

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

Ella Striem-Amit,¹ Laurent Cohen,^{4,5,6} Stanislas Dehaene,^{7,8,9,10} and Amir Amedi^{1,2,3,*}

¹Department of Medical Neurobiology, The Institute for Medical Research Israel-Canada, Faculty of Medicine

²The Edmond and Lily Safra Center for Brain Sciences (ELSC)

³The Cognitive Science Program

The Hebrew University of Jerusalem, Jerusalem 91220, Israel

⁴Université Pierre et Marie Curie-Paris 6, Faculté de Médecine Pitié-Salpêtrière, IFR 70, 75013 Paris, France

⁵INSERM, ICM Research Center, UMRS 975, 75013 Paris, France

⁶AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurology, 75013 Paris, France

⁷Collège de France, 11 Place Marcelin Berthelot, 75005 Paris, France

⁸Institut National de la Santé et de la Recherche Médicale, Cognitive Neuroimaging Unit, 91191 Gif sur Yvette, France

⁹Commissariat à l'Energie Atomique, Division of Life Sciences, Institute of Bioimaging, Neurospin, 91191 Gif sur Yvette, France

¹⁰Université Paris 11, 91401 Orsay, France

*Correspondence: amir.amedj@ekmd.huji.ac.il

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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,

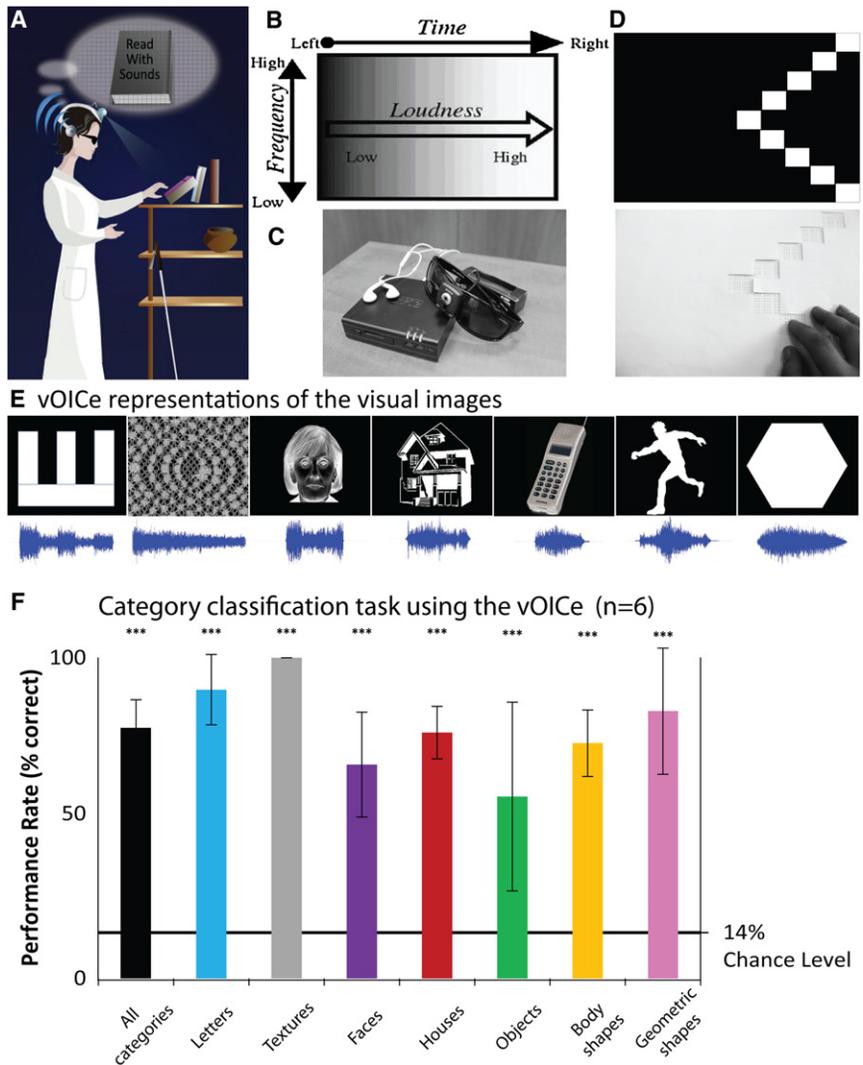


Figure 1. “Visual” Performance in Blind Users of “The vOICe” Sensory Substitution Device after Training

