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V1 Activation in Congenitally Blind Humans is Associated with Episodic Retrieval

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Recently we showed that the occipital cortex of congenitally blind humans is activated during verbal-memory tasks. Activation was found in regions corresponding to the retinotopic visual areas of sighted humans, including the calcarine sulcus (V1). No such occipital activation was found in sighted humans. One year later, the same blind subjects participated in a second fMRI scan, to study the contribution of semantic elements and episodic memory to the occipital activation. The subjects performed an episodic-memory task, requiring recognition of words that were originally presented in the first scan. We demonstrate here that the magnitude of V1 activation during the recognition task is correlated with memory performance, assessed during the scan. Across the blind, the better-remembered set of words elicited greater V1 activation than words from the poorly-remembered set, although the semantic components and the behavioral task were similar in the two sets. This indicates that on top of semantic processing (suggested previously), V1 activation in the blind is probably associated with long-term episodic memory. Indeed, within the blind, those who showed better recognition-memory performance had greater V1 activation compared with the poorer performers. We conclude that the posterior occipital cortex (including V1) of the congenitally blind is likely to be involved in episodic retrieval.

Keywords: congenital blindness, cortical plasticity, episodic memory, fMRI, visual cortex

Introduction

Unlike in sighted individuals, the occipital cortex of early-onset blind is activated by non-visual tasks (e.g. Kujala *et al.*, 1995; Sadato *et al.*, 1996, 1998, 2002; Buchel *et al.*, 1998a,b; Roder *et al.*, 1999, 2002; Weeks *et al.*, 2000; Arno *et al.*, 2001; De Volder *et al.*, 2001; Burton *et al.*, 2002a,b, 2003; Gizewski *et al.*, 2003; Noppeney *et al.*, 2003; Ross *et al.*, 2003; Lambert *et al.*, 2004). There are also indications that this reorganization may be functionally relevant. Recent transcranial magnetic stimulation (TMS) experiments in the blind show that transient disruption of the occipital cortex, while blind subjects read Braille (Cohen *et al.*, 1997; Hamilton and Pascual-Leone, 1998) or perform an auditory verb-generation task (Amedi *et al.*, 2004), leads to an increased error rate.

We have shown that verbal-memory tasks generate robust activation in the visual cortex of congenitally blind subjects, even in the absence of any sensory stimulation (Amedi *et al.*, 2003). Occipital activation was seen during a verbal-memory task (VM), requiring free recall of word lists that were extensively learned in advance, and a verb-generation (VG) task. No such occipital activation was seen in sighted controls. This differential activation was also mirrored by better verbal-memory performance in the blind compared to the sighted controls. Approximately 1 year after the original functional magnetic resonance imaging (fMRI) scan (referred here as 'scan 1') we conducted a second fMRI scan (referred here as 'scan 2'; see Fig. 1) on the same congenitally blind subjects. During the present scan (scan 2), subjects performed a recognition-memory task requiring them to identify words that were originally presented in scan 1. Two sets of words were used in scan 2. The first consisted of words from the VM lists, which were well practiced prior to scan 1. The second set consisted of words which were introduced to the subjects only once during scan 1, in the VG condition. The present experiment was designed to address two major issues:

1. Assessment of the relative contribution of semantic processing and episodic memory (retaining memories of specific events that occurred at a particular time and place; Tulving, 1972) to the blind's occipital activation.

The activation found in scan 1 could, in principle, be a result of semantic processing, as suggested previously (Burton *et al.*, 2003; Noppeney *et al.*, 2003). During scan 1 subjects were required to recall well-practiced word lists. Thus, it may be argued that the activation could stem from the semantic processing (i.e. the meaning of the retrieved words) rather than memory processes *per se*. To address this concern the present study compared the occipital activation during a recognition-memory task performed on two sets of words. While the semantic components of both sets were similar, memory performance level was markedly dissimilar due to difference in practice levels on the two sets of words. Thus, a difference in the occipital activation between the two conditions can be assigned to memory rather than semantic elements.

2. Evaluation of whether the magnitude of fMRI activation is correlated with online memory performance, assessed during the scan.

Previously, we were able to show positive correlation between the degree of visual cortex activation in the blind and their general memory skills, assessed 6 months following the fMRI scan (Amedi *et al.*, 2003). These correlations were unique to the blind: first, sighted controls had no significant occipital fMRI activation during the memory task (under the same experimental conditions as the blind). Furthermore, unlike the blind, no correlation was found between the sighted subjects' (non-significant) activation in V1 and their memory skills (see Amedi *et al.*, 2003). Therefore, in the present study, we focus only on blind subjects. We assess here the magnitude of fMRI activation, as well as online memory performance during the scan. The correlation between these measures was assessed both across the blind, i.e. whether the better-remembered set of words elicit

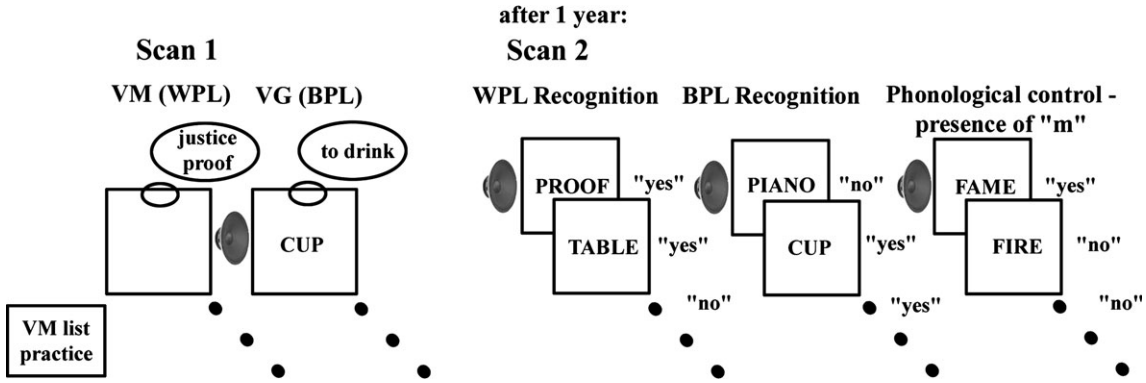

Figure 1. Experimental design. The present experiment (i.e. scan 2) was carried out ~1 year after a first fMRI scan (i.e. scan 1) was performed. During scan 1 congenitally blind subjects performed (i) a verbal-memory (VM) task, in which they covertly recalled lists of words, which were extensively learned in advance. This set of words will be referred here as the well-practiced-list (WPL); and (ii) a verb-generation (VG) task, including words which were heard by the subjects for the first time during the scan. This set of words will be referred here as the barely practiced-list (BPL). During the present study (scan 2), subjects performed three different tasks: (i) WPL recognition — judgement whether heard words were in the list of words learned for the VM condition in scan 1; (ii) BPL recognition— judgement whether heard words were present in the VG condition during scan 1; and (iii) phonological control — judgement whether the Hebrew letter equivalent to 'm' was present in each heard word. Subjects reported 'yes' or 'no' to each word, using a response box. The experiment was conducted using a block design paradigm. In each block, six words were presented, one every two seconds.

higher activation compared with the poorly-remembered set; and within the blind, i.e. whether subjects who perform better in the recognition memory task have higher activation in their occipital cortex during performance of this task.

