findings have bearings on the field of visual rehabilitation in two important ways. The first is the usefulness and feasibility of using SSDs that afford non-trivial visual abilities in the blind. The second is the implications of the metamodal theory, which is greatly supported by our findings, as concerns visual rehabilitation following long-lasting and even congenital blindness.

In terms of behavioral abilities, we have shown that using a specific high-resolution SSD along with a dedicated, structured training paradigm can result in several milestones that are not possible using other instruments: a high visual acuity (much higher than possible using any other approach), and perhaps in part resulting from this, the ability to conduct multiple visual tasks, such as recognition and categorization of real-life object images. Furthermore, our SSD trainees were able to perform other visual tasks which can only be reported anecdotally since they are currently being assessed (although the participants were all successful on these tasks as part of the training protocol). These include the ability to read letters and words (up to 5 letters, which can be further sequenced to form longer words or sentences), recognize the vantage point of various objects such as images of houses and faces, segment images which contain two overlapping or non-overlapping shapes appropriately, and identify emotional facial expressions such as smiles, frowns and a surprised expression.

Although these abilities seem trivial using normal vision, they are both more complex than what was previously believed following visual rehabilitation, and especially in the absence of visual experience. For example, in a few rare cases of surgical sight rehabilitation, the ability to segment a visual scene into separate objects was found deficient not only following a short period of sight (1-3 months) but also following long-term visual exposure of up to 10-18 months. The ability to segment simple 2-dimensional shapes overlapping geometric shapes such as circles and triangles improved, but some of these disabilities, especially for 3-dimensional objects persisted following extensive long-term constant visual experience (Ostrovsky et al., 2009). For example, Ostrovsky and colleagues reported that the visually-restored patient's segmentation was "driven by low-level image attributes; they pointed to regions of different hues and luminances as distinct objects. This approach greatly oversegmented the images and partitioned them into meaningless regions, which would be unstable across different views and uninformative regarding object identity". In contrast, our SSD trainees were able to accurately segment and perceive 3-D objects in their environment and were capable of figure-ground segregation.

Similarly, the ability to understand the vantage point of 3-dimensional shapes is striking. Although it was suggested that blind people can understand the vantage point of (haptic) drawings of a complex scene (Heller and Kennedy, 1990; Heller et al., 1995), and in some anecdotal cases congenitally blind people were even able to produce 2D drawings conveying 3D objects involving the same techniques used by sighted painters (Kennedy and Igor, 2003; Kennedy and Juricevic, 2006a, b), such abilities are not insignificant, as congenitally blind people often fail to understand that the perceived size of an object decreases with distance, and may not be familiar with many of the visual principles, such as linear perspectives, suggesting that the ability to practically implement visual knowledge is not innate (Arditi et al., 1988). We encountered this during our training procedure, when these principles had to be taught explicitly to the congenitally blind trainees and were not understood automatically. However, following training these abilities were generalized across images and real-life objects in all our blind participants, showing that these skills can indeed be learned later in life.

Although our study did not inspect SSD visual acuity or visual abilities of late-onset blind individuals, one might expect them to exhibit comparable performance, though possibly with some inferiority relative to the early-onset blind in terms of visual acuity, due to the latter's compensatory advantage in auditory processing (Collignon et al., 2009b; Gougoux et al., 2004; Hotting and Roder, 2009). In contrast, it is expected that their ability to learn to perceive complex visual scenes and apply visual perception principles should be significantly better due to their visual experience and their ability to apply visual imagery. Future studies should test this hypothesis more rigorously, even though we also trained a few sighted individuals in SSD-use (5 who completed the structured category training but did not continue to live-view training), who had no difficulty in learning to apply the SSD transformation algorithm or in extracting highly detailed information from soundscapes, supporting the usability of this system for late-onset blind.

In addition to the demonstration of multiple visual abilities in the congenitally blind using SSD, our neuroimaging findings and their support of the controversial task-selectivity or metamodal theory strengthen the notion that the problem of critical/sensitive periods may be less constraining to visual rehabilitation than assumed. Our findings are consistent with a recent combined humanitarian and scientific endeavor named "Project Prakash" (Sanskrit for light; www.ProjectPrakash.org; Mandavilli, 2006), which provides sight-restoring surgeries to congenitally blind children with curable ocular pathologies in rural India, the country with the largest population of blind children in the world. The behavioral abilities of these sight-restored children and adults show more promising behavioral results than earlier reports of sight restoration cases. In combination with our findings, this suggests that the widespread belief in a critical period for developing normal sight which was based on animals (Wiesel and Hubel, 1963) and humans (Ackroyd et al., 1974; Carlson et al., 1986; Fine et al., 2003; Lewis and Maurer, 2005; Ostrovsky et al., 2006; Ostrovsky et al., 2009) implying that the visual cortex of congenitally and early blind individuals would not be able to properly process vision if visual input is restored medically in adulthood, may require some modifications. Specifically, there are multiple differences between animal and human cases of visual deprivation, which may account for some of these discrepancies in different reports. For example, monocular visual deprivation studied in animals generates competition between inputs from the two eyes which influences development that does not exist in binocular cataract patients. Human cataract patients typically also have more light perception than fully eye-sutured animals, and their histories vary greatly.

These and other differences (reviewed in Sinha and Held, 2012) require more careful evaluation of the detail of the concept of critical and sensitive periods in visual development. This evaluation should take into consideration not only the specific visual deprivation history of each patient (residual light perception, age at the onset of visual deprivation and at its end, binocular or monocular difficulties as well as more psychological motivational effects; Carlson et al., 1986) but also the different visual tasks and abilities which are affected. For example, motion perception seems to return nearly at once following sight restoration (Ackroyd et al., 1974; Fine et al., 2003; Lewis and Maurer, 2005), while higher-order object recognition tasks, face discrimination etc. take longer and may not recover altogether (Fine et al., 2003; Geldart et al., 2002; Lewis and Maurer, 2005; Šikl et al., 2013; Sinha, 2003). Moreover, the late onset blind tend to apply different strategies for learning to associate the new visual input with their understanding of the world, and may, for example, learn to identify visual objects based on their already known haptic properties (although interestingly this does not happen immediately in the congenitally blind; Held et al., 2011; Held et al., 2008), and may also compensate for their visual deficiencies in complex shape recognition by taking advantage of a simple differentiating feature; e.g. telling people apart not by their faces but by their hair length or height (Kurson, 2007). Our findings contribute to this growing body of knowledge by showing that after several dozen hours of training, even in adulthood, some behavioral abilities and even visual cortex functional selectivities may be found in the congenitally blind, without any (even transient) visual experience. If this hypothesis of the highly flexible task-oriented sensory-independent brain applies, even the absence of visual experience should not completely restrict proper task specialization of the visual system, despite its recruitment for various functions in the blind, and the visual cortex of the blind may still retain some of its functional properties using other sensory modalities. These and the other recent sight restoration cases (although typically not from full blindness) are very encouraging with regards to the potential of visual rehabilitation.

While we may not know what role the training protocol played in the recovery or existence of the functional selectivities of the visual cortex (as detailed above, the metamodal theory does not require visual experience per-se, and our neuroimaging experiments took place following relatively short training periods; see section 4.3), our experience has been that the recovery of visual skills themselves using the SSD did require explicit teaching and may not have been achieved by SSD-visual exposure alone. This is in line with the emphasis placed on training and rehabilitation also in cochlear implant patients (Geers, 2006). Furthermore, similar findings have been found for surgical visual rehabilitation, as segmentation of 2-dimensional objects was reported to improve following a combination of visual experience and training in identifying shape from motion (Ostrovsky et al., 2009). Some additional recent support for the effectiveness of adult training in overcoming developmental visual impairments comes from recent studies of amblyopia, in which deficits were considered permanent unless treated by the age of seven. Recent studies show that combined treatment which includes visual training (along with patching of the nonamblyopic eye) can trigger adult plasticity and greatly improve the perceptual outcome, thus re-opening the sensitive period for plasticity (Bavelier et al., 2010; Maurer and Hensch, 2012). We suggest that in cases of more profound blindness this rehabilitation may involve, for example, learning to process complex images using SSDs, as done here, or using the SSD as a stand-alone sensory aid.

Therefore, SSDs may be beneficial in restoring high-resolution functional vision at very low cost (the vOICe software is free to blind users courtesy of its inventor, Dr. Meijer; the setup costs approximately $200 or much less if utilized through existing android cellphones). The factor of price may prove important to the vast majority of the world’s visually impaired population, amounting to tens of millions of individuals worldwide, who reside in developing countries (WHO, 2009) and are unlikely to benefit in the near future from expensive medical equipment (e.g. $100,000 for a retinal implant). In fact, even in developed countries not all types of blindness will be treatable in the coming years using prostheses, as these implants currently depend upon the existence of intact retinal ganglion cells, which characterize only some (such as age-related macular degeneration and retinitis pigmentosa) but not all blindness etiologies (Weiland et al., 2011).

Despite these advantages, it is important to note that SSDs and specifically the vOICe used here also have some limitations. First, its temporal resolution, while modifiable by the user to some extent, is far lower than that of natural vision. Each image is translated to a soundscape which spans between 0.5 to several seconds. Furthermore, perceiving what is in the soundscape may take even longer, depending on the “visual expertise” (which improves with training, as was done here) and the detail of the image. Thus, the vOICe SSD, as a stand-alone device, may not be a sufficient visual replacement for certain everyday circumstances (e.g. crossing the street). Another disadvantage is the potential masking of other environmental sounds while using the device, and its potential cognitive load. At least during training, the perception of soundscape images is not automatic and requires some level of attention, which is both demanding and potentially distracting. While it is our experience that our study participants could process external auditory cues during “seeing with sounds”, carry out a conversation etc., it remains to be tested methodologically if the SSD does not interfere with normal auditory processing of the surroundings, which is especially critical for the blind. Psychological and social factors, such as reluctance to try new devices might play an additional role in the limited adoption of SSDs. Last but not least, SSDs do not generate visual qualia, the sensation of sight, which is coveted by many blind people (although visual sensation may occasionally be spontaneously created by synesthesia from the SSD input; Ortiz et al., 2011; Ward and Meijer, 2009). Several of these drawbacks can be mitigated by combining the use of the visual-to-auditory SSD with other devices. For example, a combination of a tactile SSD such as the Brainport, (the visual-to-tactile SSD), which has a very high refresh rate (over 20 Hz) but lower spatial resolution (400 electrodes) may be beneficial.

Moreover, SSDs may also be beneficially used as a complement to visual prostheses or other novel medical advances (detailed in section 1.1.1) in developed countries (and later in the rest of the world). SSDs may be used for instance before a retinal prosthesis implantation, to reintroduce visual information to the visual cortex after years or life-long blindness, by addressing and strengthening the preserved “visual” task selectivities of the occipital cortex of the blind, and to teach visual processing principles (such as visual monocular depth cues) that were not in use for extended periods prior to the operation. This training might be important not only for understanding high-acuity and holistic vision again based on a smaller number of pixels (as provided by retinal prostheses, at least currently), but also to awaken the ‘visual’ system to performing its original tasks in the visual context. SSDs can also be used post- surgically, to supplement the visual qualia and higher temporal resolution of the visual prosthesis, by providing parallel explanatory "sensory interpreter" input to the visual signal arriving from the foreign invasive device (the early-onset blind may otherwise find it difficult to interpret vision; Fine et al., 2003; Gregory, 2003). At a later stage the SSD can be used to provide information beyond the maximal capabilities of the prostheses, increasing both the resolution (as shown here in results section 4.1) and the visual field-of-view (which is also currently very limited in retinal prostheses). SSDs can also be used for visual perception enhancement in individuals who have impaired natural vision, either in terms of acuity (for example in cases of cataract) or reduced visual field (such as that affecting retinitis pigmentosa or glaucoma patients).

Thus, SSDs may make a significant contribution to sight restoration efforts regardless of the impairment etiology, both in the developed but also in the developing world.

4.7. Conclusions

In this thesis I presented several studies which support the usability of SSDs (following dedicated training) for visual rehabilitation, both in terms of providing a high-acuity percept and achieving complex visual skills. Using the SSD as an experimental tool, I also conducted a neuroimaging investigation of the functional organization of the visual cortex of congenitally blind adults, and showed that some aspects of visual cortex functional specialization are retained, or at least can develop, following SSD training in congenital blindness. This can be achieved even for atypical cross-modal information (visual-to-auditory transformation) learned in adulthood, making it conceivable to restore visual input and to ‘awaken’ the visual cortex also to vision. The existence of functional organization in the visual cortex of the congenitally blind provides important support to the controversial task-selective - metamodal theory which suggests that the brain may not be divided according to the sensory modalities which elicit it, but rather to task-oriented sensory-modality invariant operators which may develop properly even without visual experience.

5. References

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6. Appendix: Extensive Cochleotopic Mapping of Human Auditory Cortical Fields Obtained with Phase-Encoding fMRI

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Extensive Cochleotopic Mapping of Human Auditory Cortical Fields Obtained with Phase-Encoding fMRI

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Abstract

The primary sensory cortices are characterized by a topographical mapping of basic sensory features which is considered to deteriorate in higher-order areas in favor of complex sensory features. Recently, however, retinotopic maps were also discovered in the higher-order visual, parietal and prefrontal cortices. The discovery of these maps enabled the distinction between visual regions, clarified their function and hierarchical processing. Could such extension of topographical mapping to high-order processing regions apply to the auditory modality as well? This question has been studied previously in animal models but only sporadically in humans, whose anatomical and functional organization may differ from that of animals (e.g. unique verbal functions and Heschl's gyrus curvature). Here we applied fMRI spectral analysis to investigate the cochleotopic organization of the human cerebral cortex. We found multiple mirror-symmetric novel cochleotopic maps covering most of the core and high-order human auditory cortex, including regions considered non-cochleotopic, stretching all the way to the superior temporal sulcus. These maps suggest that topographical mapping persists well beyond the auditory core and belt, and that the mirror-symmetry of topographical preferences may be a fundamental principle across sensory modalities.