(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 light-weight 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 substi-

tion, 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

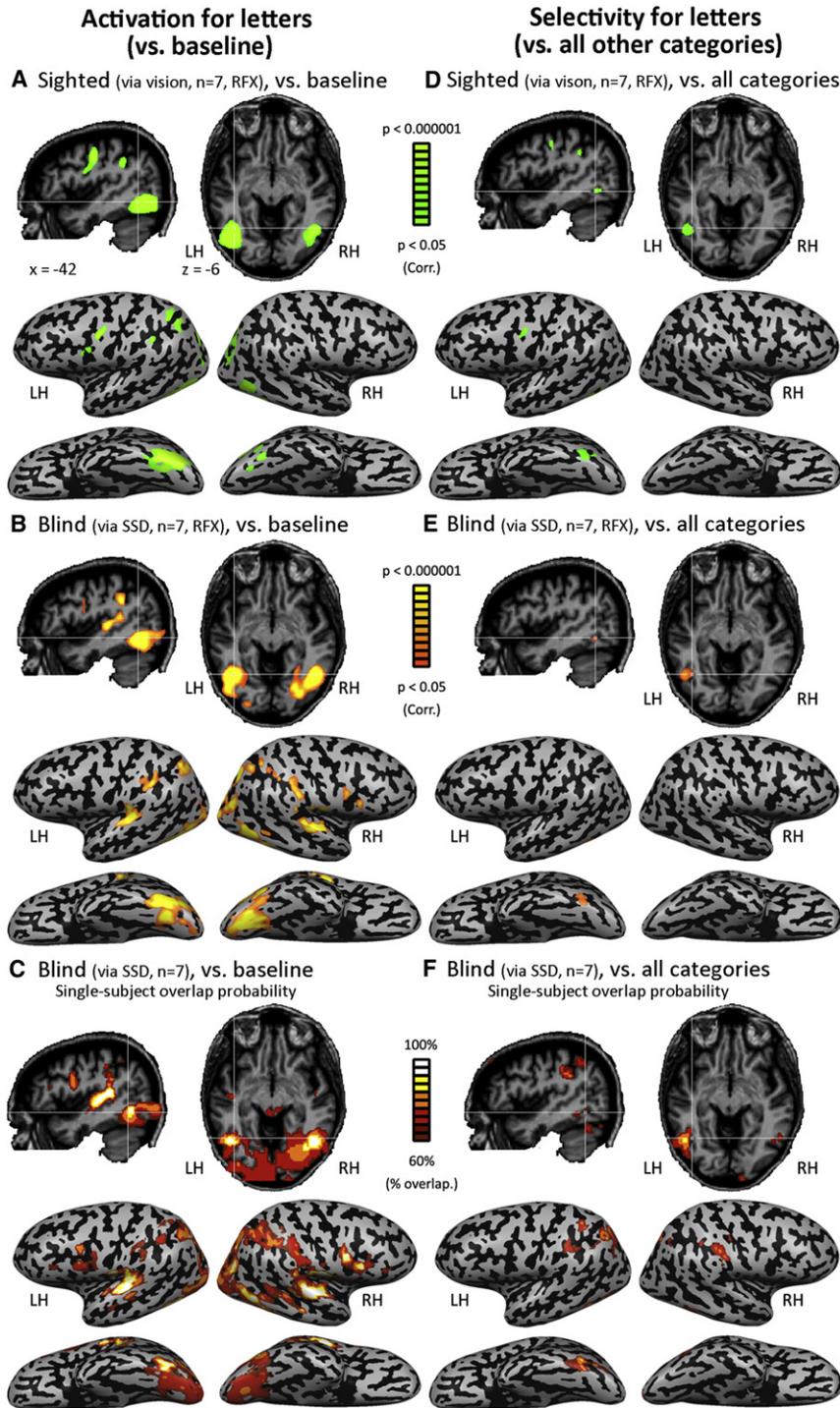


Figure 2. Comparable Selectivity in the VWFA of the Blind and Sighted

(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).