Materials and Methods

Subjects

Nine blind native Hebrew speakers participated in the experiment. Subjects' consent was obtained according to the Declaration of Helsinki. The Tel-Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure. An expert examined the blind subjects to assess the cause of blindness and the presence of any light perception. All subjects were congenitally blind and had major retinal damage, and their blindness was not due to a progressive neurological disease. None had history of further neurological or psychiatric disorders. Eight of the subjects did not have any form of light perception (see Table 1). The last subject (subject 9) could only report the presence of a strong light, but could not localize it or recognize any pattern. Eight of the subjects were right-handed, as assessed using the Edinburgh test. All the subjects that participated in the present experiment participated also in the first scan (i.e. scan 1; see Fig. 1). In the previous scan (scan 1) no significant activation was seen in the occipital regions of the sighted subjects during the verbal memory task (under the same experimental conditions as in the blind; see Amedi *et al.*, 2003). Thus, sighted controls were not included in the present experiment.

MRI Acquisition

The BOLD fMRI measurements were performed in a whole-body 1.5-T, Signa Horizon, LX8.25 General Electric scanner. The functional MRI protocols were based on a multi-slice gradient echo-planar imaging and a standard head coil. The functional data were obtained under the optimal timing parameters: T_R = 3 s, T_E = 55 ms, flip angle = 90°, imaging matrix = 128 × 128, FOV = 24 cm. The 27 slices with slice thickness 4 mm (with no gap) were oriented in the axial position. The scan covered the whole brain.

Experimental Setup

All words were aurally presented, using the same male voice as in scan 1. The auditory signals were presented binaurally to the subjects through a pneumatic device of silicone tubes into commercially available noise shielding headphones (Slimline noise guard headset, Newmatic Sound System, USA). Behavioral performance was assessed during the fMRI scan, using a motor response box. Subjects responded with the index finger for 'yes' answers and the middle finger for 'no' answers.

Table 1
Blind subjects characteristics

Subject	Age and sex	Cause of blindness	Light perception	Handedness	Preferred hand for Braille reading	Braille reading since (age)
1	32 M	retinopathy of prematurity	none	right	left	6
2	29 M	rubella	none	right	right	6
3	28 F	retinopathy of prematurity	none	left	left	6
4	52 F	leber congenital amaurosis	none	right	right	6
5	31 F	rubella	none	right	left	6
6	47 M	retinopathy of prematurity	none	right	right	7
7	22 F	microphthalmia	none	right	right	5
8	29 M	retinopathy of prematurity	none	right	left	6
9	33 M	retinopathy of prematurity	faint	right	right	6

Stimuli and Experimental Paradigm

The present experiment was carried out approximately one year after the first fMRI scan (i.e. scan 1) was performed (see Fig. 1). The present experiment (i.e. scan 2) tested the activation pattern elicited during recognition-memory of words that were present in scan 1. During scan 1, subjects performed five different tasks (for details, see Amedi *et al.*, 2003). Among the tasks were: (i) a verbal-memory task (VM), in which subjects covertly recalled lists of words, which were extensively learned in advance (1 week prior to scan 1) to the point that they were recalled flawlessly during scan 1; and (ii) a verb-generation condition (VG) in which subjects covertly retrieved a compatible verb to a heard noun (e.g. 'read' for 'book'). The subjects had no prior verb-generation practice with this set of words before the scan.

In the present study (scan 2), three experimental conditions were used: (condition 1) recognition of words from the well-practiced VM list (termed 'well-practiced-list recognition', or 'WPL recognition'), in which subjects had to judge whether heard words were in the original (well practiced) lists learned for the VM condition in scan 1; (condition 2) recognition of words from the barely practiced VG list (termed 'barely practiced-list recognition', or 'BPL recognition'), in which subjects had to judge whether the heard words were present in the VG condition during scan 1 (i.e. are part of the nouns presented only during VG, to whom subjects had to generate a verb). In both the WPL and BPL recognition, half of the words presented were old (i.e. presented during scan 1 in the VM and VG lists, respectively) and half were new. In both conditions, old and new words belonged to the same semantic category; (condition 3) phonological control task, in which subjects judged whether, in each heard word, the Hebrew letter equivalent to the letter 'm' was present. Words used for the different

experimental conditions had on average the same length and frequency rating (according to a Hebrew word frequency database; see http://micro5.mscc.huji.ac.il/~frost/download.html). The new words used in each condition were counterbalanced across subjects (such that the words in one condition for one subject were presented in the other conditions for another subject). A rest condition, in which subjects lay in the magnet with no action required, served as a hemodynamic baseline condition. The experiment was conducted using a block design paradigm. All experimental epochs lasted 12 s, followed by a 9 s rest period. In all experimental conditions, words were presented every 2 s. Each epoch was repeated six times using different words. A short (~1 s) auditory instruction was given before the beginning and at the end of all epochs. The instruction was similar for both WPL and BPL recognition tasks (i.e. 'an old word?'), making it impossible to distinguish among WPL and BPL blocks in advance (see discussion).

Data Analysis

Behavioral Data

Performance level was assessed as percent of correct responses; corresponding to the sum of hit and correct rejection responses divided by the total number of trials. The d' (an index of sensitivity in signal detection theory) is also provided by the formula $d' = Z(\text{hits}) - Z(\text{false alarms})$, where Z is the inverse of normal distribution function, transforming the hit and false alarm proportions to units of standard deviation. For further details, see Green and Swets (1966).

