

Reading in the dark: neural correlates and cross-modal plasticity for learning to read entire words without visual experience

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ABSTRACT

Cognitive neuroscience has long attempted to determine the ways in which cortical selectivity develops, and the impact of nature vs. nurture on it. Congenital blindness (CB) offers a unique opportunity to test this question as the brains of blind individuals develop without visual experience. Here we approach this question through the reading network. Several areas in the visual cortex have been implicated as part of the reading network, and one of the main ones among them is the VWFA, which is selective to the form of letters and words. But what happens in the CB brain? On the one hand, it has been shown that cross-modal plasticity leads to the recruitment of occipital areas, including the VWFA, for linguistic tasks. On the other hand, we have recently demonstrated VWFA activity for letters in contrast to other visual categories when the information is provided via other senses such as touch or audition. Which of these tasks is more dominant? By which mechanism does the CB brain process reading?

Using fMRI and visual-to-auditory sensory substitution which transfers the topographical features of the letters we compare reading with semantic and scrambled conditions in a group of CB.

We found activation in early auditory and visual cortices during the early processing phase (letter), while the later phase (word) showed VWFA and bilateral dorsal-intraparietal activations for words. This further supports the notion that many visual regions in general, even early visual areas, also maintain a predilection for task processing even when the modality is variable and in spite of putative lifelong linguistic cross-modal plasticity.

Furthermore, we find that the VWFA is recruited preferentially for letter and word form, while it was not recruited, and even exhibited deactivation, for an immediately subsequent semantic task suggesting that despite only short sensory substitution experience orthographic task processing can dominate semantic processing in the VWFA. On a wider scope, this implies that at least in some cases cross-modal plasticity which enables the recruitment of areas for new tasks may be dominated by sensory independent task specific activation.

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1. Introduction

The importance of the ability to read – the decoding of symbols aimed at deriving meaning – cannot be overestimated, as it makes it possible to overcome the inherent limitations of the one dimensional linguistic medium (Houston, 2008) while radically modifying existing brain mechanisms (Dehaene et al., 2005, 2010; Price and Devlin, 2003), leading to extensive exploration of the reading process (see reviews in Price (2010) and Hannagan et al.

(2015)). Several foci have been associated with reading letters and words in sighted individuals. The process of word perception begins in the early occipital areas (V1) (Rauschecker, 2011), and then undergoes transformations in the highly studied VWFA (Cohen et al., 2000; Dehaene and Cohen, 2011; Schlaggar and McCandliss, 2007). In addition, a bilateral dorsal intraparietal region has been associated with letter-by-letter reading of words (aka the “serial reading mode”; Cohen et al., 2008).

However, this previous exploration has been almost entirely visual, raising the question of whether the visual modality is necessary and inherently linked to the recruitment of these regions, or whether other modalities could elicit a similar pattern. The brains of congenitally blind individuals offer us a unique

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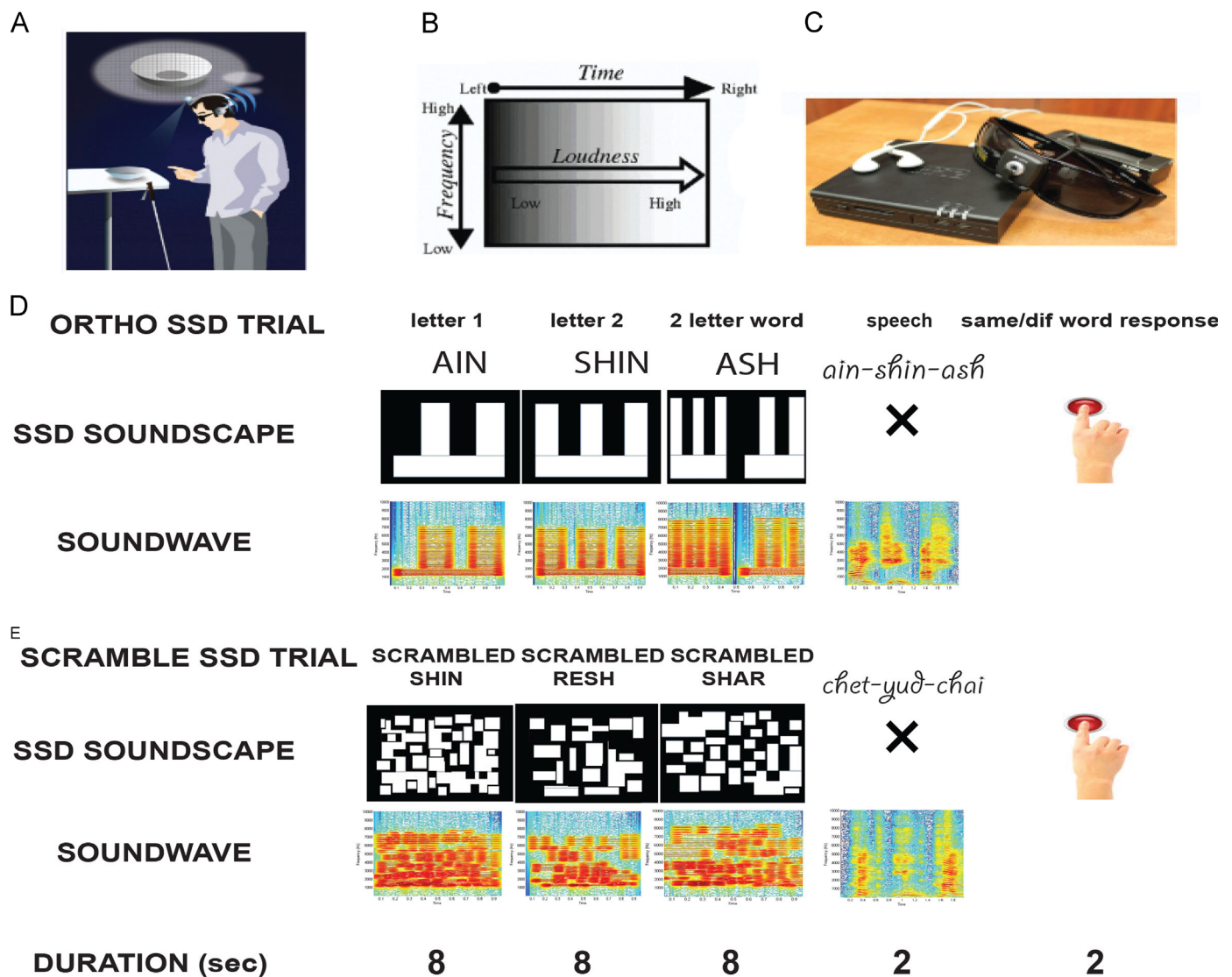


Fig. 1. Experimental Design. (A) Visual-to-auditory sensory substitution was employed to convey visual information to the blind using their intact auditory modality. (B) The transformation algorithm of the vOICe (Meijer, 1992): each image is scanned from left to right, such that time and stereo panning constitute the horizontal axis in its sound representation, tone frequency makes up the vertical axis, and loudness corresponds to pixel brightness. (C) The mobile kit for SSD usage includes a light-weight inexpensive webcam worn on eyeglasses, a computing device (such as a computer or smartphone), and earphones. (D) An example of an OrthoSSD trial: soundscapes of a letter and a soundscape of a word were heard by the subjects, followed by an auditory recording, which was either congruent or incongruent with the soundscapes. (E) An example of a ScrSSD trial: soundscapes of a scrambled letter and a soundscape of a scrambled word were heard by the subjects, followed by an auditory recording.

opportunity to explore how visually-based the process of reading and the recruitment of these areas actually is.