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Introduction

Vision, audition and touch are characterized by a topographical mapping of the sensory world onto the peripheral sensory epithelia (retinotopic, cochleotopic and somatotopic mapping), which is maintained along the pathway (e.g. thalamus and other brainstem nuclei) all the way into the primary sensory cortices. The prevalent view is that in higher-order sensory areas, such maps are gradually lost in favor of more complex or abstract representations. This view has recently been refined in the visual system [1,2,3], in which higher-order processing regions were shown to have clear retinotopic preferences in addition to their selectivity to complex visual features. For example, the parahippocampal place area (PPA) shows selectivity for place stimuli (such as pictures of houses) and a peripheral retinotopic eccentricity preference, and the fusiform face area (FFA) has a combined preference for faces stimuli and a foveal retinotopic eccentricity preference [2]. Recent studies by several groups showed that new spatial fields can be found not only in areas in the visual (occipital) cortex previously considered non-retinotopic [2] but even in the parietal and prefrontal cortices [3,4]. Both in early and higher-order areas, spatial-retinotopic mirror-symmetry reversal maps have proved to be extremely useful in defining the borders between visual areas (from V1 and V2 and up to V7/V8 and the new fields in the parietal and prefrontal cortex) and the hierarchy of the visual system in general [5,6].

In contrast to the visual domain, relatively little is known about the cochleotopic (i.e. tonotopic) organization in the *human* auditory cortex in general and beyond the primary core areas in particular. The structural anatomical division of the auditory cortex had been very thoroughly studied [7,8,9] in human and non-human primates (and well as in non-primates). These studies have divided the temporal auditory cortex to multiple fields based on cytoarchitectonic and chemoarchitectonic markers, and showed that the auditory cortex may be divided [10,11,12,13,14,15,16] to a koniocortical core area and which was further extended and divided functionally and anatomically [10,13,17,18,19] to three core areas, A1, R, and RT (and which may be further anatomically divided to multiple fields [20]). Surrounding it is a belt of smaller areas in the medial (also referred to as root [20]) and lateral aspects of the core (divided in primates and humans to at least 7 or 8 fields [15,21]), an additional area of lateral parabelt regions (anatomically divided to a caudal and a rostral field [15]), and other high-order auditory fields extending to the caudal temporal plane and parietal operculum [10,22,23,24]. These structures have been identified in non-human and human primates, and while they somewhat vary in position, size and architectonic appearance across taxonomic groups (such as relatively larger volume of the core relative to the belt in humans, but not in monkeys, and in enlargement of area Tpt in the human [20,23]), they can nonetheless be identified as homologous structures [16,20,25]. Furthermore, auditory processing continues to the frontal and parietal cortices, in a highly specified connectivity pattern [26,27,28], in which, for example, the dorsolateral prefrontal cortex is accessed by the caudal aspect of the auditory belt and parabelt (also through connectivity to posterior parietal cortex) and the rostral and ventral frontal lobe are connected to the anterior belt and parabelt region. However, despite extensive years of research, the functional division of this vast auditory network has been lacking (especially in humans), in part due to incomplete mapping of functional markers such as cochleotopic borders between these areas [29]. Studies in primates [7,16,17,18,19,21,30] and other mammals [31,32,33] have investigated areas somewhat beyond the auditory core, and defined multiple cochleotopic maps in the auditory belt. Specifically, it was demonstrated that the core areas A1, R and RT contain cochleotopic mapping, with a low-frequency border dividing areas A1 and R, and a high-frequency border dividing R and RT. The belt fields seem to show cochleotopic gradients continuous with those of the core, apart from area CL, which shows a distinct cochleotopic gradient, generating an additional mediolateral high-to-low frequency gradient posterior to A1 [34]. In humans only several cochleotopic mapping works have been conducted, and these suggest that topographic mirror symmetry organization is present in the core auditory areas around Heschl's gyrus (thus referring to human homologues of areas A1 and R [8,35,36,37,38,39]), and several studies [37,40,41] also looked beyond the auditory core to larger parts of the superior temporal plane, and reported frequency-dependent response regions, or cochleotopic gradients which may correspond to some of the auditory belt areas. However, these studies (both in humans and non-humans) only examined a limited part of the auditory cortex which did not cover the entire higher-order auditory areas in the temporal lobe (for example the parabelt areas) or beyond it.

Outside the auditory core, and even more so outside the auditory belt, in the parabelt regions and in auditory regions outside the temporal lobe, fidelity to cochleotopic organization is thought to deteriorate greatly [29,42]. This makes it much more difficult to define the borders and number of these auditory regions in humans, and thus also to distinguish them functionally, and to compare findings across groups (especially when compared to the very well defined human visual retinotopic areas). These regions are, in general, considered higher-order auditory areas, and are thought to be driven mostly by more complex auditory features and stimuli (both in humans and in other mammals) such as spatial location, source identity, pitch and melody and different types of object sounds, species-specific vocalizations, or speech rather than by pure tones [43,44,45]. Recent studies have indicated that even A1 does not only show frequency sensitivity but also partakes in relatively complex analyses such as selective responses to combinations of auditory attributes or auditory objects [46], and that belt areas may show evidence of multisensory integration [47]. However, it is important to note that these options (cochleotopic or more complex), preferences or receptive fields characteristics are not mutually exclusive, just as visual object related areas can show both object category and retinotopic preferences (e.g. face and foveal in FFA and places and peripheral in PPA). Taken together, these pieces of information paint a somewhat limited picture of human auditory cortical processing in relation to its cochleotopic or tonotopic organization (as noted in several recent reviews, e.g. [29,42]). Better understanding of cochleotopic organization of human auditory cortex (especially if organized in mirror symmetry organization) can greatly help in parceling of the high-order auditory cortex into functional units, which can then be integrated in a more general model of the auditory system within the framework of current developing putative models (e.g. the two processing streams model for different auditory functions [7,26,48,49,50,51]).

Here, we set out to study the cochleotopic preferences of the entire human cerebral cortex, in order to answer the following questions: 1. how many cochleotopic maps are there in the human cerebral cortex? 2. Is cochleotopic preference indeed limited to the auditory core and belt areas or does it extend to the higher-order parabelt regions around the superior temporal sulcus, and even beyond them to higher order auditory areas? 3. Are these areas arranged in a mirror-symmetry organization, enabling their putative parceling to auditory fields, similarly to the visual cortex? 4. If so, can we generalize the large-scale governing principles of organization regarding multiple topographical representations which are sensory modality invariant? Are the entire visual **and** auditory cortices, in addition to other functional sensory specificities, fundamentally topographical in nature?

Using functional magnetic resonance imaging (fMRI) we studied ten subjects while they listened to a logarithmically rising tone chirp spanning the range of 250–4,000 Hz in 18 seconds (**Fig. 1A**). We then applied an in-house modified version of spectral analysis techniques [32,52,53] to study the frequency sensitivity of the human cerebral cortex.

Materials and Methods

Subjects

Ten healthy subjects (4 females) aged 24–35 participated in the experiment. The Tel–Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject.

Stimuli and experimental protocol

For the main experiment (Exp. 1) subjects were presented with a rising logarithmic tone chirp spanning the range of 250–4,000 Hz in 18 seconds, followed by a 12 second baseline period with no auditory stimulation. Tones in higher and lower frequencies (though perceivable by humans) were not used in the current setting to avoid distortion of high frequency sounds inside the scanner and due to other limitations of our system. The chirp onset was ramped using a 20 ms logarithmically rising envelope to avoid an attention bias to the loud sound onset and widespread and non-specific auditory activation. This was another advantage (in addition to greater sensitivity for continuous relative mapping, see below) in using continuous stimulation rather than short chirps (separated by silent periods) each in a different frequency band. This 30 second cycle was repeated 15 times, resulting in a presentation frequency of 0.033 Hz. In addition there was a 30 second period of silence before and after the 15 cycles of auditory stimuli (**Fig. 1A**), used as baseline measurements.

Half the subjects were also scanned again in an additional control experiment (Exp. 2), in which the frequency modulation was in the opposite direction (i.e. beginning in 4 KHz and ending in 250 Hz, falling chirp), to preclude apparent tonotopic gradients resulting from the direction of the frequency modulation. In order to inspect test-retest reliability of our results, a subgroup of four subjects was scanned again on the main experiment in a different day (Exp. 3).

Subjects wore blindfolds and had their eyes shut for the duration of the scan, in order to focus on the auditory stimulus, and were instructed to listen carefully to the sounds. The stimulus was

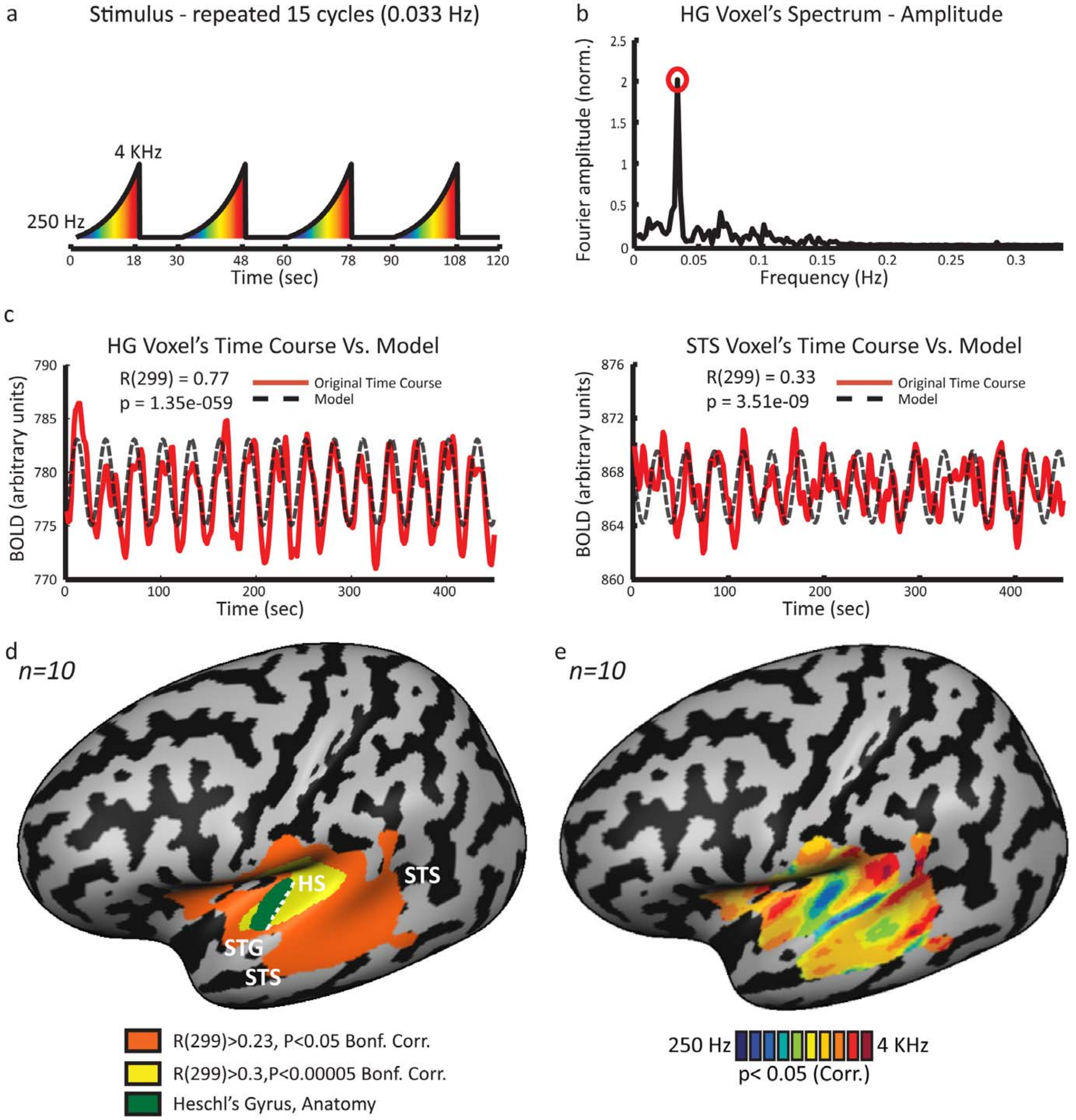

Figure 1. Experimental design and spectral analysis. A. Stimulus – the subjects heard a dynamic ascending pure tone chirp, which repeated 15 times (stimulus repetition frequency 0.033 Hz). **B.** Each voxel's time-course was Fourier transformed. Presented here is the normalized amplitude of the spectrum 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. For a presentation of Pearson's R values in a horizontal slice view see **Fig. S2C**. HS – Heschl's sulcus, STG – Superior temporal gyrus, STS – Superior temporal sulcus. **E.** Group (Session 1, *n = 10*) relative frequency preference map is presented in a lateral view of the partly inflated left 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.