Imaging Data

Data analysis was performed using the Brain Voyager 4.96 software package (Brain Innovation, Maastricht, The Netherlands). Before statistical analysis, head motion correction, slice scan time correction and high-pass temporal smoothing in the frequency domain were applied in order to remove drifts and to improve the signal to noise ratio. A general linear model (GLM) was used to generate statistical parametric maps (modeling the hemodynamic response function using parameters as in Boynton *et al.*, 1996). Across-subjects statistical parametric maps (Figs 2 and 3) were calculated using hierarchical random-effects model analysis (Friston *et al.*, 1999). This was done after the voxel activation time courses of all subjects were transformed into Talairach space (Talairach and Tournoux, 1988), Z-normalized and concatenated. Significance levels were calculated taking into account the probability of a false detection for any given cluster (Forman *et al.*, 1995) by a Monte Carlo simulation (AlphaSim, by B. Douglas Ward and R.W. Cox, 1996) using the combination of individual voxel probability threshold and a minimum cluster size of 10 functional voxels. The minimum significance level, corrected for any given cluster was $P < 0.05$. The retinotopic borders displayed on the Talairach normalized unfolded brain of the blind (across-subject statistical parametric maps, Figs 2 and 3) were roughly estimated using the rotating wedge technique (Engel *et al.*, 1997) on one sighted subject, who was scanned in the same scanner using the same sequence. The Talairach normalized volumetric time course of activation of the sighted subject was superimposed on a blind subject's Talairach normalized brain. Then the approximate retinotopic borders were assessed using the phase information.

The activation time course of individual subjects (Fig. 5) was obtained from statistically significant clusters in each region of interest (ROI), by using a fixed model GLM with correction for multiple comparisons in each subject. The averaged signal change during stimuli presentation (shifted by 1 T_R) was also calculated (Fig. 5*B*). Data from individual subjects was then averaged across all subjects.

Assessment of the V1 activation (for the purpose of correlation with performance level in each subject; see Fig. 6) was based on the BOLD signal intensity of the peak voxel in a smoothed volume within the ROI, after convolution with a Gaussian kernel of 8 mm (full width at half maximum). The same procedure was used to assess activation in the others ROIs, i.e. the retinotopic regions (V1–V4), BA7 and A1 (see below), for the purpose of correlating the fMRI activation in these regions with performance level.

ROI Selection

ROI selection was done on an individual-subject basis: (i) V1: voxels in the V1 ROI (used in Figs 4–6) were collected according to an anatomical marker: the calcarine sulcus including its upper and lower banks. The calcarine sulcus of the individual subjects was easily identified using their high-resolution SPGR slices. The approximate retinotopic borders (defined in a sighted subject and superimposed on a blind subject's Talairach normalized brain, as described above) were not used for the selection of significant voxels within the V1 ROI. (ii) A1: voxel selection for the A1 ROI was based on an anatomical marker: the transverse gyrus of Heschl and planum temporale. (iii) BA7: voxel selection for the parietal BA7 ROI was based on Talairach coordinates; in each subject we verified that the peak voxel was within BA7 according to the Talairach Deamon software (University of Texas, San Antonio). (iv) Retinotopic areas: the retinotopic areas' ROI was defined using the approximate retinotopic borders (as described above).

Results

Behavioral Data

The behavioral performance in all tasks was assessed during the fMRI scan. As expected, subjects' performance level was highest during the phonological control task (mean ± SEM correct = 98 ± 1%, d' = 3.5). Performance level during the WPL recognition (77 ± 4% correct, d' = 1.7) was significantly higher (*t*-test, $P < 0.0005$) than during the BPL recognition (52 ± 2% correct, $d' = 0.1$). This seems natural following the differences in practice level between these sets prior to scan 1. Reaction times (RTs) during the phonological control task were fastest (RT = 1026 ± 93 ms, significantly faster than the other two conditions, *t*-test, $P < 0.00001$). WPL recognition and BPL recognition elicited very similar reaction times (RT = 1256 ± 78 and 1254 ± 92 ms, respectively; $P > 0.8$). To summarize, performance during the phonological control task was best, reflecting the ease of this condition. Performance during the two recognition-memory tasks differed significantly (but the reaction times were virtually identical) indicating superior memory performance in the WPL recognition.

Functional Imaging Data

First, the group results of the cortical activation in the blind (Fig. 2) are presented using a random effect general linear model (GLM) analysis (Friston *et al.*, 1999). Activation maps are presented on a full Talairach-normalized (Talairach and Tournoux, 1988) unfolded brain as well as a lateral and medial–ventral inflated view of both hemispheres. The first maps (Fig. 2*A*) show voxels that are differentially active during WPL recognition compared to the phonological control task. The most conspicuous activation was found in the left occipital and occipito-temporal cortex. The occipital activation stretched along the 'visual' retinotopic areas, mainly in ventral regions, and included the calcarine sulcus, corresponding to V1. Significant clusters were also identified in the right occipital cortex (though these had lower significance levels). Robust and significant activation was also found in middle and inferior prefrontal cortex, the insula, and in anterior cingulate gyrus bilaterally, with some preference for the left hemisphere. Significant activation was also present in the posterior parahippocampal gyrus near the calcarine sulcus, and in posterior cingulate of the left hemisphere (see Table 2). No differential activity was observed in auditory and motor regions, demonstrating that these components were similar among the tasks contrasted. The second map presents voxels activated during recognition of words from the BPL recognition compared to the phonological control task (Fig. 2*B*). Activations were found in similar regions as in Figure 2*A* but to a much lesser extent (most