One method of exploring blind reading non-visually is by using Braille, enabling the examination of reading via touch using a special tactile script, and this direction has already seen some fruit (Burton et al., 2002a; Reich et al., 2011; Sadato et al., 1996, 1998). Another possibility is the use of visual-to-audio Sensory Substitution devices (SSDs), non-invasive interfaces which translate information from one sensory modality into another (see methods for elaboration). For example, such devices can convey to the user the full visual shape of the letters and word. To date, the reading network and process of learning to read via SSD has seen only initial exploration focused on the recruitment of the Visual Word Form Area (VWFA) for reading single letters (Striem-Amit et al., 2012a) and focusing on category selectivity aspects rather than on scrambling or semantic controls. Hence one important question we shall explore here is whether, during the building of entire words from letters through a SSD, the reading network of the CB maintains the same processing foci and hierarchy as the reading

network of the sighted.

Another important question is the effect that learning to read via SSD late in life has on the VWFA in the congenitally visually-deprived brain. On the one hand, the occipital cortex of the blind has been implicated in several key linguistic tasks, including verb generation, verbal memory of single words, speech processing, semantic processing and syntactic processing (Amedi et al., 2003; Bedny et al., 2011; Burton et al., 2002a, 2002b; Cohen et al., 1997; Hamilton et al., 2000; Reich et al., 2011; Roder et al., 2002; Sadato et al., 1996, 1998; Striem-Amit et al., 2012a). Specifically, early occipital areas including V1 and higher-tier areas including VWFA have been implicated in linguistic and verbal memory tasks in the congenitally blind (CB) (Amedi et al., 2003, 2004); Bedny et al. (2011) show extensive visual cortex activation (including in the fusiform) to semantic stimuli in the CB but not in sighted individuals; and Roder et al. (2002) show fusiform activation peaking in a location within the range of coordinates of what is known as the VWFA to overall (semantic and syntactic) linguistic stimuli and activation to semantic stimuli in the fusiform region in the CB.

These activations have been attributed to a unique pattern of cross-modal brain plasticity in which a given (visual) brain area changes the nature of the task it is performing from visual to linguistic. We term this type of plasticity *task switching cross-modal plasticity*. It has been suggested that in the absence of visual input, this system relies on and uses the remaining inputs more efficiently, including the linguistic input, in order to compensate for the absence of the visual system (Roder et al., 2002). However, in some cases the recruitment of visual circuits for language depends on the onset of blindness; hence occipital areas are not always recruited for semantics and sentence comprehension tasks in the late blind, which suggests a sensitive period for the *task switching plasticity* (Bedny et al., 2012). This approach would predict that blind subjects would recruit these areas for semantic tasks, possibly even preferentially over reading non-visually.

On the other hand, in another form of cross-modal plasticity the task or computation performed by a given brain region remains constant, while the dominant sensory modality varies, so that the relevant input is perceived via audition or touch, for example, instead of vision. This form of plasticity has been observed in the adult brain and is thought to account for Braille reading (Reich et al., 2011) and the reading of single letters through a SSD (Striem-Amit et al., 2012a) in the VWFA of the CB. It has also been demonstrated in the blind brain for a wide variety of other visual tasks such as recognizing the shapes of body postures in the EBA (Striem-Amit and Amedi, 2014) and number forms in the Number Form Area (NFA) (Abboud et al., 2015), for visual motion in MT (Ptito et al., 2005) and for object shape in the LOC (Amedi et al., 2007) (see general reviews in Elli et al. (2014); Reich et al., 2012 and Maidenbaum et al. (2014a)). Tactile examples include recognizing scenes (Wolbers et al., 2011) and visuo-haptic object processing in general (see a review in Lacey and Sathian (2014)). We term this type of plasticity *task specific sensory independent cross-modal plasticity*. This approach would predict that blind subjects reading non-visually would recruit the relevant reading areas, possibly even preferentially over semantic tasks.

Thus, it remains unclear whether the use of SSDs in the adult brain triggering *task specific cross-modal plasticity* in the VWFA can co-exist with or perhaps even dominate semantic life-long acquired *task switching cross-modal plasticity* in this region. To the best of our knowledge, this issue has not been explored directly. Here, we studied a group of congenitally (fully) blind adults trained to read words through a visual-to-auditory SSD, which converts visual images to auditory “soundscapes” using a pre-determined consistent algorithm (The vOICe) (Meijer, 1992). This technique enables the blind to process entire words comprised of letters, with sounds topographically representing visual images of letters and words while their entire brains are imaged using fMRI (see Fig. 1A). We presented the subjects with two letter stimuli in the form of SSD soundscapes, followed by a SSD word comprised of these two letters (OrthoSSD). In addition, two scrambled SSD letters, followed by a scrambled word (ScrSSD) were presented in a separate sequence of events. The SSD presentations were followed by an auditory word task to make sure that the subjects extracted the shapes of the letters and the word and serving as a semantic control to words presented through the SSD (see the Section 2 for details). Half of the auditory trials were congruent with the orthographically presented word, and half of the trials were incongruent. In this way we could monitor the subjects' behavior and performance in both the reading and semantic tasks while optimizing the experiment duration, since the SSD conversion algorithm delivered each letter separately and in a predefined order. Each letter and word was presented four times, which enabled us to inspect the various phases of the reading process (see Fig. 1). The ScrSSD control condition was identical except for the scrambling of each letter, as commonly done in reading and other

visual experiments (i.e., Szwed et al., 2011, Grill-Spector et al., 1998). The ScrSSD stimuli were designed to ascertain that activation to the OrthoSSD condition in the occipital cortex would not be due to cross-modal (*task switching*) auditory processing in this condition.

This design steps beyond previous studies which demonstrated VWFA recruitment in CB participants (Reich et al., 2011; Sadato et al., 1998; Striem-Amit et al., 2012a), by adding contrasts such as reading words with hearing the same words while performing a task that requires both reading and a semantic judgment. Furthermore, previous studies have contrasted letters to either other visual categories or to nonsense Braille patterns. In both cases, the low-level characteristics of the control stimuli differed considerably from the low-level characteristics of the letters condition. Hence, we included both a semantic condition and a sensory scramble control condition that maintained the whole wide range of frequencies and changes in the temporal domain that characterize letters.

Thus, this experimental design and the fact that the vOICe generates a slow-motion process of object shape reconstruction and identification, which can be utilized to study some of the slower aspects of the dynamics of auditory-to-visual object recognition using high-spatial-resolution fMRI, enabled us to examine four key issues regarding brain organization and plastic reorganization following short (10 h) training with a topographic SSD:

- (1) Is the VWFA of CB activated in response to a semantic task or does it show signs of *task switching cross-modal plasticity*?
- (2) What are the central processing foci of the CB reading network and do they include areas observed in the sighted, such as the VWFA and the bilateral dorsal intraparietal region?
- (3) Do early auditory areas of the CB exemplify a processing pattern congruent with the processing pattern of the sighted V1 (i.e. showing a preference for processing low-level visual-to-auditory features)?
- (4) Are the temporal processing patterns of V1 and nearby retinotopic areas of the CB congruent with (a) the sighted primary occipital areas, showing a preference for low level sensory features (as observed in the sighted) or with (b) higher-tier areas, showing a preference for processing higher-order information (and, thus, still exemplifying *task switching plasticity*, as observed in the CB)?