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presented to both ears using fMRI-compatible electrodynamic headphones (MR-Confon, Germany), specifically designed to reduce scanner noise, which were needed as the scanner noise is not equal across auditory frequencies [54] and may add biases in cochleotopic mapping. However, measures were taken to prevent the stimulus being masked by the scanner noise. Each subject heard the basic chirp inside the scanner prior to the experiment, with all insulations in place and while the scanner was working. This was done in order to make sure subjects could hear the entire chirp clearly on top of the scanner noise. Stimulus intensity was set individually at levels between 86–89 dB SPL in order to optimize hearing on top of scanner noise. The intensity was kept constant across frequencies, so overall RMS level was equal to the individual dB SPL. The continuous nature of the auditory stimulus and our data analysis techniques are not optimal for sparse sampling approaches to data acquisition, so the stimulus had to exceed scanner noise (see also above, due to non-specific auditory activation in sparse presentation). The limitations of the auditory devices in the noisy scanner environment constituted a restriction on the cochleotopic mapping. Auditory neurons tend to show frequency selectivity only near the perceptual threshold, while at relatively high sound intensities auditory filters are much broader [55], and show more moderate frequency sensitivity. However, due to the advantages of using a continuous stimulus (which, at least in retinotopy, greatly increases the sensitivity of retinotopic mapping), and since higher order auditory areas are more sensitive to chirps (see below), we chose to present the auditory chirp well above the individual hearing threshold. Additionally, presenting the stimuli at high intensities had the advantage of maximally activating the entire auditory cortex, including non-core regions which are not strongly driven by tones [34,45,56], but may still show widely-tuned frequency selectivity [30,57], and areas responsive to threshold best frequencies higher than 4 KHz. This is an additional advantage to spectral analysis, which compares the auditory response to a wide cosine wave, supporting the inclusion and inspection of widely-tuned neuronal populations, as opposed to previously used GLM approaches. However, it is possible that in future studies using lower-intensity stimuli further mapping might be more crisp and accurate. Thus, the several novel mirror symmetry cochleotopic maps reported here (see results) might even be an underestimate of the total number of topographical cochleotopic areas in the cerebral cortex.

Functional MRI acquisition

The BOLD fMRI measurements were obtained in a whole-body, 3–T Magnetom Trio scanner (Siemens, Germany). The fMRI protocols were based on multi-slice gradient echoplanar imaging (EPI) and a standard head coil. The functional data were collected under the following timing parameters: TR = 1.5 s (relatively short TR to better fit the temporal resolution needed for the phase-locking Fourier approach used here), TE = 30 ms, FA = 70°, imaging matrix = 80×80, FOV = 24×24 cm (i.e. in-plane resolution of 3 mm). 22 slices with slice thickness = 4.5 mm and 0.5 mm gap were oriented in the axial position, for complete coverage of the whole cortex. We chose to scan the entire brain despite the tradeoff with scan resolution so as to map cochleotopic fields beyond the well-known areas in superior temporal plane, both in higher-order regions of the temporal auditory cortex, and outside the temporal lobe, similar to the visually-topographic maps found in the parietal and frontal lobes [3,4].

3D recording and cortex reconstruction

Separate 3D recordings were used for coregistration and surface reconstruction. High resolution 3D anatomical volumes were collected using T1-weighted images using a 3D-turbo field echo (TFE) T1-weighted sequence (equivalent to MP-RAGE). Typical parameters were: Field of View (FOV) 23 cm (RL)×23 cm (VD)×17 cm (AP); Foldover- axis: RL, data matrix: $160 \times 160 \times 144$ zero-filled to 256 in all directions (approx 1 mm isovoxel native data), TR/TE = 9 ms/6 ms, flip angle = 8°.

Group results were superimposed on a cortical reconstruction of the standard MNI (Montreal Neurological Institute) brain, which was transformed to Talairach coordinates [58]. Cortical reconstruction included the segmentation of the white matter using a grow-region function embedded in the Brain Voyager QX 1.9.10 software package (Brain Innovation, Maastricht, Netherlands). The cortical surface was then inflated to expose the hidden sulci.

Data Analysis

We analyzed the data in our experiments using several complementary methods of analysis. These included individual subject analyses to verify the between-subject between-scans repeatability of the results, and group analyses to extend the findings to the population level. In individual subjects we examined the individual spectral maps (see the details of this analysis below in section *I. Spectral and linear correlation analysis*), as well as individual cross-correlation (section *III. Cross correlation analysis*) and raw time-course event-related averaging analysis (section *V. General Linear Model analysis*). For the group-level analyses, we looked at the group results in the spectral maps (section *II. Group analysis*), in a cross-correlation analysis (section *III. Cross correlation analysis*) in GLM random effect maps and in raw time-course event-related averaging analyses (section ***V.** General Linear Model analysis*). Additionally, in order to further assess the test-retest reliability of our results and avoid stimulus order confounds, we compared the results obtained in the main experiment (Exp. 1) with those of the two control experiments (Exp. 2–3) via spectral maps, cross-correlation, GLM and time-course analysis, and additionally applied an objective quantitative similarity analysis (section *IV. Map alignment measure*).

Prior to these extensive analyses, preprocessing data analysis was performed using the Brain Voyager QX 1.9.10 software package. This involved removal of the first eight images (during the first baseline rest condition) because of non-steady state magnetization. Functional MRI data preprocessing also included head motion correction, slice scan time correction and high-pass filtering (cutoff frequency: 3 cycles/scan) using temporal smoothing in the frequency domain to remove drifts and to improve the signal to noise ratio. All data included in the study did not exceed motion of 2 mm in any given axis, nor did it have spike-like motion of more than 1 mm in any direction. Functional and anatomical data sets for each subject were aligned and fit to standardized Talairach space [58]. General Linear Model Analysis and cross-correlation analysis were also conducted using the Brain Voyager QX 1.9.10 software package (for details see below). All additional analyses were conducted using analysis code developed in the lab on MATLAB (MathWorks, Natick, MA) and then imported back onto Brain Voyager to display on the Talairach normalized volume anatomical recording of the MNI brain or individual brain, or on the inflated MNI cortical surfaces.

Data Analysis I. Spectral and linear correlation analysis

Following standard retinotopy procedures [52,53,59,60] and auditory mapping in mammals [32,61], we applied Fourier analysis to the auditory responses locked to the stimulus repetition frequency (with some modifications, see details below and in **Fig. 1B**). Prior to frequency analysis, time-courses were de-trended to remove mean and linear drifts. The complex Fourier at the repetition frequency f_{rep} is denoted by:

$$R\left(f_{rep}\right) \equiv a\left(f_{rep}\right) \cdot e^{i \cdot \varphi\left(f_{rep}\right)} \qquad (1)$$

where $a\left(f_{rep}\right)$ represents the amplitude and $\varphi\left(f_{rep}\right)$ the phase, and calculated by:

$$F\left(f_{rep}\right) = \sum_{k=1}^{N} TC_k \cdot e^{-2\pi i\left(k \cdot f_{rep}\right)} \qquad (2)$$

where TC represents the sample time-course, and N is the number of sampled time points (300).

Following Engel and colleagues [52], both amplitude and phase parameters were used to construct a pure cosine serving as a model of the activation (**Fig. 1C,D, *Eq. 3***). A Pearson correlation coefficient was then calculated between the model and the original time-course. This procedure yielded a correlation coefficient for each voxel. This correlation coefficient can also be written as a normalized Fourier coefficient:

$$Model_{frep} \equiv a\left(f_{rep}\right) \cdot \cos\left(2\pi f_{rep} \cdot t + \varphi\left(f_{rep}\right)\right) \qquad (3)$$

$$R\left(f_{rep}\right) \equiv \sqrt{\frac{TC \cdot Model_{frep}}{\|TC\| \cdot \left\|Model_{frep}\right\|}} = \frac{a\left(f_{rep}\right)}{\sqrt{\sum_{k=1}^{N} a\left(f_k\right)^2}} \qquad (4)$$

The correlation coefficient was used as a direct measure of the voxel's response to the auditory stimulus. The correlation coefficient (R) was transformed ($\frac{R \cdot \sqrt{N-2}}{1-R^2}$) and used as t statistic with N−2 degrees of freedom (in our case N = 300), to calculate, independently for each voxel, the significance of the cortical response to the auditory stimulus.

In regions showing high correlation to the stimulus repetition frequency, the phase value was extracted from the complex coefficient (**Eq. 1**) according to:

$$\varphi_{frep} = \arctan\left(\frac{\mathrm{Re}\left(F\left(f_{rep}\right)\right)}{\mathrm{Im}\left(F\left(f_{rep}\right)\right)}\right) \qquad (5)$$

The phase corresponded to the latency of the voxel's response to the chirp, which, if each voxel has tonal selectivity (resulting from the tuning curves of the neurons in that voxel), should correspond to the preferred tone (auditory frequency) of that voxel. Phase values were distributed between −π and π, and were linearly transformed to range between 0 and 30, representing time points in each stimulus cycle. Due to the time delay of the hemodynamic response, the phase code does not temporally overlap with the stimulus presentation time. The phase onset of the response detected in the anatomically defined Heschl's gyrus (as well as its bordering sulci; at an average of 6.3±1.6 seconds after stimulus onset, in accordance with standard hemodynamic delay [62]) was considered to represent the response to a tone frequency of 250 Hz, which was the first frequency in the chirp. Similarly, the latest response (last preferred phase) observed in Heschl's gyrus surroundings (an average of 23.76±2.5 seconds after stimulus onset) was assumed to correspond to a tone frequency of approximately 4 KHz, the last tone frequency presented. Latencies between the first and last responses were interpreted as deriving from intermediate tone frequencies progressing from lower to higher frequencies (note that we do not intend to define the exact best frequency of each voxel, but rather the relative preference to a tone range, be it high, medium or low frequency range). This resulted in an individual response range, cropped according to the individual onset and offset of hemodynamic delay in responses of the auditory cortex. The average hemodynamic response duration for the group was 17.46 seconds, matching the stimulus duration (18 second), thus verifying the validity of the response ranges. These values constructed the phase code corresponding to the relative preferred tone frequency of each voxel, and resulted in individual phase code maps which correspond to individual relative frequency preference maps. While the latency could potentially also signify a lagged response due to intracortical processing in higher-order auditory cortex regions, the entire analysis of an auditory stimulus in the cerebral cortex would not typically require more than a second (for example see [48]); thus it is unlikely to manifest in belated responses in the time scale of many seconds, such as the length of the auditory stimulus. Moreover, should an entire region receive the information at a later time without having an inner cochleotopic mapping, no difference in tone sensitivity should be seen within this region.

Data Analysis II. Group analysis

Single subject correlation coefficient maps were spatially smoothed with a three dimensional 6 mm half width Gaussian in order to reduce inter-subject anatomical variability, and then averaged to create a group averaged correlation coefficient map. The average correlation coefficient map was statistically assessed in fixed effect model analysis. Specifically, in the group results, voxels that were characterized with high correlation coefficients across subjects also demonstrated high between- subject variability, compared with voxels with low correlation coefficient values. This was due to an uneven distribution between zero and one of correlation coefficients, making between-subject analyses (similar to random effect analysis in GLM, which was applied as a supplementary analysis, see below) not appropriate in our case. Voxels whose correlation coefficient satisfied a predetermined statistical threshold were chosen as a mask, and the group average phase values were computed within that mask. Due to differences in hemodynamic delay between subjects, the response range was different for different subjects. In order to normalize the response range across subjects, average initial response and final response points were calculated (as detailed above) and each subject's phase code was linearly transformed to range between them. Individual subject spectral analysis is presented at a significance threshold of $p < 0.05$. Significance levels were calculated taking into account the probability of a false detection for any given cluster [63], thereby correcting for multiple comparisons across all voxels. For group analysis, the native resolution transformed phase maps were spatially smoothed with a three dimensional, 4 mm half width Gaussian, and averaged to create a mean phase map. These maps' response range was narrowed because of the averaging procedure, and was rescaled in the same manner as the single subject maps, according to primary auditory cortex initial and final phase. This procedure yielded group phase maps that only display voxels with a phase within the group response range (phase code), masked to be displayed only in voxels whose average correlation coefficient (R) values exceeded a predetermined statistical threshold of $p < 0.05$ strictly corrected for multiple comparisons using the Bonferroni correction according to the number of voxels in the cortex.

In order to account for the hemodynamic response delay directly, without the possible confound of the interpolation in the creation of response ranges, we also directly averaged the preliminary phase maps derived from chirps moving in opposite directions similarly to [52,53] who used the same approach in retinotopic studies (n = 5: rising chirp in Exp. 1 and falling chirp in Exp. 2). This averaging cancels the phase delays resulting from the hemodynamic response function (HRF), as the HRF is expected to delay the response in opposite directions in the two scans.

To further supplement phase analysis and to address possible general confounding factors, such as compensating for comparing the hemodynamic signal to cosine function (Fourier analysis), which differs from the delayed typical hemodynamic response function [64], we also conducted supplemental cross-correlation and General Linear Model analyses in both group level and single subject level (see below), as well as applied a statistical map alignment measure to quantitatively compare the results of the different analyses and experiments.

Data Analysis III. Cross correlation analysis

As a complementary analysis, we applied a standard cross-correlation analysis using the Brain Voyager QX 1.9.10 software package to the individual time-courses following preprocessing steps only. We used the predicted standard hemodynamic signal time-course for the first 1/12 of a stimulation cycle (1 TR, 1.5 seconds) and shifted this reference function successively in time (time steps corresponded to the recording time for one volume, TR). Sites activated at particular ranges of tones were identified through selection of the lag value that resulted in the highest cross-correlation value for a particular voxel. Individual subject cross-correlation analysis is presented at a significance threshold of $p<0.05$. Significance levels were calculated taking into account the probability of a false detection for any given cluster [63]. Group analysis was conducted on the averaged data of the individual subjects for each experiment.