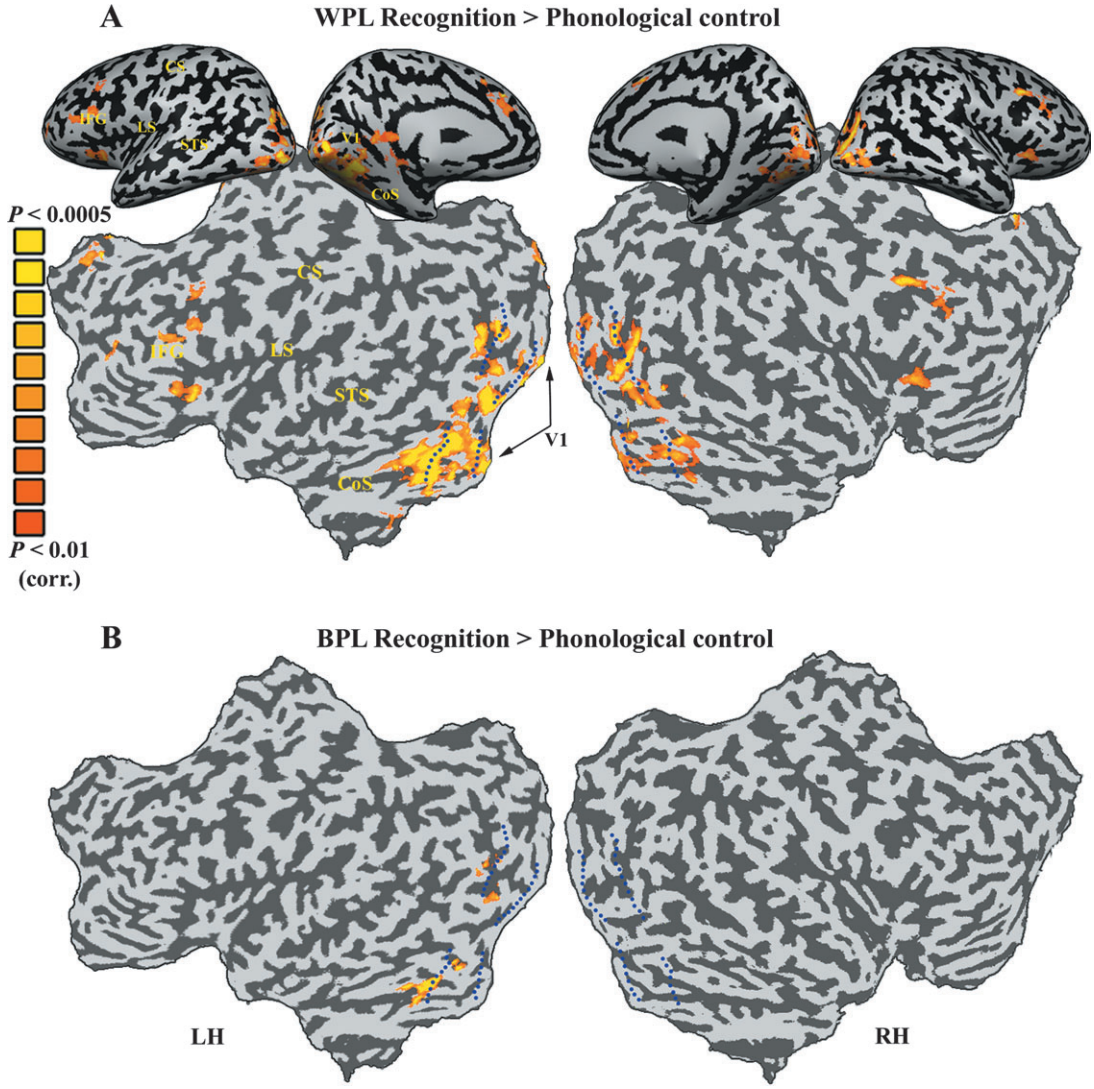

Figure 2. Posterior occipital activation during recognition-memory tasks. Statistical parametric maps of activation in the congenitally blind group ($n = 9$) using a random effect GLM analysis. The data are presented on a full Talairach-normalized unfolded brain of the left (LH) and right (RH) hemispheres, as well as a lateral and medial–ventral inflated view of both hemispheres. Color scale denotes significance ($P < 0.01$ corrected for multiple comparisons). The posterior blue dotted line indicates the approximate V1/V2 border; while the anterior dotted line denotes the estimated anterior border of retinotopic areas in the sighted (see methods for details). (*A*) Contrasting the activation during WPL recognition versus that elicited during the phonological control task shows robust and highly significant activation in the occipital cortex (mainly in the left hemisphere) including the calcarine sulcus (i.e. V1). Significant activation was also found in other cortical areas (see Table 2). (*B*) A second test, contrasting the activation elicited during BPL recognition with the phonological control task, shows significant activation in the occipital cortex (in most cases: $0.01 < P < 0.05$, corrected; see Table 3), which is much weaker in its extent and significance level compared with (*A*). Anatomical markers: IFG, inferior frontal gyrus; CS, central sulcus; LS, lateral sulcus; STS, superior temporal sulcus; CoS, collateral sulcus.

of the activations' threshold corresponds to $0.01 < P < 0.05$ corrected; see Table 3). Finally, the phonological control versus rest contrast revealed some activation in the visual cortex (not shown). However, this activation was smaller than the activation during the two other conditions (versus rest).

Next, we assessed directly the difference in the activation pattern during WPL recognition and BPL recognition. Note that all components of these two tasks were identical, except for memory performance level (significantly greater in WPL recognition). Figure 3 shows the activation observed in the WPL recognition versus BPL recognition contrast. Robust activation (somewhat left lateralized) is seen in the occipital and occipito-temporal cortex, including V1. For the complete list of regions significantly active see Table 4.

Having found significant V1 activation in the group analysis, we next tested whether this differential activation for the better-remembered words can also be seen on an individual basis. In seven of our nine blind subjects, significant calcarine activation (corrected for multiple comparisons) was seen when contrasting activation during WPL and BPL recognition (Fig. 4).

Our results (Figs 3 and 4) therefore suggest a correspondence between online recognition-memory performance level and the extent of activation in V1. To assess the degree of correspondence on a subject-by-subject basis, we first screened for active voxels ($P < 0.001$ corrected for multiple comparisons) in V1 in all conditions (versus rest), and then tested these voxels' selectivity for the different conditions. Note that since the test selected voxels showing activity in all conditions (versus rest), no a priori preference was given to one of the conditions over the others. The average time course of activation across all active voxels in V1 (from both hemispheres) were analyzed on a subject-by-subject basis and then averaged across subjects.