2. Materials and methods

2.1. Subjects

Eight congenitally blind, native Hebrew speakers with no other neurological deficits were scanned in the current study (age 22–53, two males). An expert ophthalmologist examined the subjects to assess the cause of blindness and tested for the presence of any light perception. All eight subjects were congenitally blind and had major retinal damage. Their blindness was not due to a progressive neurological disease; none of the subjects had any form of light perception (one subject had some light perception in her right eye until the age of one) (Table S1). All subjects but two were right handed, as assessed by an adapted version of the Edinburgh test (Table S1). All subjects were Braille-literate. All but two subjects were familiar with the shapes of the Hebrew capital letters before the vOICe training and at the time of the scan they could all identify these letters correctly. The Tel-Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject.

2.2. Visual-to-auditory SSD

Sensory Substitution devices are non-invasive human-machine interfaces which translate information from one sensory channel to another; in this study visual information to an auditory representation. These devices have seen wide use in recent years for both attempts at visual rehabilitation (Bach-y-Rita and S, 2003;

Ward and Meijer, 2010; Maidenbaum et al., 2014b) and for behavioral (Stiles et al., 2015; Levy-Tzedek et al., 2012; Proulx et al., 2014; Haigh et al., 2013) and neuroimaging (Abboud et al., 2015; Striem-Amit et al., 2012a,b,c; Ortiz et al., 2011; Lee et al., 2014; Hertz and Amedi (2014); Kupers et al., 2006; Kupers et al., 2010) research. While SSDs are still not in widespread practical use, most of the limiting factors have been mitigated in recent years offering increased future potential for practical visual rehabilitation (Elli et al., 2014; Maidenbaum et al., 2014a).

Here, we used a visual-to-auditory sensory-substitution device (SSD) known as “the vOIce” (Meijer, 1992) (Fig. 1A), which enables “seeing with sound” for highly trained users. This device consists of a video camera connected to a computer and stereo headphones. Images are converted into “soundscapes” using a predictable algorithm, allowing the participants to listen to and then interpret the visual information coming from a digital video camera (Fig. 1B and C). 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. Remarkably, proficient users are able to differentiate the shapes of different objects, identify the actual objects, and locate them in space (Amedi et al., 2007; Auvray et al., 2007; Proulx et al., 2008; Striem-Amit et al., 2012a,b,c). Visual information in the sound representations of complicated gray-scale images is preserved up to a resolution of about 144×176 pixels, for a 2 s sound scan and a 5 kHz audio bandwidth. Note that in this experiment we used pre-recorded soundscapes within the fMRI scanner.

2.3. Training

Subjects were trained with the vOIce algorithm in a step-by-step training program, starting with simple geometric shapes and progressively reaching more complex shapes – including Hebrew letters and words – comprised of the simpler shapes taught earlier. The subjects were trained for 10–15 h on the orthographic category, during weekly sessions each lasting for two hours, the variable length of training representing the variable time it took the subjects to master the conversion algorithm across the wide range of “soundscapes” within the training program. Tactile stimuli which matched the “soundscapes” were created on Braille dot homogenous displays as a feedback and to improve the subjects’ ability to extract shape. In addition, the subjects were encouraged to draw the shapes that they extracted. The “soundscapes” were presented with a progressively higher scanning speed. Seven Hebrew capital letters were used in the imaging experiment and presented through vOIce: hei (ה), resh (ר), shin (ש), yud (י), ain (א), kaf (כ) and chet (ח).

2.3.1. Stimuli

The letters chosen were the easiest to extract using vOIce, as assessed during the training sessions. During the behavioral training, subjects were instructed to recognize the letters. In order to avoid the creation of associations, we used visually-similar and confusing letters (like hei (ה) and chet (ח), which have a very similar shape to ascertain that the subjects had to rely on the vOIce shape extraction algorithm rather than on associations between the shape and the sound that represents it. In this way, we were able to inspect the putative neural correlates of the online computation of discerning shapes, as opposed to possible memory effects (in themselves activating the occipital cortex of the blind (Amedi et al., 2003; Roder et al., 2001)). Ten two-letter Hebrew words were composed from the six letters.

2.3.1.1. Letter size and resolution. The letters and the words were white against a black background and were created in MS Paint software. The scrambled letters/words were created by cutting pieces from real letters/words and shifting them to a slightly different location, while adapting them precisely to the original letter size (Fig. 1D and E). They matched the real stimuli in terms of their local features (they had the same luminance-the amount of black and white-as the OrthoSSD stimuli), but not in their global shape (they did not preserve the shape of orthographic stimuli). Note that the scramble could have been performed on the waveform and not on the original image (i.e. preserving low-level auditory attributes instead of low-level visual ones), but we chose to scramble the visual input as it led to the more strict of the two in terms of the potential activations (i.e. if an activation would be due to cross-modal task switching plasticity for auditory processing we wanted to make sure the stronger activation would be elicited by the scrambled condition and not the main condition). This choice is consistent with previous SSD work for both reading and other tasks (Szweid et al., 2011; Grill-Spector et al., 1998). In addition, note that previous work exploring reading via Sensory Substitution used other visual categories as contrasts and not scrambled stimuli.

The orthographic and the scrambled orthographic visual stimuli were converted to vOIce soundscapes; each individual presentation (of either letter or word) lasted for 2 s (i.e., the scanning speed of the vOIce for each stimulus was 2 s). The vOIce stimuli are scanned from left to right and, therefore, the word was scanned in an order reversed to the canonical right to left Hebrew letter reading order. The resolution of individual letters was 176×144 pixels (the highest technical resolution of the vOIce SSD). The audio session, which was recorded using GoldWave 5.58

software, consisted of two letters and a word comprised of them (Fig. 1D and E).

2.3.2. Slow event related design

Stimuli were presented in the scanner using Presentation® software (Neurobehavioral System, CA, USA). Each block was made up of two letters and a word comprised of these letters presented through the vOIce. These vOIce stimuli were either orthographic (OrthoSSD) or scrambled orthographic (ScrSSD). The SSD stimuli were followed by an audio recording and by a task condition that required the subjects to decide and respond as quickly as possible whether there was correspondence between the vOIce stimuli and the audio recording, which either did or did not match. The task condition was designed to call the subjects’ attention to the decoding of the letters. There were fourteen epochs in the experiment, four of which were scrambled epochs, presented in a fixed pseudo-random order. Each epoch included 4 repetitions of the first letter through vOIce, 4 repetitions of the second letter through vOIce, and 4 repetitions of a two-letter word through vOIce. The audio session was presented for 2 s. A 12 s rest period separated the blocks and followed the 2 s response (task) phase. A 26 s rest period preceded the first block.

2.3.3. Experimental setup

During the entire experiment the subjects were wearing fMRI compatible headphones and had both their thumbs on a four button response box. Outside the scanner they were instructed to press on the response box with their right thumb if there was a match between what they heard through vOIce and the audio recording that followed, and with their left thumb otherwise; if they could not decipher the vOIce recording they were asked to press randomly.

2.4. Functional and anatomical MRI acquisition

The BOLD fMRI measurements were conducted in a whole-body GE 3-T scanner. The pulse sequence used was the gradient-echo echo planar imaging sequence. All images were acquired using a standard quadrature head coil. The scanning session included anatomical and functional imaging. 3D anatomical volumes were collected using a T1 SPGR sequence. Functional data were obtained under the following parameters: TR=2 s, TE=30 ms, FA=70°, imaging matrix=64 × 64, FOV=20 × 20 cm². Twenty-nine slices with slice thickness=4 mm and no gap were oriented in the axial position, for complete coverage of the whole cortex. The experiment had 293 data points. The first 5 TRs were excluded from the analysis because of non-steady state magnetization. High resolution 3D anatomical volumes were collected using T1-weighted images using a 3D turbo field echo T1-weighted sequence (equivalent to magnetization prepared rapid gradient echo). Typical parameters were: FOV 23 cm (RL) 3 23 cm (VD) 3 17 cm (AP); fold over-axis: RL, data matrix: 160 3 160 3 144 zero filled to 256 in all directions (approximately 1-mm isovoxel native data), TR/TE=9/6 ms, FA=8°.