(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 base-

line 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

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

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 sound-scapes 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

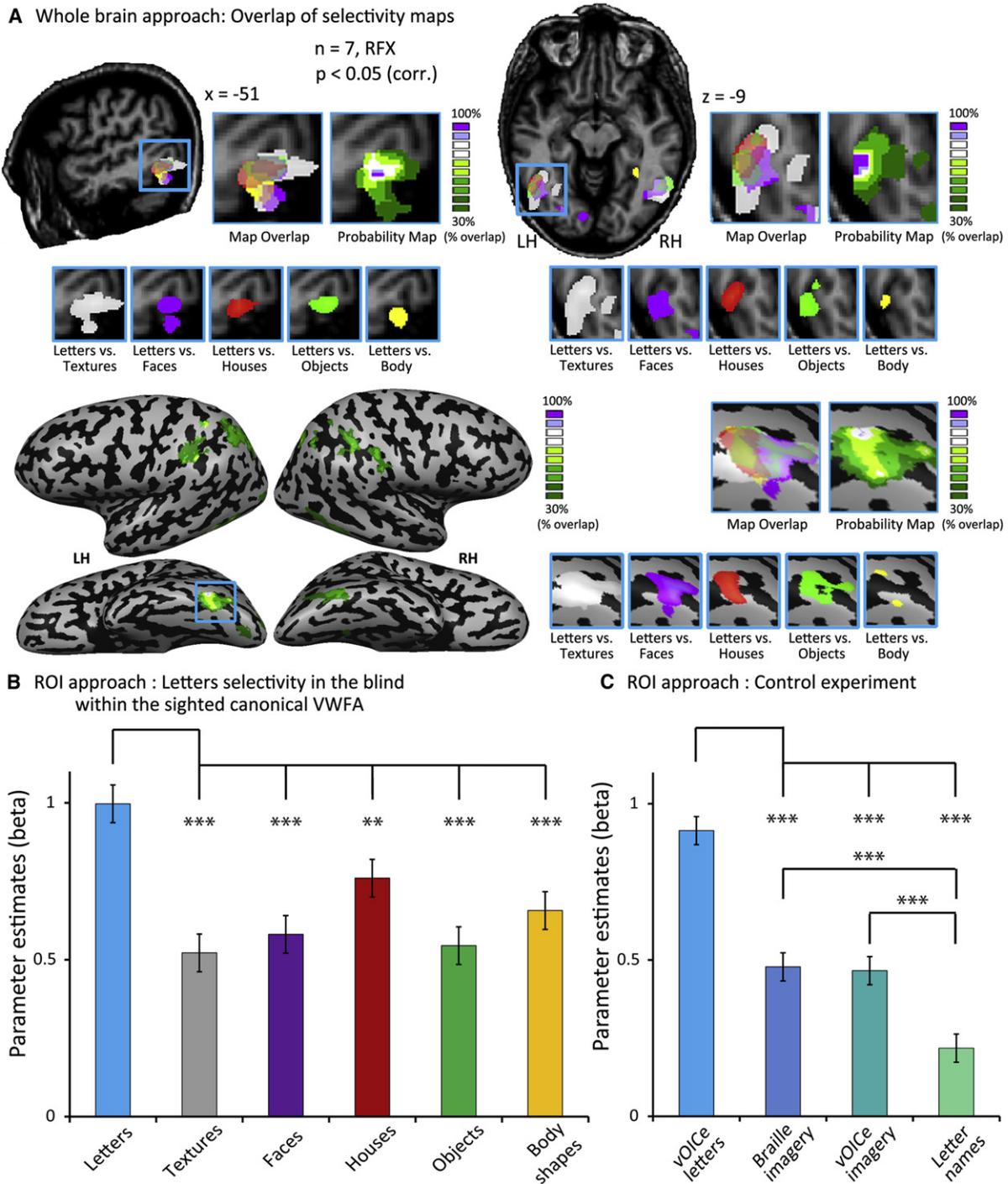


Figure 3. Selectivity to Soundscape Letters in the VWFA of the Blind

(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