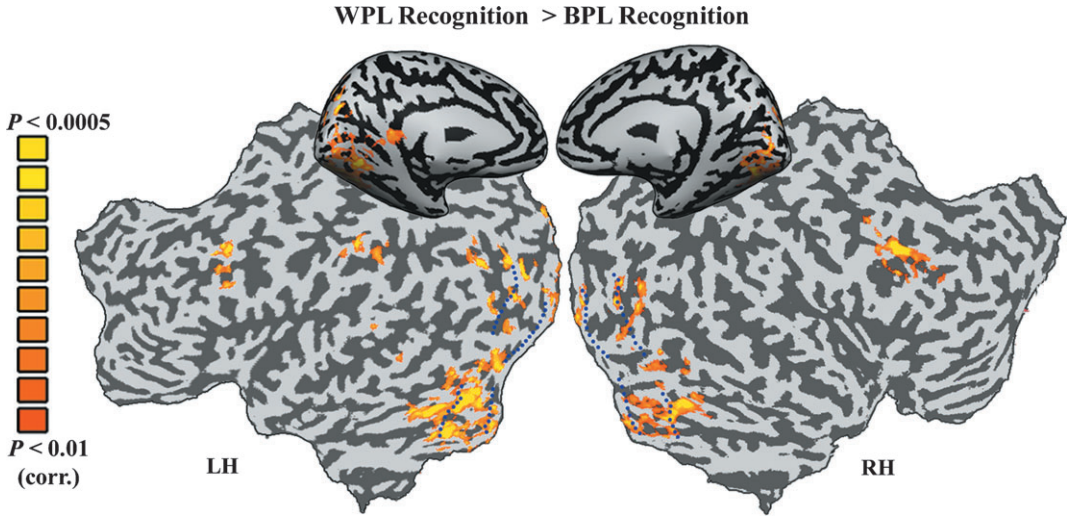

Figure 3. Differential activation of the better-remembered set of words in comparison to the barely practiced set. A Talairach-normalized unfolded brain; in addition, a medial–ventral inflated view of both hemispheres is shown. The figure delineates significant voxels ($P < 0.01$, corrected for multiple comparisons) active during WPL recognition (average performance level: 77% correct) versus BPL recognition (52% correct), using a random effect GLM analysis. Robust recognition-memory related activation is found in the occipital cortex, including V1, with some preference for the left hemisphere. For a list of other regions active see Table 4.

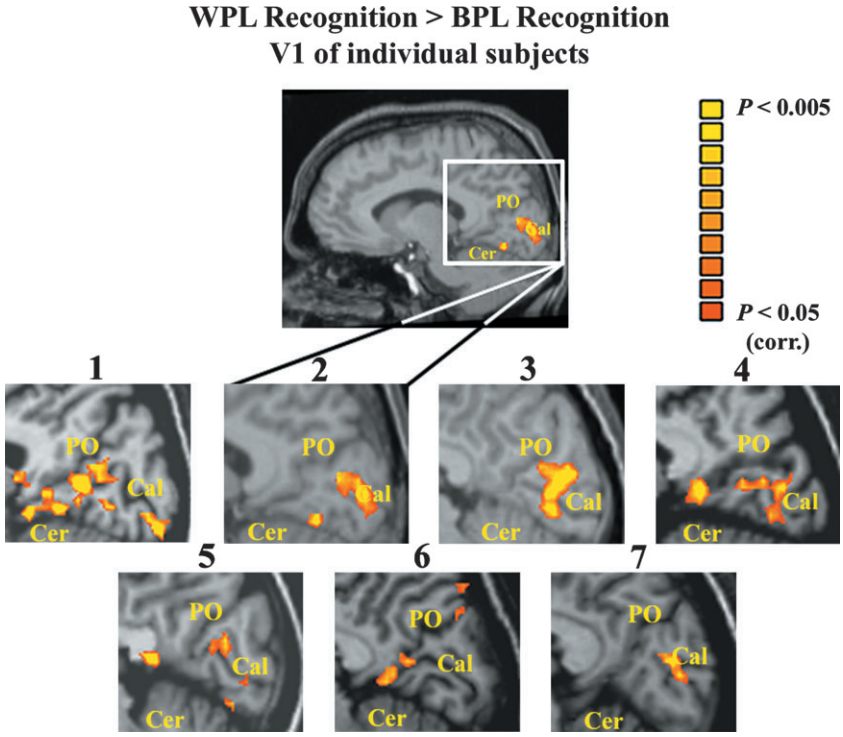

Figure 4. V1 is differentially activated by the better-remembered set of words. Subject-by-subject activation in the calcarine sulcus during WPL versus BPL recognition. The upper figure shows a sagittal view of the brain of one subject, focused on significant voxels ($P < 0.05$ corrected for multiple comparisons) within the calcarine sulcus. Blow-ups for corresponding view of the calcarine sulcus in the other subjects (indicated by numbers) are also shown below. Significant V1 activation was found in seven out of nine blind subjects. Anatomical markers: Cal, calcarine sulcus; PO, parieto-occipital sulcus; Cer, cerebellum.

The results are shown in Figure 5. The activation profile and time course of the V1 clusters during WPL recognition epochs was significantly higher then during the BPL recognition and the phonological control epochs (Student's *t*-test, $P < 0.0005$, $P < 0.001$, respectively). In marked contrast, the activation elicited in A1 was similar among all conditions, indicating that the conditions did not differ significantly in their basic auditory components (averaged percent signal changes in bilateral A1 were 0.72, 0.66 and 0.74 for WPL recognition, BPL recognition and the phonological control conditions, respectively, $P > 0.1$ in all comparisons). Significantly higher activation in V1 during WPL recognition compared with BPL recognition is mirrored by a much better memory performance in the WPL recognition task during the scan (across subjects, Fig. 5*C*). Thus, higher V1 activation is found for the better-remembered set of words (from WPL) compared with the barely-remembered set of