2.5. Data analysis

2.5.1. Preprocessing

Data analysis was performed using the Brain Voyager QX 2.3.1 software package (Brain Innovation, Maastricht, Netherlands). Before statistical analysis, head motion correction and high-pass temporal (cutoff frequency: 2 cycles/scan) smoothing in the frequency domain were applied to remove drifts and to improve the signal-to-noise ratio. Functional and anatomical datasets for each subject were aligned and fit to standardized Talairach space (Talairach and Tournoux, 1988). For group level analysis, single subject data were spatially smoothed with a three dimensional 6 mm half width Gaussian (2 functional voxels) to reduce inter-subject variability.

2.5.2. Group analysis

A general linear model (GLM) (Friston et al., 1995) approach was used to generate statistical parametric maps. Across-subject statistical parametric maps were calculated using hierarchical random effects model (RFX) analysis (Friston et al., 1999). Unless indicated otherwise, all statistical parametric maps shown here are presented with a statistical threshold of $p < 0.05$ corrected for multiple comparisons (Forman et al., 1995) using a cluster-size threshold adjustment, based on the Forman Monte Carlo simulation approach extended to 3D datasets using the threshold size plug-in BrainVoyager QX. The cluster-size for contrasts to the baseline condition was elevated to 90 functional voxels. Only positive BOLD was included before correction in all the maps, unless indicated differently.

Except for the ROI analyses (see below), the data were analyzed using a whole-brain group analysis for all the contrasts. All GLM contrasts displayed in this study, except comparisons to baseline, also included a conjunction (or a mask) of the comparison of the main condition to baseline in addition to the main contrast, to verify that only positive BOLD for the main predictor would be included in the analysis (e.g., in a contrast of the OrthoSSD letter phase vs. ScrSSD letter phase (see below), the OrthoSSD letter phase was also contrasted with baseline and the two contrasts were analyzed in conjunction; thus, only voxels that showed significant RFX positive BOLD to the OrthoSSD letter phase and also significantly higher activation to the OrthoSSD letter phase vs. ScrSSD letter phase were highlighted on

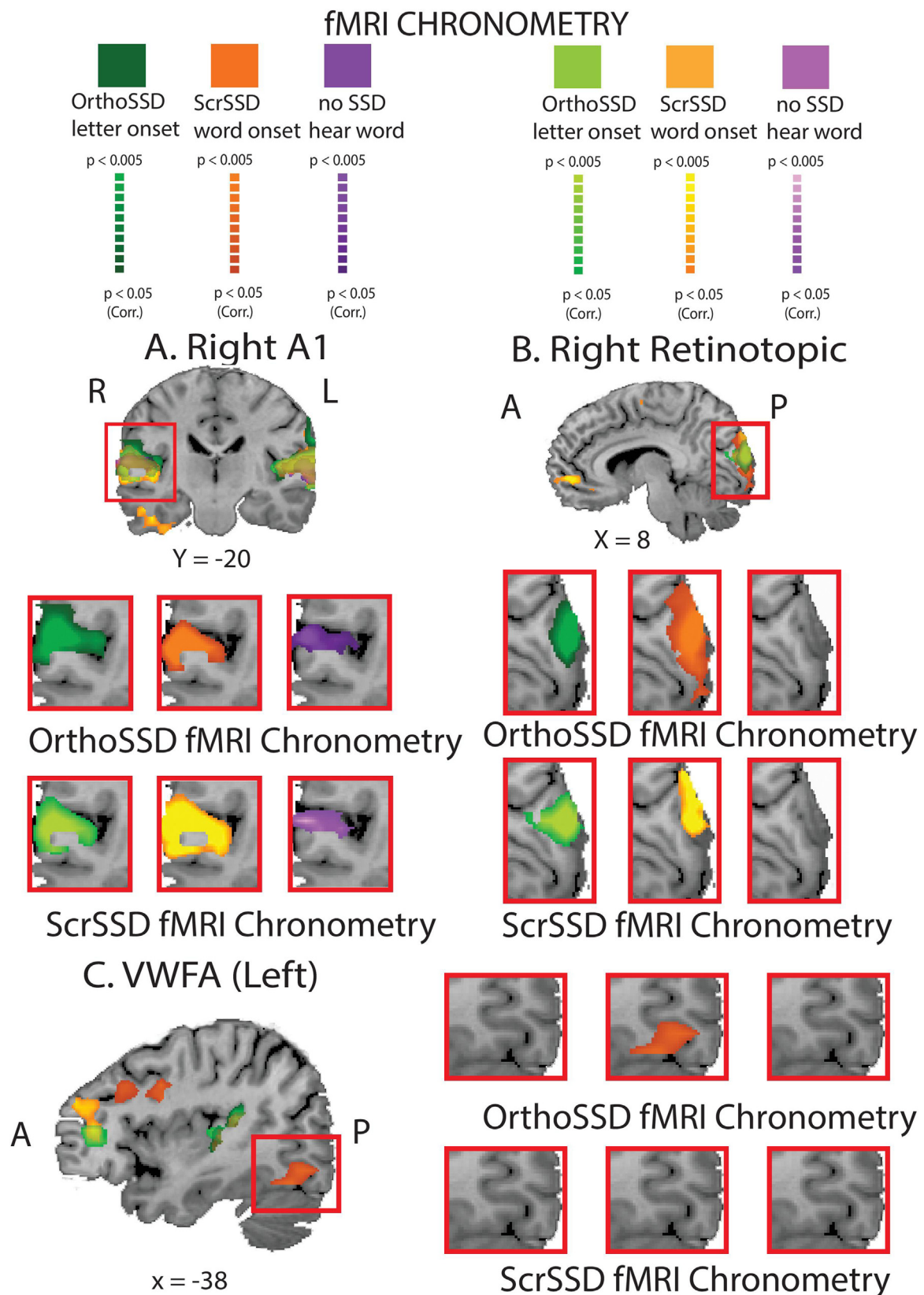


Fig. 2. The temporal progression (Neurochronometry) of the reading process during the OrthoSSD and the ScrSSD trials. The temporal progression of the OrthoSSD and the ScrSSD conditions in three key regions: (A) early auditory (right), (B) visual retinotopic (right) and (C) the VWFA (left). Each map is a random-effect GLM contrast of each temporal phase vs. baseline. The temporal division consisted of the letter onset (green), the word onset (orange) and the hear word (purple) phases. The slices show the superimposition of the different phases in each of the key regions, whereas the temporal progression of the phases is shown below each region. Colored areas represent significant differences in activity. The color bar shows the range of the Z statistic. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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 the OrthoSSD letter onset phase and significantly more deactivation to the ScrSSD letter onset phase from appearing on the map).

We created a GLM that included five predictors: the OrthoSSD stimuli, the ScrSSD stimuli, the corresponding audio (hear word) conditions and the task. We used this GLM to measure the overall auditory impact of the OrthoSSD and the ScrSSD stimuli. In addition, we created a GLM that contained subdivisions within the OrthoSSD and the ScrSSD stimuli to inspect the neurochronometry (i.e. the temporal progression of the signal) within these stimuli.