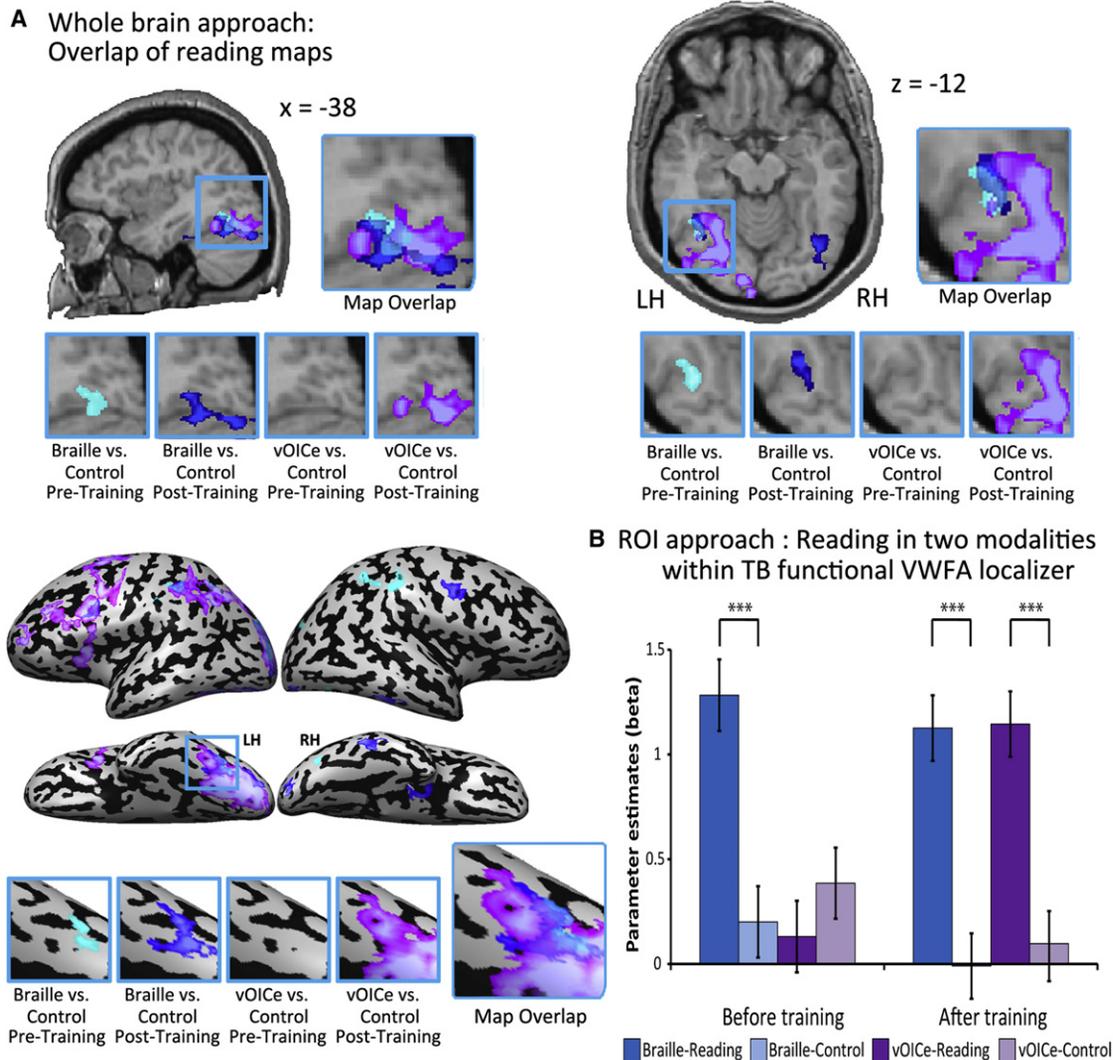


Figure 4. Rapid Adult Plasticity in the VWFA in a Single Case Study of Learning to Read Using Sounds

(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/late 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 re-opening 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% ($\pm 8.8\%$ 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 (β , 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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