Data Analysis IV. Map alignment measure

In order to quantify the compatibility between the different cochleotopic maps we used an alignment index introduced by Sereno and Huang [3]. This measure was used to compare the group phase maps, i.e. rising chirp, falling chirp and returning rising chirp group. We also used it to compare the replicability of tonotopic pattern across subjects. Alignment index was calculated voxel-wise, defined as

$$Alignment\_Index = 1 - \frac{|\Delta\phi|}{\pi}$$

Where $\Delta\phi$ is the difference between the phases of two voxels (in radians). This index is 1 when the phases are identical across the maps, and reaches 0 when the phases are opposite one another. The similarity of two maps can be therefore evaluated by comparing the distribution of its alignment indexes to that of random maps. If the maps are similar, alignment indexes will distributed with a sharp peak towards 1. Random maps indexes are distributed with linear increase towards 1 (see [3] for further details). Random distribution was marked on the histograms of the group maps alignment indexes with red line for comparison. We tested the diversion from random distribution statistically by using t-test between two groups to get a p value. When testing single subjects' maps replicability, a pair-wise comparison between each map pairs was conducted, resulting with a matrix of alignment indexes. Each was compared with random distribution, as well as the average of all indexes.

Data Analysis V. General Linear Model analysis

In order to assess the tone selectivity using an independent supplementary analysis, the continuous auditory stimulus was divided into low, medium and high frequency tones (250–1000 Hz, 1–2.25 KHz, 2.25–4 KHz; lasting 4 TRs or 6 seconds each) periods, which were used as conditions in a block design protocol. Predictors for a general linear model (GLM) were built by convolving the auditory conditions with a typical hemodynamic response function [64]. GLM maps present the contrast of each of these tone predictors compared to the other predictors (e.g. high frequency vs. low and medium frequency tones), at a $p<0.05$ threshold (corrected for multiple comparisons [63]). The average time-course of activation for individual subjects was sampled from peaks of iso-frequency bands, and averaged at the time of peak hemodynamic response (4.5–7.5 seconds after the frequency bin stimulus onset, TRs 3–5) to extract the average percent signal change. In the group analysis, across-subject statistics were calculated using a hierarchical random effects model [65] allowing for generalization of the results to the population level. The average time-course of activation was sampled and averaged to extract the average percent signal change. The standard error was also calculated across subjects and is displayed in the error bars. This analysis, though less optimal for continuous stimuli, serves as a way to acquire the **raw** averaged percent signal change and to illustrate the frequency preferences of iso-frequency bands, as determined by the phase code maps.

Results

In order to examine our results in different ways and validate them, we applied several complementary methods of analysis. These included individual subject analyses to verify the between-subject between-scans repeatability of the results, and group analyses to extend the findings to the population level. In individual subjects, we examined the individual phase maps, displayed both on the anatomical recording of each subject's auditory cortex and on the inflated cortical sheet, as well as individual cross-correlation and raw time-course analysis. For group-level analyses, we looked at the group results in the phase maps on the 3D brain recording, on the inflated cortical sheet, in a cross-correlation analysis, in GLM random effect map and averaged raw time-course analyses of the entire cortex. This helped us test how many cochleotopic maps there are in the human cerebral cortex within and outside the auditory core and belt areas and to examine the putative mirror-symmetry organization of these cochleotopic maps. Additionally, in order to further assess the test-retest reliability of our results and avoid stimulus order confounds, we also scanned a subgroup of the original subjects in a falling chirp control experiment (Exp. 2), and a subgroup of subjects in a second repetition of the main experiment (Exp. 3), and compared the results obtained via phase maps, cross-correlation, GLM and time-course analysis to that of the main experiment (Exp. 1).

For our main analysis method, we adapted spectral analysis ([52,53], see full description in methods section) to extract the correlation coefficient of each voxel's response to a model of the auditory stimulus repetition frequency and its phase (see **Fig. 1**). The correlation coefficient (R) was used as a statistic to calculate the significance of the cortical response to the auditory stimulus. The minimum significance level was set to $P<0.05$, strictly corrected for multiple comparisons using the Bonferroni correction. An area covering vast parts of the temporal lobe showed a highly significant correlation to the auditory stimulus repetition frequency, and the most strongly correlated area was located in the auditory core areas (Heschl's gyrus and its surroundings; **Fig. 1D, Figs. S1, S2C**). Each voxel within the responsive area was 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. 1**) of that voxel.

As our aim was to look for broad cochleotopic mapping in the entire human cortex, even outside the "traditional" auditory cochleotopic cortex within the temporal lobe, we initially inspected several regions which showed significant responses to our stimulation protocol; i.e. a highly significant correlation coefficient in all three experiments (**Fig. S1**). These regions included bilateral activation in the posterior-inferior frontal lobe, medial superior frontal gyrus\premotor cortex, precuneus, and a left inferior parietal cluster, regions sporadically reported previously to be involved in various auditory localization and recognition tasks [48,50,77,78]. However none of these regions showed a clear and consistent full cochleotopic arrangement across the experiments and between the subjects. Hence, we focused our attention on the temporal lobe, which showed robust, extensive and reliable responses, stretching all the way from Heschl's gyrus to the superior temporal sulcus.

The cochleotopic organization of the core auditory areas was highly replicable across individual subjects (see **Fig. S2A** for **unsmoothed** tone-preference maps of all 10 subjects) and highly consistent with previous studies. Most (9/10) single subjects clearly displayed a topographical mapping pattern of tone-preference shift from high-frequency tones to low-frequency tones and back along the superior temporal plane with Heschl's gyrus (HG) located within this mirror-symmetric large scale organization. This is highly consistent with the general pattern found in primates [30] and in recent neuroimaging studies in humans [35,38,40,41]. 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. This large scale cochleotopic organization pattern was present in both hemispheres (**Figs. 2, 3**). However, in the right hemisphere we found another putative anterior mirror-symmetry map resulting in a possible large scale organization of high-low-high-low (see **Fig. 3** for inflated and horizontal views, and the sagittal view in **Fig. S2B**). This additional map is also in general agreement with the organization of primate core areas [30], and may correspond to a human analogue of area RT. Some of our single subjects (6/10) also showed evidence of a medial-lateral cochleotopic gradient on medial HG (see **Fig. S2A**) [39,66]. However, this gradient was not as consistent as the large scale high-low-high frequency mirror-symmetric pattern (again consistent with human imaging findings [35,38,41]). This could be ascribed to a different of orientation of the gradients in humans (see discussion for details of the contemporary controversy in the matter) or to the high variability of the position and extent of the primary auditory cortex in relation to the location of HG [8,67]. Alternatively, this could be due to our limited resolution, a problem which could be resolved in future studies focusing on HG with higher spatial resolution and also possibly using higher-field scanners (for example, see [30], which used a 7-Tesla MRI scanner).

As observed in most individual subjects, group analysis of cochleotopic selectivity indeed showed large scale high-low-high frequency mirror- symmetric cochleotopic maps in the core auditory cortex of humans (**Figs. 1E, 2, 3, Fig. S2B**; see also **Movie S1** depicting the propagation of frequency sensitivity).

While the peak of the correlation to the auditory stimulation was located in the primary auditory cortex region, the significantly responsive area (**Fig. 1D**, **Fig. S2C**, $p<0.05$, Bonf. corrected) extended well beyond core areas all the way to parts of the superior temporal sulcus, and parts of the middle temporal gyrus, regions considered to be higher-order auditory and multisensory cortices responsive to complex sounds or even multisensory integration areas. A phase analysis of these areas revealed gradients between multiple bands of tone frequency selectivity (see **Figs. 1E, 2, 3** – on both cortical and volume views). These large-scale mirror-symmetric tone-selective bands extended 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 that there are additional maps extending as far as the middle temporal sulcus in the left hemisphere (see relative frequency preference map in **Figs. 2, 3** and in further analyses below; see also **Movie S1**). In order to assess the number and location of the possible auditory fields, we delineated (**Figs. 2, 3**, left upper panel) putative cochleotopic map borders according to preferences for the lowest and highest frequency tones which represent the mirror-symmetry flipping lines, and marked the approximate gradient seen between such flipping lines (marked in arrows and numbers in **Figs. 2, 3**, left middle panel). Despite the reliance on the tone extremities for the auditory field parceling, it is important to note that the entire stimulus tone range, with a gradual shift in the cortical preference, is represented in the mapping (e.g. **Movie S1** and note the middle tone frequencies in the GLM analysis below). These novel cochleotopic maps were also consistent across subjects with certain expected variability (**Figs. S3, S4**).

The direction of the frequency modulation could cause attention biases towards the stimulus onset or offset or other order effects and may also cause a percept of moving or looming objects [68]. Could some of the maps that appear to be cochleotopic actually result from stimuli order or inferred spatial information? To account for this possible confound, a subgroup of five subjects was scanned again in a control experiment comprised of a falling-tone chirp (Exp. 2). The group map of this control experiment is highly consistent with that of the experiment 1, both in single subjects and group level analysis (**Figs. S5, S6**), suggesting these confounds are unlikely. Additionally, following the classical retinotopic studies of Engel and Sereno [52,53], we averaged the phase maps of the two opposing chirp directions (Exp. 1 – rising chirp and Exp. 2 – falling chirp) to control for the hemodynamic response delay and any other possible confounds resulting from stimulus direction (**Fig. 4B,E**, $n=5$), replicating the main findings. Spectral map averaging was also performed for the entire group of subjects (while taking into account the individual variability of response onset), showing the same consistent cochleotopic gradients. These results are presented on a corresponding Talairach normalized brain of Brodmann areas (**Fig. S7**; [69]), confirming that the cochleotopic gradients presented here exceeded Brodmann areas 41 (primary auditory cortex) and 42, covered a substantial part of Brodmann area 22 (which corresponds in part to the auditory parabelt area [70]) and continued as far as Brodmann area 21, extending far beyond the known cochleotopic areas.

In order to verify this consistency quantitatively, the spectral maps of the rising-chirp group (Exp. 1) was tested for replicability with the falling-chirp group (Exp. 2; **Fig. S5**) and with the averaged results from Experiments 1 and 2 (**Fig. 4G**). Alignment indexes between the experiments were highly significant (**Fig. 4G**: between Exps. 1 and 2: right hemisphere 0.91 ± 0.1, $p<0.00001$, left hemisphere 0.9 ± 0.09, $p<0.00001$, between Exp.1 and the averaged Exps.1+2: right hemisphere 0.87 ± 0.2, $p<0.00001$, left hemisphere 0.87 ± 0.09, $p<0.00001$). Maps' similarity can also be

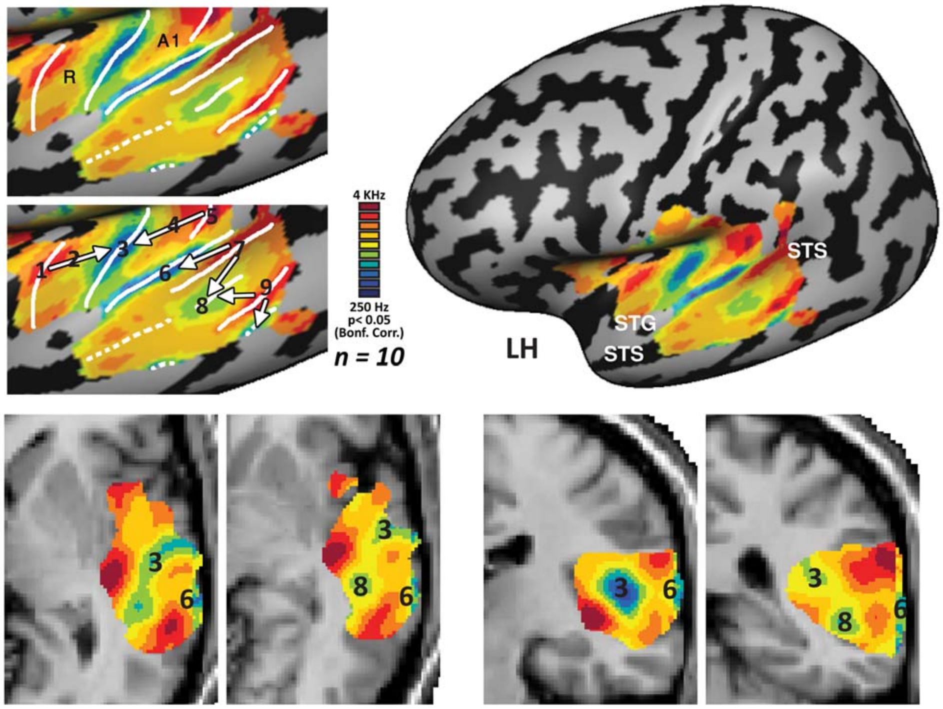

Figure 2. Multiple mirror-symmetric cochleotopic maps in the left hemisphere of the human auditory cortex. Group (Exp. 1, *n* = *10*) relative frequency preference map is presented in a lateral view of the inflated left cortical hemisphere of the standard MNI brain, exposing the entire cochleotopic organization of the multiple iso-frequency bands (STG – Superior temporal gyrus, STS – Superior temporal sulcus). On the left panels, the auditory cortex region is magnified, showing Exp. 1 relative frequency preference 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 between the homologues of A1 and R in the core auditory cortex, and between multiple additional cochleotopic fields. Numbers indicate points along the cochleotopic gradients (similar to those depicted in **Fig. 6**, from which raw time-courses of activation were sampled), with white arrows demonstrating the gradient direction in each filed. On the lower panels, the same gradients are depicted in volume views in horizontal (z = 2, −1), and coronal (y = −21, −32) slices, numbered similarly to the surface view (for demonstrative and orientation purposes only), to enable the identification of the same gradients in the three-dimensional based views.
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implied from the distribution of the alignment indexes (marked in black in **Fig.4G**). A peak towards index value of 1 implies high similarity between the maps, compared with linearly increase of random distribution of alignment indexes (in red line).