2.5.2.1. Temporal phases. The OrthoSSD and the ScrSSD stimuli were divided evenly into two temporal phases: the early temporal phase (the *letter phase*) and the late temporal phase (the *word phase*). The other predictors were identical to the ones included in the undivided GLM. The four presentations of the first letter and the first two presentations of the second letter comprised the *letter phase*, whereas the two remaining presentations of the second letter in addition to the four presentations of the word comprised the *word phase*.

2.5.2.2. Retinotopic mapping. We used standard retinotopic mapping (Sereni et al., 1995) of sighted individuals from a different experiment conducted in the lab to define retinotopic areas, since comparison of areas BA17/V1 and BA18/V2 revealed good agreement of the anatomical (cytoarchitectonic) and functional (retinotopic) maps (Wohlschläger et al., 2005). We superimposed these maps on the extrastriate activations we found in our blind subjects to check for overlap. Whenever we found overlap, the equivalent retinotopic area of the sighted as revealed by the mapping is indicated (Figs. 2 and 3).

2.5.2.3. Region of interest (ROI) analysis. A complementary independent region of interest (ROI) analysis of the major auditory and visual areas was carried out. The ROIs were defined as follows. The bilateral A1 and retinotopic areas were defined based on the Julich cytoarchitectonic atlas, (Eickhoff et al., 2005). The VWFA was defined by the Braille words vs. nonsense Braille words contrast (Reich et al., 2011).

From all the regions, we derived beta values and their corresponding *t* values for the contrast OrthoSSD *word phase* vs. ScrSSD *word phase*. In addition, we derived the beta values and their corresponding *t* values for the contrast OrthoSSD *letter*

phase vs. ScrSSD *letter phase* for A1, retinotopic and the VWFA regions.

3. Results

3.1. General

To address the above-mentioned questions, we tested the activations induced by letters and words comprised of these letters (both conveyed by a SSD) in a group of CB individuals (see details in Table S1). The behavioral performance of seven out of the eight subjects was recorded inside the scanner and was high ($87.15\% \pm 13.8$ SD correct; the behavioral performance of the eighth subject could not be analyzed for technical reasons).

We analyzed the data in several ways. First, we conducted several whole-brain analyses: (1) we examined the activations of the different temporal phases of the reading process and during the *hear word* phase in both the OrthoSSD and ScrSSD conditions relative to baseline (Figs. 2 and 3) and (2) we contrasted the OrthoSSD temporal phases with their respective ScrSSD temporal phases (Fig. 4A). In addition, we conducted zoom in regions of interest (ROI) analyses of seven key regions (including the bilateral primary auditory and visual areas and the VWFA) (Fig. 4B). Lastly, we conducted an additional whole brain analysis contrasting the OrthoSSD condition with the ScrSSD condition to control properly for the auditory content of reading via SSD (Fig. S1).

3.2. Whole brain analyses

3.2.1. Different temporal phases relative to baseline

We first examined activations during the early – *letter onset* and the late – *word onset* processing phases in both the OrthoSSD

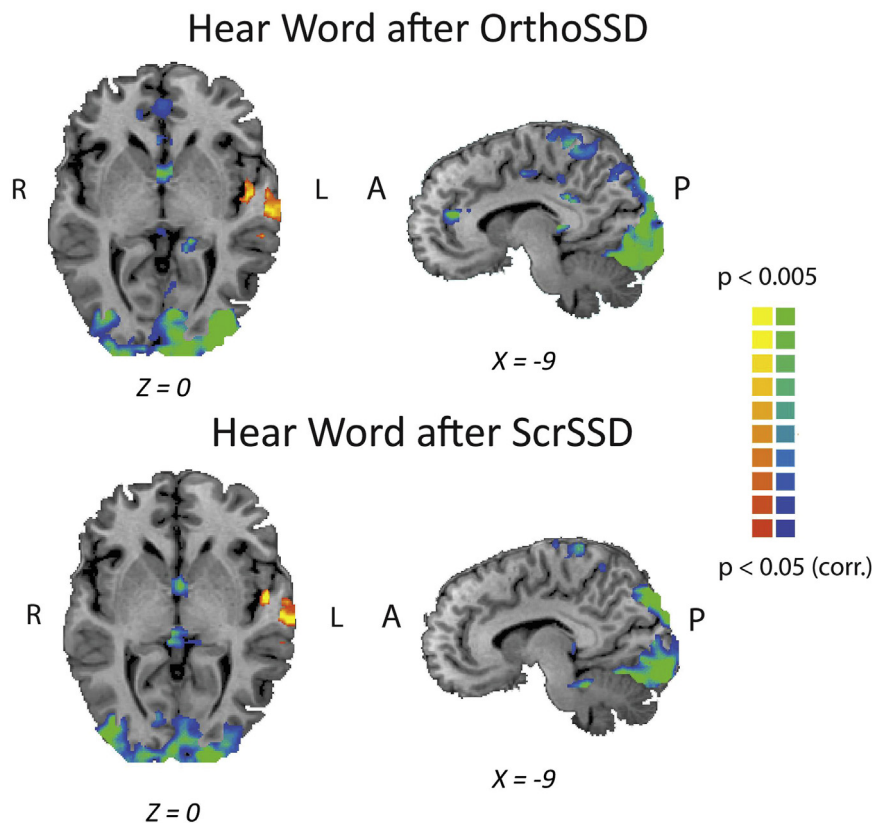


Fig. 3. Deactivations to the hear word (semantic) conditions. A random-effect GLM contrast of the hear word condition to baseline after the OrthoSSD and the ScrSSD trials, showing extensive deactivation in the occipital cortex. Colored areas represent significant differences in activity. The color bar shows the range of the *Z* statistic. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