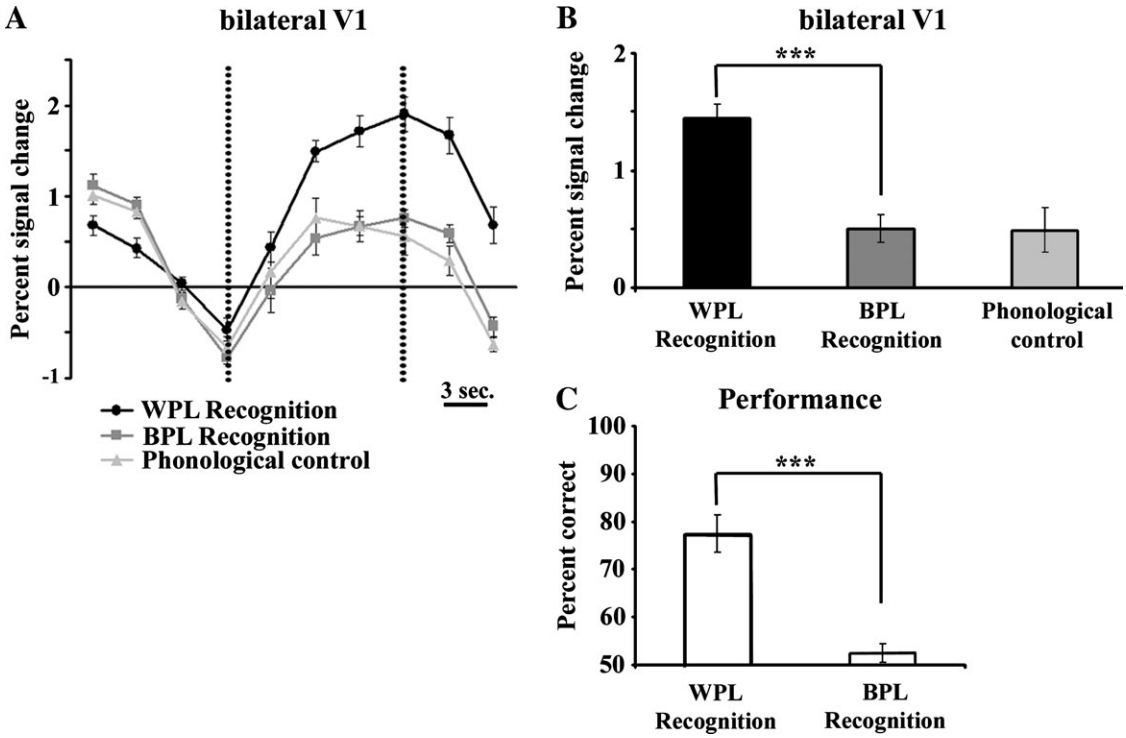

Figure 5. V1 activation during recognition-memory is associated with online memory performance level: across-subjects analysis. The time course of activation was constructed by pooling significant voxels ($P < 0.001$ corrected for multiple comparisons) activated in all experimental conditions with respect to the rest (GLM test: all > rest) on a subject-by-subject basis, and then averaging the activation in each condition across subjects. Error bars denote SEM. (*A*) The averaged time course of activation in V1 (defined anatomically in each subject, see methods). Dotted vertical lines indicate the onset and offset of the experimental epoch. (*B*) Histograms of the average percent signal change in V1 during stimuli presentation (shifted by 1 T_R). Asterisks denote significance level (in comparisons between the two recognition-memory tasks; *t*-test, $P < 0.001$). (*C*) Histograms of the memory performance level during WPL recognition and BPL recognition, showing that the average memory performance (across subjects) is correlated with the magnitude of V1 activation in the blind. Asterisks as in (*B*).

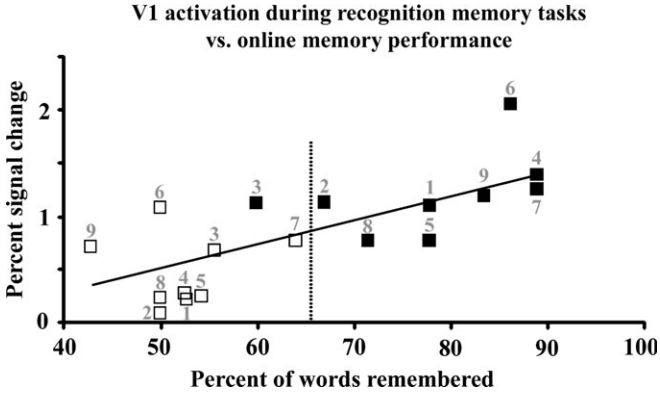

Figure 6. V1 activation during recognition-memory is associated with online memory performance level: within-subjects analysis. A scatter diagram showing the level of V1 activation in individual subjects versus their memory performance. V1 activation was measured by the BOLD signal intensity in each subject (of the peak voxel in a smoothed volume within the calcarine sulcus, defined anatomically, see methods). Peak voxels were selected using two tests: (i) WPL recognition versus rest; and (ii) BPL recognition versus rest. Thus, each subject contributed two data points — for WPL recognition (filled rectangles) and for BPL recognition (open rectangles) — plotted against the subject's performance level in that recognition-memory task. Numbers indicate the individual subjects' data points (twice, for the WPL and BPL recognition levels and their associated fMRI signal, in each subject). Symbols placed right to vertical dotted line denote performance significantly better than chance ($P < 0.05$). A positive, statistically significant correlation is found between the fMRI elicited activation in V1 and online memory performance (Pearson's $r = 0.74$, $P < 0.005$).

words (from BPL). Since the recognition tasks were identical, this again suggests that the occipital activation is related to the memory performance level.

Next, we tested for possible correlation between fMRI activation and memory performance level during the recognition-memory tasks, within the individual blind subjects. Specifically, we tested whether subjects who show higher activation level in V1 during recognition-memory tasks perform better in these tasks, focusing on the subject-by-subject co-variation of the V1 activation during recognition of words (from either the WPL or BPL) with performance level in these same tasks (Fig. 6). Voxels were selected using two tests: WPL recognition versus rest and BPL recognition versus rest. The activation elicited by the memory recognition tasks was assessed in each subject by the BOLD signal intensity of the peak calcarine voxel in a smoothed volume (see Materials and Methods). Each subject contributed two data points — for WPL recognition and for BPL recognition — plotted against the subject's performance level in that recognition-memory task. Performance during BPL recognition was not significantly different than chance level in any of the subjects. In contrast, performance during the WPL recognition was significantly better than chance level (one-sample *t*-test, with respect to a proportion of 0.5, $P < 0.05$) in all but one of the subjects (see Fig. 6; symbols located right of the vertical dotted line denote performance which is significantly better than chance level). A statistically significant correlation was found between memory performance and the V1 BOLD signal (Pearson's $r = 0.74$, $P < 0.005$; see Fig. 6). Thus, subjects