Moreover, to further validate the reliability of our results across scans, four of the ten subjects were scanned again (Exp. 3), a month following the first scan. The returning subject group results are also highly consistent with the maps from the original group (**Fig. 4C, F**, for single subject analysis see **Figs. S6, S8**). Alignment indexes of the test-retest comparison (**Fig. 4G**) were highly significant (right hemisphere 0.93±0.9, $p<0.00001$, left hemisphere 0.9±0.08, $p<0.00001$).

As the relative frequency preference maps of individual subjects (**Figs. S3, S4**) suggest, the pattern of these novel iso-frequency bands was also consistent across subjects for both hemispheres. The similarity of cochleotopic maps between subjects was tested with a pair wise alignment index (see methods). Each of the alignment indexes was found significantly different from random ($p>0.0001$, Bonferroni corrected for multiple comparisons), with average value of 0.81±0.075. The putative borders of all the new cochleotopic maps in the group (white lines in **Figs. 2, 3** left upper panel) are presented on the individual subjects' maps (**Figs. S3B, S4B**), further demonstrating the high similarity in the location and number of the maps at the single subject level. An additional view of the cochleotopic maps of four individual subjects on their anatomical recordings (**Fig. 5**, also see for more views in **Fig. S6**) also demonstrates the cochleotopic maps in extra-core temporal cortex, extending to the superior temporal gyrus and parts of the superior temporal sulcus.

To verify the results of the phase analysis (**Figs. 1E, 2, 3**) through complementary analyses methods, we conducted standard cross-correlation (an alternative method used for retinotopic mapping: e.g. [71,72]) and general linear model (GLM) analyses. Cross-correlation was used to compute the lags (in TR resolution units i.e. 1.5 sec) within a stimulus cycle at which each voxel correlated best to the frequency of stimulation (i.e. in cochleotopic mapping, its preferred tone). Cross-correlation maps of the averaged single-subject data was highly consistent with the spectral analysis maps, in all three experiments (**Fig. 4**, middle column), and proved consistency in single subject level (**Fig. 5**, extended at **Fig. S6**). The similarity of the cross-correlation analysis and the phase analysis (**Fig. 4G**) results confirms that the two analyses yielded statistically similar cochleotopic gradients (alignment index of 0.88±0.16 for both hemispheres, $p<0.00001$). GLM analysis was also used to independently assess the preferred tone of each voxel (though it is less optimal for the current design and generally less sensitive for topographical mapping, e.g. it is rarely used in retinotopic experiments). To compute this, the continuous auditory stimulation was divided into three separate equal intervals: low, medium and high frequencies. In each experiment, the activation elicited by each of the three intervals was contrasted to that of the other intervals, resulting in random effect GLM contrast maps (e.g. high vs. medium and low; etc. **Fig. 4**, right column). While these complementary analyses are statistically

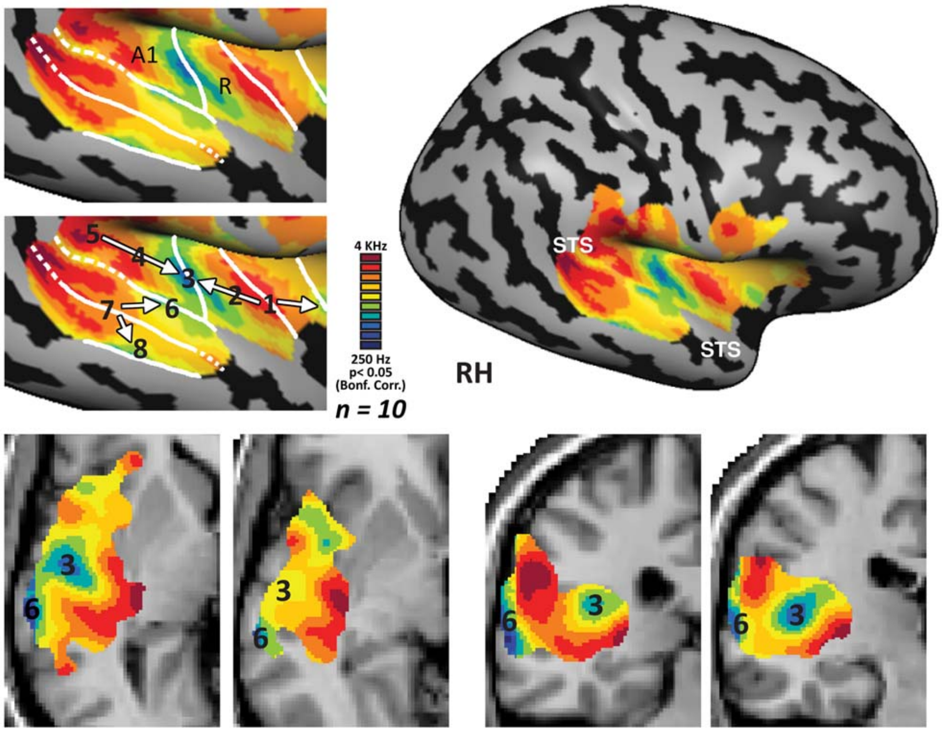

Figure 3. Multiple mirror-symmetric cochleotopic maps in the right hemisphere of the human auditory cortex. Group (Exp. 1, *n* = *10*) relative frequency preference map is presented in a lateral view of the inflated right cortical hemisphere of the standard MNI brain, exposing the entire cochleotopic organization of the multiple iso-frequency bands (STG – Superior temporal gyrus, STS – Superior temporal sulcus). On the left panels, the auditory cortex region is magnified, showing Exp. 1 relative frequency preference 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 between the homologues of A1 and R (and possibly, anterior to it, RT) in the core auditory cortex, and between multiple additional cochleotopic fields. Numbers indicate points along the cochleotopic gradients (similar to those depicted in **Fig. 6**, from which raw time-courses of activation were sampled), with white arrows demonstrating the gradient direction in each filed. On the lower panels, the same gradients are depicted in volume views in horizontal (z = 4, 0), and coronal (y = −28, −22) slices, numbered similarly to the surface view (for demonstrative and orientation purposes only), to enable the identification of the same gradients in the three-dimensional based views.
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weaker than the main spectral analysis technique, the same trends can be seen across analyses.

Additionally, we investigated the magnitude of activation assessed by the average percent BOLD signal change of the *raw time-courses of individual subjects* using random-effect GLM (**Fig. 6**). The raw time-course was sampled across the subjects from 5 points representing the mirror-symmetry flip axes of 3 iso-frequency bands seen in core areas, as well as two intermediary points (**Fig. 6B**, sampling points marked in **Fig. 6A** on the cortical view, with approximate marking of the same points on volume views), and from 3 additional points from the putative superior-to-inferior iso-frequency bands in the extra-core areas (**Fig. 6C,D**), and the average magnitude of activation for each frequency band was computed. The average activation for each point was highly consistent with the tone preference presented in the phase maps, thus confirming the reliability of our phase analysis in determining tone selectivity of both core and novel extra-core cochleotopic regions. Furthermore, the average response patterns were replicated in individual subjects (see averaged responses in **Figs. S3B, S4B**) and additionally was replicated across experiments in the falling-chirp experiment (Exp. 2, *n* = *5*; **Fig. 6B,D**) and across scanning days on the second scan (Exp. 3, *n* = *4*; **Fig. 6B,D**) using the same sampling points selected in the main experiment (Exp. 1), demonstrating the reliability of the cochleotopic maps reported here across subjects and scan days.

Discussion

Using spectral analysis fMRI, we showed that: 1. There may be as many as 6 cochleotopic maps in the human cerebral cortex: at least two core areas, corresponding to A1 and R (and their neighboring belt areas), and possibly RT, (see **Figs. 2, 3, Fig. S2**) and as many as 4 novel cochleotopic maps in the temporal cortex (see **Figs. 2, 3, 4, 6**, **Figs. S3, S4** and **Movie S1**). 2. Cochleotopic preference is by no means limited to the auditory core but rather extends to the higher-order auditory regions within the temporal lobe (as far as the STS/MTG, see **Figs. 2, 3**, **Figs. S3, S4, S7** and **Movie S1**). 3. Cochleotopic maps in high-order auditory areas are also arranged in a mirror-symmetry organization (see the borders of mirror symmetry drawn in **Figs. 2, 3**, **Figs. S3, S4** and **Movie S1**), which may help define and parcel the auditory cortex into distinct auditory fields (for example, as done in **Figs. 2, 3**, left upper panel). 4. It would appear that similar to the visual cortex, the auditory cortex (at least in the temporal lobe) is also fundamentally topographical in nature, which may suggest that this large-scale governing principle of organization is sensory modality invariant.

Previous work has provided evidence for the existence of cochleotopic mapping in core areas, probably the human homologues of areas A1 and R [35,38,41], as well as a thorough cochleotopic mapping of the surrounding belt areas in primates [16,17,18,19,21,30], including using fMRI in a high-field 7T

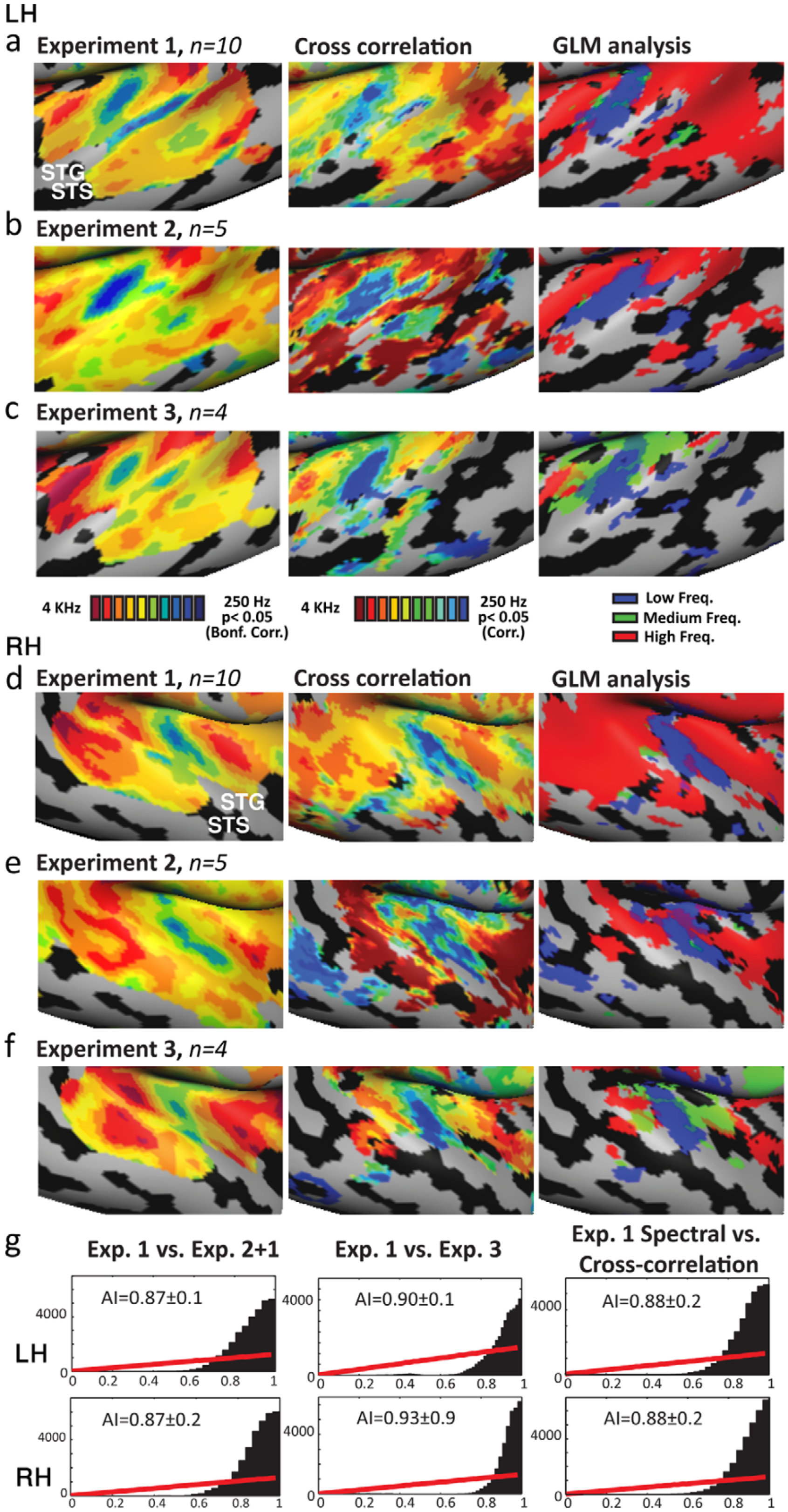

Figure 4. Consistency of the mirror-symmetric cochleotopic maps across experiments and analyses. A. (left hemisphere) and **D.** (right hemisphere) display, on the left column, auditory cortex relative frequency preference map magnification as seen in **Figs. 2** (LH) **and 3** (RH), showing the mirror- symmetric cochleotopic maps inspected using spectral analysis. In the middle column cross-correlation analysis for the averaged single-subject time-course is displayed, showing remarkably similar trends to that of the spectral analysis. On the right column, 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. **B.** (left hemisphere) and **E.** (right hemisphere) display cross-