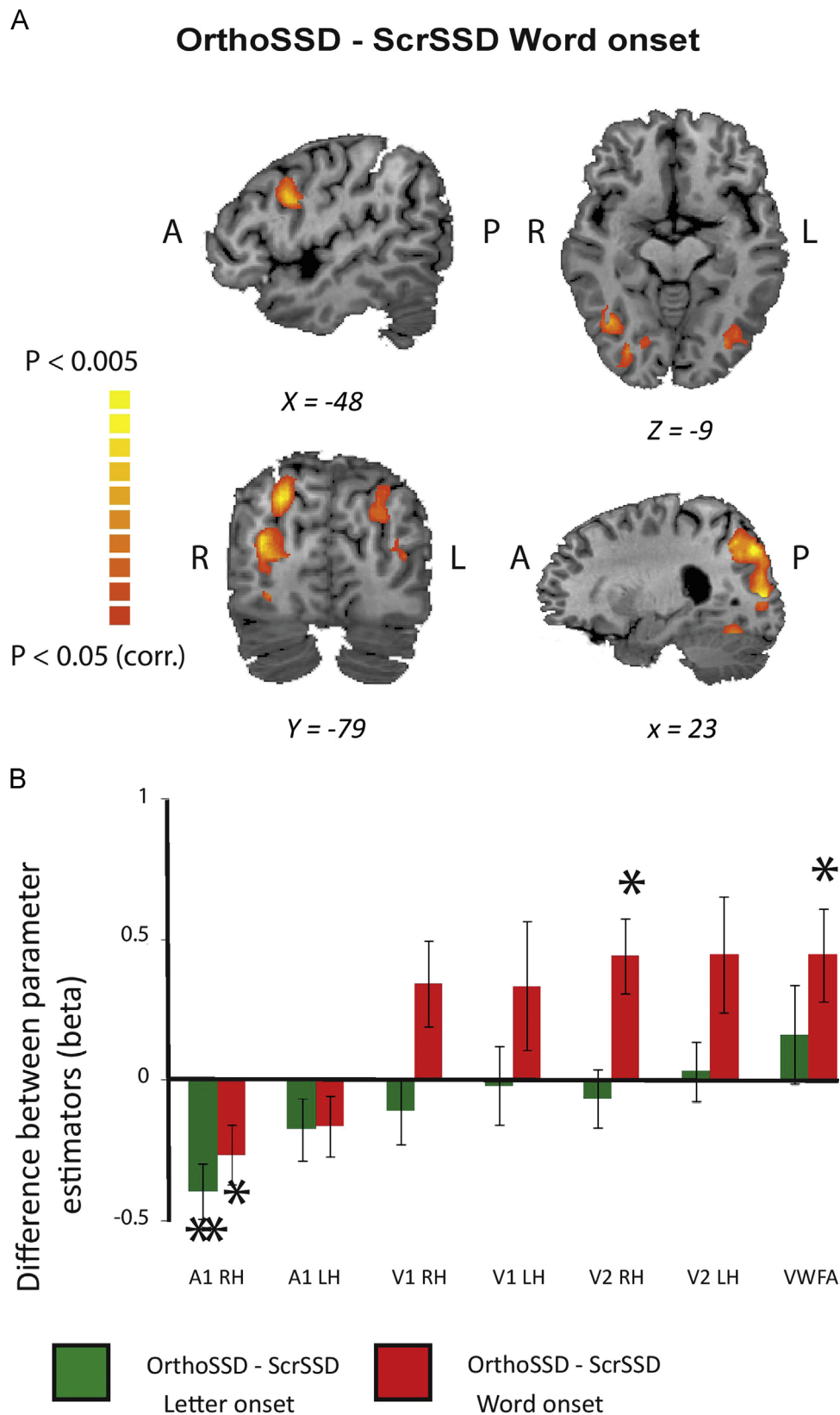


Fig. 4. The reading-with-sounds network of the congenitally blind. (A) A random-effect GLM contrast of the OrthoSSD word phase vs. ScrSSD word phase, showing the key regions of the reading-with-sounds network in the blind. Colored areas represent significant differences in activity. The color bar shows the range of the Z statistic. (B) The difference between the OrthoSSD parameter estimate value (GLM-beta) and the ScrSSD parameter estimate value in the letter and word phases, in auditory, visual-retinotopic and VWFA independent ROIs. (C) The difference between the OrthoSSD parameter estimate value (GLM-beta) and the ScrSSD parameter estimate value in the word phase, in the "degradation network" ROIs (Cohen&Dehaene, 2002). Error bars denote SE. * $p < 0.05$, ** $p < 0.005$ (corrected for multiple comparisons). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and the ScrSSD conditions and in the *hear word* condition to inspect the processing preferences of regions in the visual and auditory cortices during the different temporal (reading and semantic) phases (see details about the temporal phases in the Section 2). The activations during the letter phase were mostly identical, although there were some small differences (Fig. 2, letter onset phases (green), Table S2). Similar to the ScrSSD letter phase relative to the baseline condition, the OrthoSSD letter phase showed bilateral auditory cortex activation (including the Planum Temporale and Heschel's gyrus), early visual cortex activation on the right (roughly speaking the sighted equivalent of the top/dorsal V2/V3 area (as defined by retinotopic mapping in the sighted (see Section 2)) and frontal activation (the bilateral inferior frontal cortex (IFG)/precentral gyrus (preCG) (BA 6)). The activations to OrthoSSD during this phase also included early visual cortex activation on the right and the inferior parietal lobule (BA 40).

During the word phase there were fewer common activations (Table S3). These included bilateral auditory and frontal (IFG, BA 9) cortex activations. In addition to these common activations, the OrthoSSD elicited bilateral striate and extrastriate activations in retinotopic areas (including bilateral V1 and V2 regions) and the inferior parietal lobule. Moreover, we found activations in areas compatible with the classical reading network: the left occipito-temporal area, within the range of coordinates of what is known as the VWFA (Cohen et al., 2002), (peak activation: TC -31, -62, -19, $t > 5.87$, $p < 0.001$) (Fig. 2.C), its right homolog (peak activation: TC 38, -61, -6, $t < 4.57$, $p < 0.005$), and the bilateral dorsal intraparietal region known to be involved in the letter-by-letter "serial reading mode" (Cohen et al., 2008) (BA 19) (peak activations LH: TC -25, -77, 42, $t > 4.08$, $p < 0.005$; RH: TC 23, -65, 36, $t > 4.78$, $p < 0.005$) (Table S3). When using a less rigorous but still significant cluster-size threshold adjustment, (Forman et al., 1995), this contrast also activated Broca's area (BA 45) (peak activation LH: TC -49, 34, 6, $t > 3.73$, $p < 0.01$).

In order to examine whether the occipital cortex was indeed sensitive to semantic input, we inspected the activation pattern during the semantic *hear word* condition that followed the SSD conditions. In the heard word phases following both OrthoSSD and ScrSSD presentations, activations were mainly auditory (including the left BA 21 and 22) (Fig. 2A and Table S4). Generally speaking, if we had observed similar or increased activity relative to the preceding phases in the visual cortex during this condition in this chronometric design, it would have been hard to tell to what this activation should be attributed, since there is no rest condition after each condition in this kind of design. However, we found extensive bilateral *deactivation* in the occipital lobe during the *hear word* phase after both the OrthoSSD and the ScrSSD conditions (Fig. 3), and in words that were both congruent and incongruent with the OrthoSSD condition. This result also rules out possible adaptation effects as in such a case we would expect a difference in the reaction to the different conditions.

3.2.2. OrthoSSD contrasted with their respective ScrSSD temporal phases

We next contrasted the OrthoSSD letter phase and the OrthoSSD word phase with their respective ScrSSD temporal phases to explore the central foci of the reading network of the CB during the early and late stages of the reading process. There were no significant preferences in the letter phase contrast. This may suggest that the auditory and early visual cortices respond in a similar way to the soundscape onset and initial analysis of letters and scrambled letters which reflects a more sensory-based low level analysis of the frequencies, volume etc. By contrast, in the word phase contrast there were several foci of activation that included bilateral activations in the occipital primary cortex (BA 17)

and in the occipital association cortex (BA 19) (Fig. 4). Moreover, there were activations in the left occipitotemporal gyrus (peak activation: TC -31, -62, -19, $t > 4.5$, $p < 0.005$) in a location within the range of the coordinates of what is known as the VWFA (Cohen et al., 2002) (Fig. 4A). We also found activation in its right homolog (peak activation: TC 41, -62, -4, $t > 3.84$, $p < 0.01$) and in the bilateral dorsal intraparietal region (peak activations LH: TC -28, -65, 29, $t > 3.75$, $p < 0.01$, RH: TC 23, 80, 36, $t > 4.23$, $p < 0.005$ and 29, -86, 12, $t > 4.8$, $p < 0.005$). Finally, activations were found in the left (IFG) and the inferior parietal lobule on the right, both of which are associated with training-induced audio-visual integration (Naumer et al., 2009). This network of areas implicated in reading words cannot be attributed to low level auditory processing, as it was contrasted with the ScrSSD equivalent of this temporal phase (see also Fig. S1).