Table 2
Brain regions active during WPL recognition > phonological control

Area (nearest BA)	Talairach coordinates	*t* value in peak voxel	Adjusted *P* value (corrected)
L MFG (BA 9)	−47, 16, 36	3.9	0.005
L MFG (BA 10)	−34, 56, 18	3.4	0.008
R MFG (BA 9)	43, 23, 28	3.9	0.005
L IFG (BA 46)	−47, 28, 19	3.5	0.008
L DFG (BA 6)	−5, 15, 45	3.9	0.005
R DFG (BA 6)	5, 14, 47	3.5	0.008
L CG (32)	−8, 32, 24	3.9	0.005
R CG (32)	6, 22, 33	3.1	0.02
L IFG/ INS (BA 47/13)	−32, 19, 2	4	0.004
R IFG/ INS (BA 47/13)	32, 18, 11	3.9	0.005
L PCu (BA 31)	−28, −76, 23	5.1	0.001
L SOG (BA 19)	−25, −85, 16	5.1	0.001
R SOG (BA 19)	24, −83, 18	4.6	0.002
L MOG (BA 18)	−29, −86, 7	5.1	0.001
R MOG (BA 18)	27, −86, 10	5.4	0.0007
L IOG (BA 19)	−42, −76, −5	4	0.004
R IOG (BA 19)	39, −76, −4	3.9	0.005
L CaS (BA 17)	−6, −86, 2	5.3	0.0008
R CaS (BA 17)	7, −87, 0	4.3	0.003
L LG (BA 18)	−17, −84, −9	5.1	0.001
R LG (BA 18)	13, −84, −8	4.3	0.003
L FG (BA 19)	−27, −67, −8	6.8	0.0002
L FG (BA 37)	−37, −56, −13	5.3	0.0008
R FG (BA 19)	24, −62, −9	4.3	0.003
L PH (BA 27)	−14, −37, 0	3.4	0.01
L CG (BA 29)	−8, −44, 9	4	0.004

Table 3
Brain regions active during BPL recognition > phonological control

Area (nearest BA)	Talairach coordinates	*t* value in peak voxel	Adjusted *P* value (corrected)
L MFG (BA 9)	−49, 20, 32	3.1	0.02
R DFG (BA 6)	5, 15, 45	2.9	0.02
L IFG/ INS (BA 47/13)	−32, 19, −2	3.2	0.02
R IFG/ INS (BA 47/13)	35, 15, 7	2.8	0.03
L MOG (BA 18)	−34, −83, 10	3.5	0.009
R MOG (BA 18)	30, −82, 6	2.9	0.02
L CaS (BA 17)	−18, −94, −3	3.2	0.02
L LG (BA 18)	−22, −73, −8	4	0.004
R LG (BA 18)	13, −85, −9	2.4	0.05
L FG (BA 19)	−24, −53, −8	4.2	0.003

Table 4
Brain regions active during WPL recognition > BPL recognition

Area (nearest BA)	Talairach coordinates	*t* value in peak voxel	Adjusted *P* value (corrected)
L MFG (BA 9/44)	−50, 11, 36	4.2	0.001
R MFG (BA 8/9)	44, 15, 33	4.3	0.003
R MFG (BA 6)	40, −1, 46	3.4	0.01
L PCG (BA 2)	−55, −30, 46	3.7	0.007
L SPL (BA 7)	−31, −60, 48	3.2	0.02
L IPL (BA 40)	−44, −31, 38	3.5	0.009
R IPL (BA 40)	39, −43, 46	3.1	0.02
L PCu (BA 7)	−19, −76, 37	4.4	0.003
L SOG (BA 19)	−17, −84, 30	4	0.004
R SOG (BA 19)	25, −78, 27	3.8	0.006
L MOG (BA 18)	−28, −82, 10	4	0.004
R MOG (BA 18)	26, −83, 9	3.9	0.005
L IOG (BA 18)	−31, −84, 0	3.8	0.006
R IOG (BA 19)	36, −80, −11	3.9	0.005
L CaS (BA 17)	−7, −80, 8	4.6	0.002
R CaS (BA 17)	4, −80, 2	4.6	0.002
L LG (BA 18)	−14, −89, −13	3.8	0.006
R LG (BA 18)	18, −82, −11	3.8	0.006
L FG (BA 19/37)	−31, −65, −11	5.4	0.0007
R FG (BA 19/37)	26, −62, −10	5.4	0.0007
L MTG (BA 21)	−59, −45, 7	3.5	0.009
L PH (BA 27)	−13, −39, 2	3.1	0.02
L CG (BA 29)	−9, −45, 12	3.4	0.01

MFG, middle frontal gyrus; IFG, inferior frontal gyrus; DFG, medial frontal gyrus; CG, cingulate gyrus; INS, insula; PCG, precentral gyrus; SPL, superior parietal lobe; IPL, inferior parietal lobe; PCu, precuneus; SOG, superior occipital gyrus; MOG, middle occipital gyrus; IOG, inferior occipital gyrus; CaS, calcarine sulcus; LG, lingual gyrus; FG, fusiform gyrus; PH, parahippocampal gyrus; MTG, middle temporal gyrus.

demonstrating higher recognition memory performance tended to have higher activation levels in V1. This trend was preserved when analyzing memory performance in the cases in which performance was significantly better than chance level (Pearson's $r = 0.56$). Positive correlation was also found between memory performance and the BOLD signal intensity of the peak voxel, when this voxel was selected not only in V1 but among the whole retinotopic regions (Pearson's $r = 0.76$, $P < 0.001$). This indicates that in the blind the networks involved in long-term memory retrieval may expand to include a constellation of early visual areas (in addition to other memory regions).

The correlation between memory performance and BOLD signal in the blind was also measured in a region outside the visual cortex which is commonly associated with the familiarity effect, i.e BA7 (Wheeler and Buckner, 2003; Herron *et al*., 2004; see also Discussion). BA7 was robustly activated during both WPL recognition (versus rest) and BPL recognition (versus rest). As in V1, significant correlation between memory performance and the BOLD signal was found in BA7 (Pearson's $r = 0.51$, $P < 0.05$). On the other hand, no significant correlation was found between recognition memory performance (including both WPL recognition and BPL recognition results; as done for V1) and the primary auditory cortex (A1) BOLD signal (Pearson's $r = 0.34$; $P > 0.1$). This indicates that the observed correlation was not a global cortical phenomenon and was not due to variation in acoustic levels or awareness to the acoustic stimuli.

Discussion

To summarize, we present evidence suggesting that occipital activation in the congenitally blind is related to long-term episodic memory retrieval. The fMRI activation in V1 (i.e. it's extent, significance level and percent signal change values) was associated with online memory-performance level. Across subjects, the better-remembered set of words elicited greater activation compared with the barely-remembered set. Furthermore, between-subjects analysis revealed that the subjects having better online recognition-memory performance showed higher activation in V1 during the memory tasks.