correlation (middle) and GLM (right) analyses for Exp. 2 (*n* = *5*) in which the chirp was reversed (i.e. from high to low frequencies). Spectral analysis (left) is the averaged phase map of Exp. 2 with Exp. 1, thus fully controlling for the hemodynamic delay of both experiments ([52,53]; for the spectral maps of Exp. 2 alone see **Fig. S5**). The consistency of these results with the main experiment show that the auditory fields and cochleotopic gradients displayed for Exp. 1 do not result from the frequency modulation direction. **C.** (left hemisphere) and **F.** (right hemisphere) display spectral (left), cross-correlation (middle) and GLM (right) analyses for Exp. 3, in which a subgroup (*n* = *4*) of subjects was scanned again one month after the original scan, revealing 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. See also **Fig. S8** for further single subject analysis of this experiment. **G.** Similarity alignment histograms are presented for three main contrasts, between the main experiment (Exp. 1) and the two control experiments (Exps. 2 and 3) and between the spectral and cross-correlation analyses in Experiment 1, for both hemispheres. The distribution of each comparison's alignment indexes (between 0 and 1 in each comparison) show a sharp peak towards 1, demonstrating their significance, and differ significantly ($p<0.00001$ in all comparisons presented) from random maps indexes (marked on the histograms with red line for comparison). Therefore, the similarity indexes of the correspondence between the relative frequency preference maps across analyses and experiments support the high replicability of the cochleotopic maps.
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fMRI scanner [30]. Two studies [37,41] examined the cochleotopic mapping in humans along the superior temporal gyrus and showed that it may also extend, as is seen in primates, to the areas immediately surrounding the human auditory core, which may correspond to some of the belt areas. However, our study is the first to look for the cochleotopic mapping of the entire human cortex, a mapping which was enabled by the combination of a continuous chirp stimulus, spectral analysis (which reveals also widely-tuned responsive regions), and whole brain scanning. In addition to providing data from single subjects using unsmoothed data, our relatively large group of subjects allowed us to develop and apply group analysis that enabled us to generalize spectral analysis in cochleotopy to the population level [65], which allows to look at similarities between single subjects analysis not only by comparing individual maps (as also done here in **Fig. 5, Figs. S2, S6, S8**, and by applying a similarity measure of alignment index) but also to look for consistent large-scale results in the group level (for review on the importance of this approach combined with single subject analysis see [65]). Here we demonstrate that even the higher-order human auditory cortex, outside the traditional cochleotopic regions, is organized on a large scale by cochleotopic gradient patterns. This analysis method allowed us to delineate the location and frequency gradients in uncharted cortical cochleotopic regions, which we interpret as distinct auditory cortical fields (which may, of course, be further divided according to functional or anatomical markers, for example the division of caudal and rostral parabelt fields [15]). These cortical fields are organized in a mirror- symmetric fashion, and are consistent across subjects and across recording days, suggesting that they correspond to segregated anatomical areas employed in auditory processing. There appear to be two mirror-symmetry axes: one centered around Heschl's gyrus in the anterior-posterior axis (**Figs. 2–6**), which is likely to correspond to the core and belt areas, as seen in primates and humans [30,41] and the other one is stretching from STG to STS (**Figs. 2–6**), which may extend to the parabelt areas. The first mirror-symmetric axis is in accordance with previous literature of both humans and primate findings (and see details below), demonstrating the cochleotopic mapping in the core auditory cortex, including areas A1 and R (corresponding to gradient between 2 high-frequency bands encompassing a low-frequency band centered around Heschl's gyrus) and the surrounding belt areas, most of which continue the cochleotopic gradients of the core areas, and thus identifiable only by their cytoarchitecture [20,22,24,73,74] or functional differences (such as lower responsiveness to pure tones [34,45,56]; for example of functional discrimination of the core and belt using this principle see in [30]). Our results mirror the gradient direction of the core as presented in several recent findings [37,41] who reported gradients perpendicular to the long axis of Heschl's gyrus (i.e. isofrequency bands along the HG long axis, and gradients in an anterior-posterior axis), rather than gradients following a slightly more oblique orientation, more resembling that of the anatomy of Heschl's gyrus [35]. The topic of gradient direction of the core is currently still debated in humans. Recent findings [41] comparing surface and volume cochleotopic maps suggest that this controversy may have at least partially resulted from the resolution of the cochleotopic gradients with regard to the proximity of the sulci bordering Heschl's gyrus, and their high intersubject variability. While our study does not focus on the core gradients (also due to the limited spatial resolution), it offers support to the posterior–

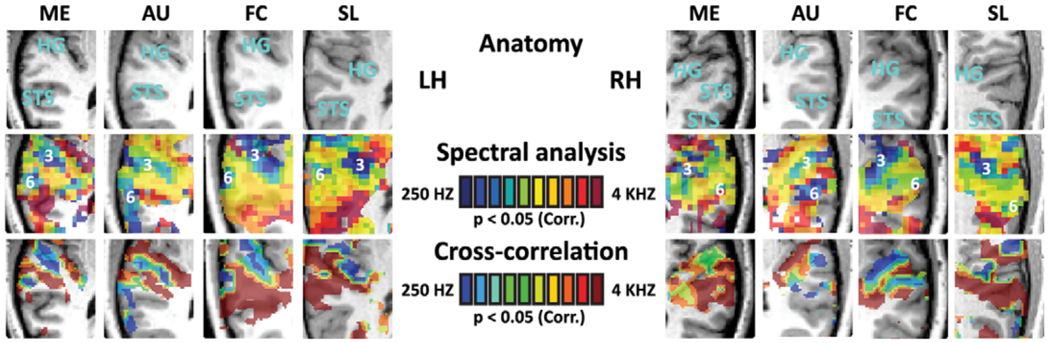

Figure 5. Multiple cochleotopic maps in single subjects. Anatomical structures of the horizontal views of each subject in the magnified area of the auditory cortex, unsmoothed spectral analysis relative frequency preference maps (individual $R>0.18$, $df=299$, $p<0.05$, corrected for multiple comparisons) and cross-correlation maps ($p<0.05$, corrected for multiple comparisons) and shown for four different subjects (these and similar maps from additional horizontal slices are presented in **Fig. S6**). Overlaid on the spectral analysis maps are numbers (3, 6) representing the low-frequency peaks corresponding to those presented in the group results. Point 3 corresponds to the border between A1 and R and point 6 represents the low frequency band on the lateral STG possibly corresponding to a homologue of area CL of the belt. Single subject maps show cochleotopic maps that extend beyond the auditory core to the superior temporal gyrus and superior temporal sulcus. HG - Heschl's gyrus, STS – Superior temporal sulcus.
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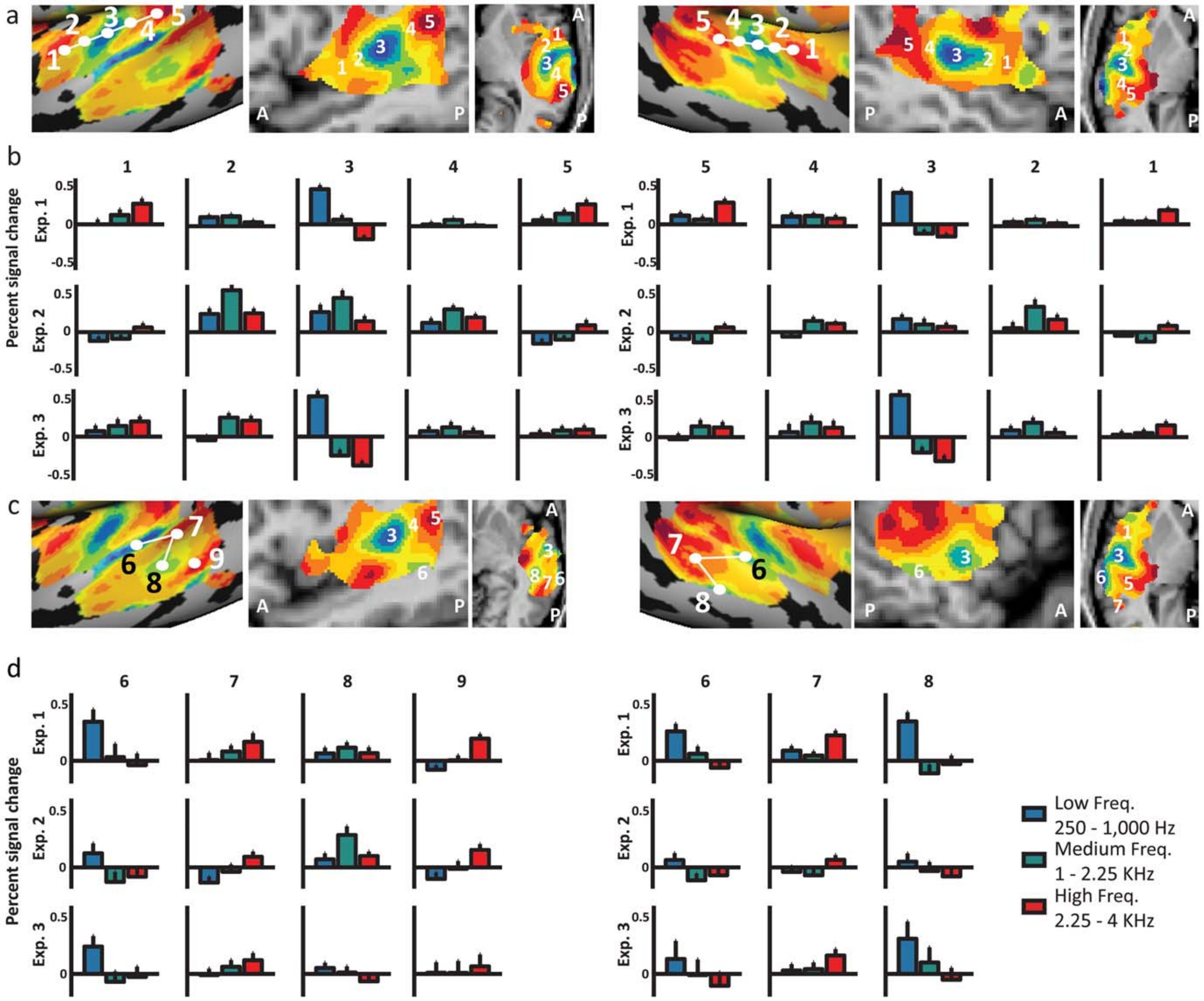

Figure 6. Cochleotopic maps in the human auditory cortex verified by RFX-GLM raw time-course analysis. A. Auditory cortex relative frequency preference map magnification is the same as in **Figs. 2 and 3**, with points (1–5, see Talairach coordinates at **Table 1**) along the auditory core gradients that were used to sample individual time-courses and compute random effect GLM time-course analysis. The approximate location of the same sampling points is also presented in a volume view of sagittal and horizontal slices. **B.** Time-courses of activation and response averages were sampled from points (1–5) along the anterior-posterior cochleotopic gradient (of the core areas), in **both** cortical hemispheres. Response averages were calculated for Exp. 1 group (*n* = *10*), Exp. 2 group (falling chirp, *n* = *5*) and for Exp. 3 group (scan repetition, *n* = *4*) from the same locations. 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. Error bars denote standard error of the mean (SEM). Tone preference examined using this complementary analysis was consistent with relative frequency preference maps revealed by spectral analysis. **C.** Auditory cortex relative frequency preference map magnification is the same as in **Figs. 2 and 3**, with points (6–9) marking the lowest and highest frequency tones which represent the mirror-symmetry flipping points between the extra-core cochleotopic maps (see Talairach coordinates at **Table 1**). These points were used to sample individual time-courses and compute random effect GLM time-course analysis, similarly to A-B. The approximate location of the same sampling points is also presented in a volume view of sagittal and horizontal slices, with reference to the sampling points of the core. **D.** Similar to B, response averages of activation were sampled from points 6–9 in the left hemisphere, and 6–8 in the right hemisphere, along the superior-inferior cochleotopic gradient in both scan sessions, validating the tone preference of the iso-frequency bands in the extra-core areas of auditory cortex.
doi:10.1371/journal.pone.0017832.g006

anterior axis of core gradients, in hope that future high-resolution studies focusing on the exact anatomical-functional link in Heschl's gyrus will contribute to the resolution of this debate.

In addition to the well-known core gradients of A1 and R, the first mirror symmetric axis includes partial evidence for an additional low frequency focus anterior to the high-low-high bands (evident in the right hemisphere) on the surface of the superior temporal gyrus, possibly corresponding to area RT of the macaque [30] for which inconclusive results have been seen in previous human studies [41]. However, further high-resolution scans specifically analyzing individual subjects in this area (for instance to see if this gradient indeed exists in the temporal plane of both hemispheres) is required to reach decisive conclusions as to the existence in humans. In addition to the core gradients, a low-frequency band somewhat perpendicular to the low frequency band along the axis of HG (in which sampling point 6 was taken in **Fig. 6**) may at least partly correspond to posterior belt field CL of the macaque (whose cochleotopic gradient does not continue that of the core, and is thus easily definable, according to findings in primates and humans [30,34,40,41], thus defining the possible extent of the belt to the cochleotopic areas within the superior temporal gyrus and Heschl's gyrus. This functional localization and its correspondence to the known gradients of the belt in macaques and humans enables us to assume that the additional maps in the more inferior temporal lobe, corresponding to the second mirror-symmetry axis, specifically in the superior temporal sulcus, belong to the parabelt and other high-order auditory regions, extending beyond the belt to areas corresponding to CP and RP of the parabelt [15,21,27,28,75], and perhaps beyond them. Superimposing our cochleotopic maps on the Talairach normalized Brodmann areas [69] further demonstrates that the maps within the superior temporal sulcus and inferior to it coincide with Brodmann area 22 (**Fig. S7** and **Table 1**), parts of which are considered to be homogenous to the auditory parabelt [70], to areas in which selectivity for complex auditory properties has been demonstrated, for example voice-sensitivity preference [43] and preference for animals vs. tools sounds [44].