3.3. ROI analyses

3.3.1. Auditory and visual

In order to test the hypothesis concerning specific regions of interest and to independently verify the results from another complementary angle, we conducted a region of interest (ROI) analysis of seven key regions: the bilateral A1, the bilateral V1, the bilateral V2 (all defined by the Julich cytoarchitectonic atlas, Eickhoff et al., 2005), and the VWFA defined by the peak of the Braille words vs. nonsense Braille words contrast (Reich et al., 2011); TC -38, -60, -8). In the right auditory region the difference between the OrthoSSD and the ScrSSD parameter estimators (beta values) in both the letter and word phases was significantly negative (in other words the trend was indicative of increased activation to the ScrSSD. See discussion for possible explanation of this result). In the right V2 and the VWFA this difference was significantly positive in the word phase only (V2: $t > 3.25$, $p < 0.05$; VWFA: $t > 2.65$, $p < 0.05$) (Fig. 4B).

3.4. Ortho vs. scramble whole brain

Finally, to measure the overall auditory impact induced by the processing of the OrthoSSD stimuli in the occipital cortex of the congenitally blind, we conducted a whole-brain analysis, contrasting the OrthoSSD stimuli with the ScrSSD stimuli. While we did not find any auditory cortex activation to the OrthoSSD condition vs. ScrSSD condition, there was significant auditory cortex activation (including A1/Heschl's gyrus) to the opposite contrast, thus showing the larger auditory impact of the ScrSSD stimuli (see Fig. S1). Thus, the auditory ScrSSD control was very conservative (see discussion and methods for further details), as it activated the auditory cortex more than OrthoSSD, indicating that any activation we found in the visual cortex for the OrthoSSD condition (as in the occipital primary (BA 17), association (BA 19) and occipitotemporal (VWFA) areas, Fig. 4A) cannot be attributed to the low level auditory component of the SSD algorithm or auditory input.

4. Discussion

4.1. General

By studying the reading process through visual-to-auditory sensory substitution in CB individuals (Fig. 1), we found that after a very short (10 h) training period, the VWFA shows a preference for processing words (OrthoSSD word phase) and does not show activation for semantic stimuli (*hear word phases*), despite previous reports (Bedny et al., 2011) (Figs. 2 and 4). This held true when the auditory words were identical to the OrthoSSD stimuli except for shape extraction, as they were administered through the same

sensory modality and contained the same linguistic information. In fact, we found deactivation in this area during the semantic condition (while there was robust positive activation in left auditory areas (left Wernicke)) (Fig. 3).

Furthermore, our ScrSSD control enabled better inspection of the reading process through SSD than previously reported (Striem-Amit et al., 2012a), as it was at least as auditorily rich as its OrthoSSD counterpart (and included more temporal transients due to the nature of scrambling, as happens when scrambling in vision (i.e., Grill-Spector et al., 1998)); its activation of the auditory cortex more than the experimental OrthoSSD condition (Fig. S1) showed that the activity attributed to OrthoSSD in visual areas was not due to possible auditory (*task switching*) cross-modal plasticity effects (Weeks et al., 2000). Thus, the activation we found in the VWFA to the OrthoSSD condition singles out the reading component of the task, and implies a possible domination of *task switching* (visual to linguistic) cross-modal plasticity by *task specific sensory independent cross-modal plasticity* engendered by training with a topographical SSD algorithm.

Moreover, the progression of reading began in the early auditory and visual (retinotopic) areas during the early (*letter*) phase of the process (Fig. 2) and moved to higher-tier visual areas, including the VWFA and the bilateral dorsal intraparietal region involved in the reading of stimuli that call for a non-parallel, serial reading mode in sighted individuals (Cohen et al., 2008) (Figs. 2 and 4) during the later (*word*) phase of the process. This implies that the processing hierarchy of reading follows to a large extent the hierarchy observed in the sighted (Rauschecker, 2011) regardless of modality, though with the addition of auditory activations in visual-to-auditory SSD reading. The recruitment of early visual areas joins other recent results demonstrating their multi-sensory nature as reviewed by Murray et al., 2015.

A somewhat surprising result in our study was the similar pattern of activation of V1 and A1 (V1 is early, showing no selectivity and even showing a trend of preference to the ScrSSD condition). There are several ways to explain this result, including extension of the network that processes early auditory patterns into the early visual cortex as well (i.e. an extreme view of this approach can be duplication of neurons to perform the same task more efficiently). Another possibility is a more ordered organization in which A1 is activated slightly earlier (so that processing begins in A1 due to the auditory nature of the task) and then moves to V1 where the processing of elementary topographical visual features of the soundscape might begin – to serve as the building blocks for the VWFA). This kind of approach is supported by Collignon et al. (2013), who showed that auditory-driven activity in primary visual cortex can be explained by direct connections with primary auditory cortex in the congenitally blind. Such a timing difference was not clearly revealed in our results, but it may have been masked by the inherently low temporal resolution of fMRI imaging. Further research is needed to elucidate this interesting issue (e.g. perhaps using techniques with higher temporal sensitivity like EEG and MEG).

4.2. Theories of cross-modal plasticity and processing hierarchy

As described above, two types of cross-modal plasticity have been identified in the blind occipital cortex: *task switching cross-modal plasticity*, where a given (visual) brain area changes the nature of its computational task from visual to linguistic (Amedi et al., 2003; Bedny et al., 2011; Burton et al., 2002a, 2002b; Cohen et al., 1997; Hamilton et al., 2000; Roder et al., 2002; Sadato et al., 1998, 1996), and the *task specific sensory independent cross-modal plasticity*, where the sensory modality varies while the task or computation performed by a brain region remains constant (Reich et al., 2011; Striem-Amit et al., 2012a). Our results here

demonstrate that after training with a topographical SSD for a limited period and very late in life, *task specific sensory independent cross-modal plasticity* in the VWFA can, at least in some cases, dominate the life-long *task switching cross-modal plasticity* for semantics (which accounts for occipital activation to linguistic stimuli in the CB) reported by previous studies (Bedny et al., 2011; Roder et al., 2002) at least when both types of tasks are done sequentially (Figs. 2–4). Further longitudinal research in which blind participants are scanned for both semantic and language tasks before and after SSD learning is needed to fully evaluate the time frame and the relative balance of this dynamic.

These two types of plasticity correspond closely to two opposite general theories regarding the hierarchical processing of CB's occipital cortex.

The *inverted-hierarchy* theory (Amedi et al., 2003; Buchel, 2003; Raz et al., 2005), which is in line with the *task switching cross-modal plasticity* type, suggests that due to the dysfunctional main bottom-up geniculocortical pathway in the blind (Noppeney et al., 2005; Shimony et al., 2006), the retinotopic areas (especially V1) will be much farther (in terms of the number of synapses) from the remaining functional sense organs (in particular the auditory and tactile modality). This, in turn, should lead V1 to resemble the prefrontal cortex (which is similarly remote from any direct sensory input) rather than becoming a primary sensory area in the blind. Another finding that implies that the functional preferences of the early occipital areas in the blind might not correspond to those of the sighted is that the functional organization of early retinotopic areas (in the sighted) has been shown to be correlated with their cytoarchitectonic organization (Wohlschlager et al., 2005) and CB has been implicated in inducing a different cytoarchitectonic organization in early retinotopic areas in the primate brain (Rakic et al., 1991). If function in retinotopic areas indeed correlates with cytoarchitectonics, it is problematic to expect that the functional characteristics of the occipital cortex of the blind would parallel those of the sighted. This theory offers a strong theoretical basis to the notion of *task switching cross-modal plasticity* and the recruitment of these “visual” areas for semantic tasks, but does not adequately explain the results of this work.