Although it is extremely difficult to link a cochleotopic gradient observed at a greater neuroimaging resolution in a human group to a specific cytorachitectonically, anatomically defined region (especially due to the high inter-subject variability of such cytoarchitecture structures, as well as discrepancies between different anatomical methods [20]), we will attempt to suggest a putative initial model of how our observed cochleotopic gradients correspond to the extensive anatomical mapping effort of the human auditory cortex, according to the most recent and elaborate architectonic scheme suggested by Fullerton and Pandya [20]. According to their anatomical division of the human auditory cortex into multiple fields, our functional cochleotopic division is likely to refer to (and extend beyond) a large number of cytoarchitectonically-defined fields, within the core (divided into as many as 8 fields; Ts1I, Ts2i, PaAr, Km(1–3), Kl, PaAc [20]), lateral belt (divided into as many as 6 fields; Ts1e, Ts2e, Ts3, PaAi, PaAe, Tpt) and medial belt or root (divided into as many as 4 fields; ProI, PaI, ProK, Reit) auditory cortex. The multiplicity of the anatomical fields with regard to cochleotopic gradients suggests that the link between anatomy and topographic gradients is a complex one. While the cytoarchitectural fields may indeed represent segregated functional units comparable to the elaborate auditory functions in the human brain, they may still share cochleotopic gradients, as is indeed known for the continuous gradients between the core and some of the belt areas in the macaque [30]. For example, areas KI and Km1 to Km3 of the core and areas ProI, PaI, ProK of the root (or medial belt) appear to be organized in parallel and in a general perpendicular angle to the long axis of Heschl's gyrus [20], along the anterior-posterior cochleotopic gradient of this part of the core and belt (corresponding to our sample points 1–5 in **Fig. 6**). When comparing human cytoarchitectonic mapping [20] and macaque [30] and human [35,37] cochleotopic mapping, the border line between KI+Km1 and Km2+3 in the core may correspond to the border between A1 and R, thus forming the mirror-symmetric axis of the core (on which sampling point 3 in **Fig. 6** is located), which is continued to belt area CM of the macaque, possibly corresponding to cytoarchitectural areas PaAc and Reit in the belt and root [20]. This gradient-axis also continues anteriorly, or rostrally, to the root areas ProI, PaI, ProK, which may be located in the high-frequency selective area at the anterior end of this gradient. The additional gradient we assume corresponds to area CL of the macaque (sampling point 6 in **Fig. 6**), manifesting most prominently in an additional low-frequency selective band, may correlate to the approximate location of areas PaAe, PaAi and possibly bordering Tpt [20]. It is more difficult to determine how the additional superior-inferior cochleotopic gradients (sampling points 7–9 in **Fig. 6**) correspond to cytorachitectonic structures. There is already inconsistency in the interpretation of different studies to the exact architectonic organization of these more lateral areas (for example areas PaAi and PaAe), and to their definition as belt [12,20]] or parabelt [15,25,75] auditory cortex. In any case, due to the consistent mapping of all cytoarchitectural core, root and belt areas to the superior temporal plane extending maximally to encompass STG, and the functional mapping of the corresponding areas to cochleotopic mapping on the anterior-posterior axis [30], we can assume that the additional cochleotopic gradients we observed (sampling points 7–9 in **Fig. 6**) extend beyond the core, root and belt at least to the (less charted and agreed upon) parabelt fields and perhaps beyond them, to anatomical areas numbered by Brodmann [69] as parts of areas 22 and 21, (as can also be seen in **Fig. S7**, presenting our cochleotopic mapping on an anatomical estimate of the Brodmann areas). Ultimately, the attribution of the in-vivo cochleotopic functional data to the detailed anatomical division of the human auditory cortex can best be accomplished by future studies applying high-resolution microanatomy MRI analysis in addition to cochleotopic mapping to identify individual lamination structures and their functions (for example, [76] applying such analysis to the visual cortex).

Here we found multiple cochleotopic maps in the temporal lobe, however we did not find consistent maps beyond it. Interestingly we did find several other regions which showed significant responses to our stimulation protocol (i.e. highly significant correlation coefficient in all three experiments; see **Fig. S1**). These regions included bilateral activation in the posterior-inferior frontal lobe, medial superior frontal gyrus\ premotor cortex, precuneus, and a left inferior parietal cluster,

Table 1. Talairach coordinates of mirror-symmetry flipping points between the cochleotopic maps in the temporal lobe.

Sampling point	X	Y	Z	Brodmann Area
LH				
1	−43	−16	2	BA 22
2	−46	−16	10	BA 41
3	−45	−22	10	BA 41
4	−48	−28	14	BA 41
5	−55	−35	20	BA 42
6	−64	−23	7	BA 42
7	−54	−36	9	BA 22
8	−42	−30	3	BA 22
9	−56	−37	5	BA 22
RH				
1	38	−19	1	BA 22
2	40	−18	8	BA 22
3	46	−21	9	BA 41
4	50	−24	10	BA 41
5	54	−30	16	BA 42
6	62	−22	7	BA 42
7	47	−29	5	BA 22
8	63	−27	5	BA 22

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regions sporadically reported previously to be involved in various auditory localization and recognition tasks [48,50,77,78]. However none of these regions showed clear and consistent cochleotopic arrangement across the experiments and between the subjects. This does not preclude finding such maps in the future, using for instance specific stimuli that match the functional preferences of these areas, higher resolution and focused scanning of such specific areas outside the temporal cortex. Additionally, we did not observe a clear cochleotopic gradient, but rather a general preference for medium and high-frequency tones, caudally to the core and belt in the planum temporale (PT; part of which corresponds to Tpt of the monkey and possibly of the human [20,23,25,79]). This area is thought to be involved in speech processing [80,81], perhaps as part of a computational hub for discerning complex spectro-temporal auditory objects and their locations [82,83], and may thus have been less likely to be activated by our relatively simple stimulus type (i.e. tonal sweep). Future studies directing their attention to more complex and appropriate stimuli may reveal this the tonal preference of this area.

Our results clearly verify the organization of core areas [35,38] previously reported. However they also show that at least two large-scale previously unreported cochleotopic maps beyond core and belt areas exist in the right hemisphere, and at least three exist in the left hemisphere (with mirror symmetry axis flipping from STG to STS (**Figs. 2, 3**). This is a conservative estimate, and there are hints that additional maps may be present in the occipito-temporal cortex. These areas clearly extend far beyond typical core [35,38] and belt [37,41] areas, all the way to superior temporal sulcus, well into regions which are traditionally considered non-cochleotopic [56], and which engage both in complex auditory processing and multisensory integration [43,44,45,84,85,86,87]. Our results show that while even relatively early auditory cortical areas may exhibit sensitivity to complex sound features [46,87], the large scale organization of most of the auditory cortex still maintains clear cochleotopic preferences. Combining our results with previous studies, suggests that the organization of the auditory cortex may be that the cochleotopic mapping is relatively coarse, stretching all the way from A1 to STS (covering core, belt and parabelt areas) while local populations of neurons are more heterogeneous in their preference. Indeed recent studies found [88,89] that the cochleotopic mapping in primary auditory cortex of mice is only present on a (relatively) large scale, whereas local neuronal populations show less organized cochleotopic gradients. It will be interesting to combine in future studies between cochleotopic mapping and high order auditory functions (like voice recognition). For comparison's sake, it is useful to look at the balance between topographical mapping and functional specialization in the visual modality. It is important to note that visual fields may have combined eccentricity, polar angle and other specific functional characteristics. For example, V4 shows color sensitivity in addition to being part of a large scale retinotopic organization; the fusiform face area (FFA) has a combined preference for faces and a foveal retinotopic eccentricity preference, and the parahippocampal place area (PPA) has combined selectivity for place stimuli and a peripheral retinotopic eccentricity preference [2,90]. In the same manner, a given auditory area might have several orthogonal receptive field characteristics (for example preference for species-specific vocalizations or communication calls [43,45]); one of them appears to be, as our findings show, a cochleotopic topographical organization.

Along this line, multiple topographical maps delineating parallel and divergent functional regions have been accounted for in terms of computational efficiency or even developmental and evolutionary advantages and efficiency [91,92]. As found in the visual cortex, which is mapped both according to polar and eccentricity topographical mapping, additional axes of topographical mappings may be exposed in the auditory cortex in the future, possibly, for instance, in modules for tuning width or binaural interactions [29,55]. A recent study [93] suggest that the additional axis may be that of temporal sound features, with slower temporal modulation rates represented more medially and faster modulation rates more laterally on Heschl's gyrus, creating an additional modulation axis orthogonal to cochleotopic gradient, at least in the core areas. Such additional axes may, in turn, aid in better defining the axes of frequency selectivity shift, as was done in the visual domain [53]. Our results, in addition to the well-known retinotopic mapping of the visual cortex (including that of high-order visual cortex, and parietal and frontal spatial maps [2,3,4], may indicate that topographical mapping could be a more common, fundamental principle of sensory cortex organization well beyond primary and secondary cortices, perhaps as suggested previously [91,92], due to its computational advantages.

The discovery of new cochleotopic map borders might greatly aid future characterization of the functions of the new auditory fields in humans, and help define their possible connectivity patterns, interactions and hierarchical processing structure, as well as test them with regard to the suggested theoretical framework of the two auditory processing streams [7,26,48,49,50,51]. For example future studies in ultra-high field scanners further exemplifying cochleotopic mapping in the prefrontal lobe may be able to show cochleotopic mapping in the prefrontal cortex, and even draw a cochleotopic border between the ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortex, thought to be high-level stations in the dual 'what' and 'where' processing scheme [49,50], thus testing in more detail this hypothetical model. It will also allow for better comparisons between results reported in different studies and standardize references to them (as opposed to comparisons on the basis of brain anatomy such as gyri and sulci which are very variable with relation to function [67]), which will also potentially lead to better theoretical comprehension of their common characteristics across studies.

The understanding of the topographical structure of the auditory cortex could also be utilized for studying plastic changes in the auditory cortex in a non-invasive manner: both changes which are specific to the tonal frequency, for instance in musicians [94], or to a specific auditory function (and perhaps auditory stream), such as auditory localization in the blind [95]. Additional possible future directions are the study of the plastic changes of the cochleotopic maps in congenitally blind individuals [96], in general (due to their excessive reliance on non-visual senses) and also following the prolonged use of auditory sensory substitution devices [97]. Other fascinating lines of research are the effect of tinnitus on auditory fields [98], and monitoring the awakening of auditory cortex cochleotopic responses following cochlear implants at different ages and various types of deafness [99]. Such studies may provide opportunities to study the development, plasticity and other characteristics of cochleotopic maps, an opportunity with no parallel to date in retinotopic mapping and vision.

Conclusions

Using spectral analysis fMRI, we showed additional cochleotopic maps in the human temporal lobe outside the auditory core and belt. Cochleotopic preference is thus by no means limited to the auditory core or belt but rather extends to the higher-order auditory regions within the temporal lobe, as far as the multisensory cortex in STS/MTG, extending at least to auditory parabelt areas. Cochleotopic maps in high-order auditory areas are also arranged in a mirror-symmetry organization, which may help define and parcel the auditory cortex into distinct auditory fields. It would appear that similar to the visual cortex, the auditory cortex (at least in the temporal lobe) is also fundamentally topographical in nature, which may suggest that this large-scale governing principle of organization is sensory modality invariant.

Supporting Information

Figure S1 Auditory-responsive areas outside the temporal lobe. Conjunction of significant ($p<0.05$, Bonf. Corrected) correlation coefficient maps of all 3 experiments is presented in medial and lateral views of the inflated cortical hemispheres of the standard MNI brain transformed to Talairach coordinates. In addition to the auditory-responsive areas within the temporal lobe, several regions showed significant auditory response patterns at the group level. These regions included bilateral activation in the posterior-inferior frontal lobe, medial superior frontal gyrus\ premotor cortex, precuneus, and a left inferior parietal cluster. While these areas showed correlation to the auditory stimulus timing, they did not present a clear and consistent cochleotopic arrangement. CS – Central sulcus, IFS – Inferior frontal sulcus, STS – Superior temporal sulcus.
(TIF)

Figure S2 Single subject cochleotopic maps of the auditory core. A. Relative frequency preference maps are shown for each of the ten subjects. A horizontal view of each subject's brain is shown, with the delineated (cyan lines) borders of Heschl's gyrus (HG). Unsmoothed relative frequency preference maps are shown in individual highly significant responsive auditory areas (highly significant Pearson's R of the correlation between the time-course and the pure cosine model, $R>0.26$, $df=299$, $p<0.05$, corrected for multiple comparisons). Single subject maps display a gradual cochleotopic preference shift in their native, unsmoothed, resolution. The maps demonstrate that the core auditory cortex large- scale mirror symmetric cochleotopic mapping in the human homologues of regions A1 and R is present across subjects (in 9/10 subjects). Moreover, there is evidence of a medial-lateral cochleotopic gradient on the medial part of HG in some (6/10) subjects. Additional posterior-lateral cochleotopic gradients outside the core areas can be seen in some of the subjects even in horizontal views of the brain. For a full view of the extra-core maps see **Fig. 5**, **Figs. S3, S4, S5** displayed on the cortical surface and horizontal slices, and for test-retest reliability see **Fig. S7**). On the lowest panel for each subject, Pearson's R map is displayed, with the delineated (cyan lines) borders of HG. The peak correlation in most subjects is located approximately near HG, around and posteriorly to the low-frequency peak representing the border between putative A1 and R, demonstrating a preference for simple tone stimuli and thus supporting the identification of this region as the core auditory cortex. B. Group ($n=10$) averaged relative frequency preference map displayed on a horizontal ($z=11$), a sagittal ($x=41$) and a coronal ($y=-16$) view of a standard MNI brain, with the delineated (cyan lines) borders of HG. The maps display the cochleotopic mapping in the core and beyond it, as seen in single subjects. Note also an additional map which includes an anterior low-frequency selective area seen in the sagittal view. This cochleotopic map possibly corresponds to a human homologue of primate core area RT (Petkov *et al.*, 2006). C. Group ($n=10$) averaged Pearson's R map displayed on a horizontal ($z=11$), a sagittal ($x=41$) and a coronal ($y=-16$) view of a standard MNI brain, with the delineated (cyan lines) borders of HG. The peak correlation is in the core auditory cortex, but is significantly high in a large portion of the temporal lobe.
(TIF)