An alternative account for the (hierarchical) preferences of the occipital cortex of the congenitally blind draws on the *metamodal brain organization model* (Pascual-Leone and Hamilton, 2001). It proposes that each brain area specializes in a particular type of computation rather than being tied to a specific input modality. As long as the relevant computation information is presented, the task will be performed by the relevant brain area. Thus, it predicts that the early visual cortex will retain its function or characteristic computation regardless of its input, and in the case of CB it may be involved in low-level auditory or tactile processing (due to the direct connectivity between V1 and the early auditory and somatosensory cortices or even thalamic nuclei (Karlen et al., 2006; Laemle et al., 2006; Piche et al., 2007; Robitaille et al., 2008; Wittenberg et al., 2004; Murray et al., 2015; Stilla and Sathian (2008); Kupers et al., 2006). To date, the concept of metamodal operators has received wide experimental support (see reviews at Maidenbaum et al. (2014a), Ricciardi et al. (2014) and Kupers and Ptito (2014)) for relatively complex operations such as object shape extraction (LO) (Amedi et al., 2007), depth perception (Renier et al., 2005), number form extraction (Abboud et al., 2015) and letter form extraction (VWFA) (Reich et al., 2011; Striem-Amit et al., 2012a,b,c), which are situated in higher-tier non-retinotopic visual areas. This model is in line with the *task specific sensory independent plasticity* type and is supported by our results. Our results here offer further support for the metamodal nature of the (higher-tier) VWFA (Figs. 2 and 4), using more rigorous sensory (ScrSSD) and semantic (hear word) controls.

Furthermore, there are some results demonstrating that

metamodal recruitment also exists in early visual areas (Pascual-Leone and Hamilton, 2001; Striem-Amit et al., 2015 in humans; Fishman and Michael, 1973; Morrell, 1972 in animals). Our findings demonstrate the existence of metamodal characteristics in early visual areas, which were activated during the early (*letter*) reading phase along with auditory areas, but not during the semantic condition (Figs. 2 and 3), implying that if the stimuli introduce a visually relevant task or information, early visual areas can likewise act as metamodal operators and process the aspects of a letter that are computed before its form is extracted (Murray et al., 2015). These properties could potentially be the primitive features of letters (i.e. horizontal lines, closed curves, intersection etc) (Gibson, 1971), which, given the nature of our SSD, are processed before these features are combined into letters or the word they form with its corresponding global shape (i.e. (Coltheart et al., 2001)). Since evidence that supports the *metamodal model* in early areas is scarce, even though the latter finding provides weak support for this model, it is nevertheless intriguing. As our design did not allow direct contrasts between the OrthoSSD and the *hear word* conditions, further experiments are required to further elucidate this important issue.

Other versions of the cross-modal plasticity theories, both wider and more limited have potentially interesting relation to our results.

On the one hand, in the minimalistic version, some researchers restrict the *sensory independent cross-modal plasticity* activations to the CB population and consider most metamodal results to be similarly limited. These groups suggest that the visually deprived brain is able to recruit brain areas for the same tasks through compensatory modalities but that sighted, or even late blind, cannot. This approach is supported by a series of results demonstrating the lack of such neural recruitment in late blind or sighted individuals in several regions, including Burton et al. (2002a,b), Sadato et al. (2002), Ptito et al. (2005), Burton et al. (2006), Saenz et al. (2008), Azulay et al. (2009) and Bedny et al. (2012), but is challenged by other areas in which it has been clearly demonstrated in sighted individuals (see Lacey and Sathian (2014) for a review in the case of visuo-haptic object processing and Amedi et al. (2007) for shape conveyed through visual-to-auditory SSD) and late blind individuals as well (Thaler et al., 2011). For a recent review on VWFA and NFA see Hannagan et al. (2015). To further explore this direction it would be important to look at the reading-via-SSD network in sighted and late blind users as well.

On the other end of the spectrum, it has been suggested that the task switching activations reported in the literature are actually innate functions of these areas in general which are only strengthened in the CB. This includes in our context (limited) evidence for semantic processing in the ventral stream of sighted individuals (e.g. Bruffaerts et al., 2014). However, this does not contradict the *metamodal model*, as the latter focuses on a potential or a predilection for processing, rather than on exclusive processing. Future work should explore both conditions of this task with sighted users searching for such activity, including a visual version to enable direct comparison.

4.3. The reading network in the congenitally blind

Reading is a pivotal expertise acquired during an individual's lifetime. This central human skill enables individuals to overcome the inherent limitations of human memory and is an example of an ingenious application of the visual system to convey linguistic information:

[t]he visual medium is so enormously superior because it offers structural equivalents to all characteristics of objects, events, relations. The variety of available visual shapes is as great as

that of possible speech sounds, but what matters is that they can be organized according to readily definable patterns of which the geometric shapes are the most tangible illustration. The principal virtue of the visual medium is that of representing shapes in two-dimensional and three-dimensional space, as compared with the one-dimensional sequence of verbal language. This polydimensional space not only yields good thought models of physical objects or events, it also represents isomorphically the dimensions needed for theoretical reasoning (Houston, 2008).

In sighted individuals, the process of word perception begins in the early occipital areas (Rauschecker, 2011), and undergoes transformations in the highly studied left VWFA (Cohen et al., 2000; Dehaene and Cohen, 2011; Schlaggar and McCandliss, 2007), as the visual system efficiently transforms a complex input of contrast-defined strokes of ink into phonological and semantic word representations. Furthermore, a bilateral dorsal intraparietal region has been associated with a serial reading mode (Cohen et al., 2008). In addition, posterior language-processing areas are thought to be highly connected with anterior systems such as the inferior frontal gyrus (IFG) (see Hernandez et al., 2015 and references within). Our findings show that a similar network and processing hierarchy can be found in CB while reading through a topographical SSD after a short training period (Figs. 2 and 4 and Table S2).

The extraction of letter and word shape through a SSD is serial and considerably slower than usual letter and word perception due to the inherent nature of the SSD algorithm. This made it possible to combine the relatively high spatial resolution of functional imagery with temporal analyses (Fig. 1). Moreover, in this setup, possible artifacts such as mental imagery (Kosslyn et al., 1999) and possible holistic perception of letters (Taylor, 1976) that are usually associated with the reading process in the sighted could for the most part be minimized. These artifacts usually make it very difficult to isolate the neural correlates of the process of combining primitive features to letters (Gibson, 1971) in sighted individuals.

5. Conclusions

To conclude, neuroscience has long attempted to determine how cortical selectivity develops and how much can be attributed to nature vs. nurture, a question which the late Prof. Bentin devoted much work to (e.g. Carmel and Bentin, 2002). CB presents an opportunity to test these questions, as it provides a brain model developed without visual experience. Our findings suggest that the same reading network active through vision is still recruited when reading through other senses such as audition – both early visual areas and higher-order ones. Furthermore, in some higher-order areas such as VWFA, when relevant sensory information compatible with the computation type of a given module is introduced, this module will process this information despite the life-long acquired compensatory information it processed before the introduction of the relevant information. In addition, our results demonstrate that at least in cases where the two conditions are immediately subsequent, the response of such regions to the compensatory task might not be exhibited, and indeed they might exhibit deactivation for this task, implying that the *task specific computation* can dominate the *task switching cross-modal computation*. In this way, even though the occipital cortex is plastic enough to process different kinds of information (including linguistic), it nevertheless preserves potential preferences based on the computation type of the modules of which it is comprised. Further research is needed to elucidate this important question.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [10.1016/j.neuropsychologia.2015.11.009](http://dx.doi.org/10.1016/j.neuropsychologia.2015.11.009).

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