Figure S3 Multiple cochleotopic maps in single subjects – Left hemisphere. A. Group ($n=10$) relative frequency preference maps, as well as 3 single subjects' maps, are presented in a lateral view of the inflated left cortical hemisphere of the standard MNI brain transformed to Talairach coordinates, as displayed in **Fig. 2**. Single subjects' maps are presented, for the sake of comparison with the group results, on the standard MNI brain, in the entire significantly responsive auditory region of the group. All relative frequency preference maps are located within the groups' highly auditory-responsive region ($R>0.23$, $P<0.05$ Bonf. corr.). All maps show multiple iso-frequency bands, in addition to the known tone selectivity of the core auditory cortex. These iso-frequency bands extend in a superior-to-inferior axis along the temporal cortex. **B.** The auditory cortex region is magnified, showing the relative frequency preference map on the cortical surface. The estimated borders between the putative mirror symmetric cochleotopic maps, as acquired from the group's relative frequency preference maps (**Fig. 2**) are indicated (white line), showing the similarity of the single subject maps to the group results. Response averages of activation were sampled individually from points (1–7) along the core auditory cortex, as well as the superior-inferior cochleotopic gradient, validating the tone preference of the iso-frequency bands in the core and the accessory auditory cortex in 3 single subjects. Error bars denote standard error of the mean (SEM).
(TIF)

Figure S4 Multiple cochleotopic maps in single subjects – Right hemisphere. A. Group ($n=10$) relative frequency preference maps, as well as 3 single subjects' maps, are presented in a lateral view of the inflated right cortical hemisphere of the standard MNI brain transformed to Talairach coordinates, as displayed in **Fig. 3**. Single subjects' maps are presented, for the sake of comparison with the group results, on the standard MNI brain, in the entire significantly responsive auditory region of the group. All relative frequency preference maps are located within the groups' high auditory-responsive region ($R>0.23$, $P<0.05$ Bonf. corr.). All maps show multiple iso-frequency bands, in addition to the known tone selectivity of the core auditory cortex. These iso-frequency bands extend in a superior-to-inferior axis along the temporal cortex. **B.** The auditory cortex region is magnified, showing the relative frequency preference map on the cortical surface. The estimated borders between the putative mirror symmetric cochleotopic maps, as acquired from the group's relative frequency preference maps (**Fig. 3**) are indicated (white line), showing the similarity of the single subject maps to the group results. Response averages of activation were sampled individually from points (1–6) along the core auditory cortex, as well as the superior-inferior cochleotopic gradient, validating the tone preference of the iso-frequency bands in the core and the accessory auditory cortex in 3 single subjects. Error bars denote standard error of the mean (SEM).
(TIF)

Figure S5 Consistency of spectral maps across experiments. Spectral maps are displayed for the left and right temporal lobes in all the experiments conducted in this study. Panels **A, C** and **D** replicate the spectral maps of Exp.1, averaging of Exps. 1+2 and Exp. 3 respectively, also presented in **Fig. 4**. Panel **B** shows the spectral map of Exp. 2, which is highly consistent with the main findings. For each spectral map, the alignment indices on the right indicate the quantitative similarity with the spectral map of the main study (Exp. 1; $p<0.00001$ for all maps).
(TIF)

Figure S6 Multiple cochleotopic maps in single subjects. Anatomical structures in the magnified area of the auditory cortex in horizontal views of each subject, unsmoothed spectral analysis relative frequency preference maps (individual $R>0.18$, $df=299$, $p<0.05$, corrected for multiple comparisons) and cross-correlation maps ($p<0.05$, corrected for multiple comparisons) are shown for five different subjects. For subject ME maps of the same horizontal view are also displayed for Exp. 2 (falling chirp, lower panel) and for subject AU maps of the same horizontal view are also displayed for Exp. 3 (second scan, lower panel), showing high test-retest reliability. Single subject maps show cochleotopic maps that extend beyond the auditory core to the superior temporal gyrus and superior temporal sulcus. HG - Heschl's gyrus, STG – Superior temporal sulcus, STS – Superior temporal sulcus.
(TIF)

Figure S7 Cochleotopic maps projected on a Talairach normalized brain of Brodmann areas. Relative frequency preference maps of the averaged rising chirp group ($n=10$) and falling chirp group ($n=5$), within the groups' high auditory responsive areas ($R>0.25$, $p<0.05$ Bonf. Cor.). The map is presented on a depiction of the Brodmann's areas in a horizontal view. Brodmann areas 21, 22, 41, 42 are depicted upon the maps, and cochleotopic gradients' peaks are marked with white triangles. Cochleotopic gradients could be found beyond primary auditory areas (Brodmann areas 41,42) in the temporal lobe towards STS (Brodmann areas 21, 22).
(TIF)

Figure S8 Single subject cochleotopic maps are consistent across repetitions. A. A horizontal view of the auditory cortex of 4 subjects who were scanned twice in two different days (Exp. 1 and Exp. 3) is shown, with the delineated (yellow lines) borders of Heschl's gyrus. Spectral analysis relative frequency preference maps (in individual significantly responsive areas, $R>0.26$, $df=299$, $P<0.05$, corrected for multiple comparisons) are shown below. Cochleotopic maps seen on the primary auditory cortex in an anterior-posterior pattern are highly replicable across scans and across subjects. B. Group averaged maps ($n=4$) for the first and second scans are presented on the MNI (Montreal Neurological Institute) standard brain, transformed to Talairach coordinates. The average maps, as well as the single subject maps, are remarkably similar in the two repeated scans.
(TIF)

Movie S1 Spread of best frequency areas according to auditory stimulus. Group (Session 1, $n=10$) relative frequency preference maps are presented in a lateral view of the partly inflated cortical hemispheres of the standard MNI brain, as presented in **Fig. 1E**. The video depicts the progressions of tonal frequency sensitivity in the auditory cortex. Cortical response of the group to the heard rising tone chirp is displayed in white for successive sampling points. Note the impressive mirror-symmetric pattern revealed in this tonal frequency progression movie. (can also be found at: http://brain.huji.ac.il/stuff/cochleotopy_movie.html).
(AVI)

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Author Contributions

Conceived and designed the experiments: ESA UH AA. Performed the experiments: ESA UH. Analyzed the data: ESA UH AA. Contributed reagents/materials/analysis tools: ESA UH AA. Wrote the paper: ESA UH AA.

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תקציר

אנו חיים בחברה המבוססת על ראיה. מידע ראייתי משמש אותנו להתמצאות בסביבה, לזיהוי חפצים בה, להתריע על אירועים הדורשים את תשומת ליבנו, לפעול בסיטואציות חברתיות ופעולות רבות נוספות הדרושות לתפקוד יעיל בחיי היומיום. לכן, אבדן ראיה מקטין את איכות החיים ומייצר מגבלה אמיתית לתפקוד עבור מליוני אנשים בעולם.

למרות ההתקדמויות הרבות ברפואה המודרנית, שחזור ראיה לעיוורים נתקל עדיין בקשיים טכניים ומדעיים רבים. "עיניים ביוניות" או פרותזות ראייתיות מפותחות כיום בעיקר עבור גורמי עיוורון המייצגים מיעוט בקרב אוכלוסיית לקויי הראיה בעולם. יתר על כן, הפתרונות הקיימים עדיין אינם מספקים מידע ראייתי בחדות אבחנה (רזולוציה) גבוהה.

חשוב מכך, גישות אלו לשחזור ראיה לוקחות כמובן מאליו את יכולת המוח האנושי, לאחר שנים רבות או אף חיים שלמים של עיוורון, לפענח מידע ראייתי מרגע שזה הופך לזמין. הקונצנזוס המדעי לגבי התפתחות הקורטקס (קליפת המוח) הראייתי הינו שחסך ראייתי במהלך תקופות קריטיות או רגישות בתחילת החיים עשויות להוביל לעיוורון פונקציונלי, כיוון שהמוח אינו מתארגן בצורה המאפשרת עיבוד מידע ראייתי באופן תקין, ומצב זה עשוי להיות בלתי הפיך בהמשך החיים. אכן, מספר מצומצם של שחזורי ראיה ניתוחיים (ע"י הסרת קטרקט) לאחר שנים של עיוורון הראו כי יתכנו ליקויים חמורים בראיה באותם אנשים, גם לאחר חשיפה ממושכת לקלט ראייתי. בנוסף, מחקרים באנשים שהתעוורו בלידתם או בגיל צעיר מצביעים על כך שהקורטקס הראייתי שלהם התארגן מחדש לכדי עיבוד של מידע מאופנויות (חושים) אחרים. כלומר, ישנן עדויות רבות שמאמצי שחזור ראיה עשויים להתקל בבעיות משמעותיות עקב ארגונו מחדש של הקורטקס הראייתי בעיוורים.

בתזה זו בדקתי את הטענה הזו, על ידי שימוש בכלי חליפי לשיקום ראיה, בו המידע הראייתי מועבר באופן שאינו חודרני דרך החושים הקיימים בעיוורים. השתמשנו בתוכנת התמרה חושית הממירה מידע ראייתי לצלילים באמצעות אלגוריתם המרה קבוע. כיוון שהצלילים הנוצרים מתרגום תמונות טבעיות הינם מורכבים מאד, פיתחנו מערך אימון באמצעותו לימדנו עיוורים מלידה לעבד, באופן הדרגתי, את הצלילים המורכבים של ההתמרה החושית. תוכנית האימון איפשרה לנו לבדוק אם אכן העיוורים מסוגלים ללמוד לפענח מידע ראייתי מורכב ללא נסיון ראייתי בילדות המוקדמת, וכן לבחון מהם המאפיינים המוחיים של עיבוד כזה בעיוורים.

מצאנו כי העיוורים היו מסוגלים ללמוד לעבד מידע ראייתי בחדות ראיה גבוהה, עד כדי מעבר סף חדות העיוורון של ארגון הבריאות העולמי וכן להגיע לחדות ראיה הגבוהה מזו שהושגה בכל אמצעי חליפי עדכני של שיקום ראיה. בנוסף, העיוורים היו מסוגלים למיין תמונות לסוגים שונים, ולבצע מגוון מטלות ראייתיות.

חקירת ההדמיה המוחית הראתה שלמרות החסך בנסיון וקלט ראייתי במהלך ההתפתחות, הקורטקס הראייתי של העיוורים מלידה הראה פעילות במהלך עיבוד של קלטי ההתמרה החושית. חשוב מכך, הפעילות שנצפתה חיקתה את

הסלקטיביות למטלה ולסוג תמונה שמאפיין את הקורטקס הראייתי התקין. מצאנו כי מוחם של העיוורים הראה הפרדה כפולה בין עיבוד הצורה במסלול העיבוד הוונטרלי (הגחוני) לבין עיבוד המיקום במסלול הדורסלי (הגבי), בהתאם לעיקרון החלוקה המוכר בקורטקס הראייתי. בנוסף, מצאנו כי במסלול הונטרלי, העדפה לקטגוריה או סוג תמונה מסוים יכול להמצא ביחס לכל שאר סוגי התממונות שנבחרו. איזור הקריאה הראייתי, ה-visual word-form area (VWFA) הראה בעיוורים כמו גם ברואים העדפה לתפיסת אותיות על פני תמונות של טקסטורות, פרצופים, בתים, חפצי יומיום וצורות גוף.

בשני המחקרים הללו הקורטקס הראייתי הראה שימור של הסלקטיביות התפקודית למרות העדר הנסיון הראייתי, מיעוט האימון על ההתרה החושית, שנעשתה בגיל בגרות בלבד, וכן למרות העובדה שהמידע סופק באמצעות חוש שאינו טיפוסי (שמיעה). ממצאים אלו תומכים בתאוריה שנויה במחלוקת לפיה החלוקה התפקודית של המוח אינה לפי אופנויות (חושי) הקלט המפעילים את החלקים השונים, אלא לפי העדפה לביצוע מטלות או חישובים שונים באיזורים השונים, ללא תלול בחוש הקלט. תאוריה זו מציעה כי שילוב של חיבורי המוח באכוונה מאיזורי עיבוד גבוהים לנמוכים יותר בהירככיית העיבוד, יחד עם העדפה מובנית לביצוע עיבוד מסוג מסוים, עשויים לייצר את אותה התמחות תפקודית גם בהעדר מידע ראייתי כקלט במערכת. לתאוריה זו השלכות מעניינות על היכולת לשחזר ראיה בגיל מבוגר, כיוון שהיא מציעה שהמוח העיוור עשוי שלא לאבד את יכולתו לבצע עיבודים של מידע ראייתי ולכן עשוי להיות מסוגל ללמוד לראות גם בגיל מבוגר, אם מידע ראייתי יסופק למוח ע"י התמרה חושית, כמוצע כאן, או באמצעים חודרנים יותר.

עבודה זו נעשתה בהדרכתו של

פרופ' אמיר עמדי

נוירופלסטיסיות בעיוורים והתמרה חושית לראיה

חיבור לשם קבלת תואר דוקטור לפילוסופיה

מאת

אלה שטרים-עמית

הוגש לסנט האוניברסיטה העברית בירושלים

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