In principle, the pattern of activation observed in the occipital cortex of the blind might be due to the auditory input (i.e. hearing words). This seems unlikely, however, since words were heard in all experimental conditions, and there were no significant differences in the fMRI activation in A1. On the other hand, the occipital activation was markedly different between those conditions. The observed differential activation could have possibly been a result of differences in task difficulty between conditions. Such an explanation would predict that the activation level be correlated with task difficulty. However, our results do not support this explanation. Both the BPL recognition (the most difficult task; see Behavioral Data) and the phonological control (the easiest task) elicited similar activation levels, significantly lower than the activation observed during the WPL recognition, the mid-level performance task.

What Does the Activation in the Visual Cortex Reflect?

We have found higher activation during the recognition memory tasks compared with the phonological control. During the former, subjects had to relate to the semantic content of the words in order to judge whether the presented word is old or new, while during the latter, they were directed to focus on phonological components of the words. Thus, the differences in activation level might be a result of semantic components *per se*. As was reported by Burton *et al.* (2003), higher activation in the occipital cortex of blind is found when subjects are required to focus on the semantic content of words compared with the requirement to relate to the words' phonological content. This is also in agreement with a recent study showing that applying repetitive TMS pulses to the occipital pole of blind subjects results in an increase in the number of semantic errors (but not in sighted peers) while phonological errors are very rare (Amedi *et al.*, 2004). However, we think that such a description explains only part of the picture. We show here that although the two recognition-memory tasks had similar semantic components, these conditions elicited significantly different fMRI activation levels. Moreover, the individual subject's occipital activation level was correlated with his/her memory performance in an episodic memory task. This indicates that activation in the occipital cortex of congenitally blind probably reflects episodic memory processes in addition to semantic processing.

One might posit that the differences in occipital activation between the two recognition tasks do not reflect memory performance level but, rather, the mere involvement in a memory task, evident only in the WPL recognition. According to such a claim, due to the difficulty to perform the BPL recognition task, subjects were not involved in memory process during this condition. Instead, they generated random answers during BPL recognition, avoiding the memory process altogether. However, WPL recognition and BPL recognition were performed with similar reaction times (notably longer compared with the phonological control task), suggesting that the subjects were engaged in a memory task in both cases. One might claim that subjects learned which blocks belonged to the BPL recognition task from the first words presented in each block and when they identified a BPL recognition block they started to respond by guessing. Thus, the first words in BPL recognition blocks are expected to induce a long RT while the last words would indce a short RT. RTs during the WPL recognition are not expected to differ according to their position within the block, as subjects were engaged in the memory tasks during the whole block. However, the analysis of RT during WPL and BPL recognition blocks showed that no such difference was evident, even when comparing the average RT for words in each position within the block during WPL and BPL recognition (see Supplementary Material Fig. 1 online).

In the current study, the well-practiced words (WPL) and the barely practiced ones (BPL) were presented in separate blocks. Thus, it is feasible that subjects might have experienced greater 'retrieval success' in the WPL recognition blocks compared with the BPL recognition blocks. Accompanying aspects of such success could have potentially influenced satisfaction (or anxiety) levels in the subjects. To avoid such possible confounding effects, an event-related design is necessary. However, such a design could not have been applied effectively in the current study, since the subjects were required to recognize words which appeared in the original scan (scan 1) lists a year before. There were only 36 words in the original lists (in the VM and VG conditions of the former scan), too few to obtain a reliable measure of the signal using an event related design. Obviously, if subjects can reliably remember a longer list of words, it would be useful to test the activation during episodic retrieval using an event-related design.

Behavioral data indicate that subjects tended to correctly classify words as old (i.e. appeared in scan 1) in WPL recognition more than in BPL recognition (d' rates were 1.7 and 0.1 for the WPL and BPL recognition, respectively), reflecting the fact that words from the first set were more familiar to them. When contrasting the two tasks, a network of regions was activated in the blind (Fig. 3), corresponding to regions preferentially active during a recognition-memory task of familiar (compared with new) words in sighted subjects. These included the inferior and superior parietal regions near BA 40 and 7, the precuneus and the posterior cingulate gyrus, that are most consistently observed displaying a familiarity effect (old > new) in sighted (Wheeler and Buckner, 2003; Herron *et al.*, 2004). Activation was also seen in the parahippocampal gyrus and in inferior and middle frontal gyri, corresponding to additional regions (reported by Wheeler and Buckner, 2003) that showed the familiarity effect. The activation in all these regions was suggested to be the neural correlate of successful recovering verbal information from memory (Wheeler and Buckner, 2003; Herron *et al.*, 2004) [see also Kahn *et al.* (2004) for a discussion of the role of these regions in recollection]. In the blind, regions within the occipital cortex showed a similar preference, in addition to the regions listed above. This suggests that in the blind, the network of cortical area engaged in recognition-memory is expanded (compared to the sighted) to include parts of the visually deprived occipital cortex (in addition to other memory regions).

We suggest here that occipital activation in the blind is related to retrieving information from episodic long-term memory. How does this claim fit with previous results, showing activation in the visual cortex of blind during various tasks, such as tactile and auditory discriminations or language processing? One possibility is that different anatomical regions within the occipital cortex of the blind acquire new specialized functional characteristics (much like the 'division of labor' principle in the sighted brain). Indeed, we have previously found evidence for topographical specialization in the occipital cortex of the blind: while anterior regions showed preference for tactile Braille reading, the posterior regions were more active during memory retrieval (Amedi *et al.*, 2003).

Superior Memory in the Blind: a Compensatory Adjustment?

Several studies indicated that the deprived visual cortex of early blind is active during functions other than vision. However, the changes in the pattern of activity could be irrelevant to the neuronal response (reflecting artifacts such as higher metabolism; see Wanet-Defalque *et al.*, 1988; Veraart *et al.*, 1990). Alternatively, they could reflect a true compensatory adjustment. If, indeed, cortical reorganization following blindness has behavioral benefits, it should be correlated with improved behavioral performance. Some evidence for such functional adjustment was found in animal models. Rauschecker (1995) has shown that, in the visually deprived cat, both an expansion of the tactile and auditory cortical maps and improved sound localization responses were found. Superior sound localization

(e.g. Muchnik *et al.*, 1991; Lessard *et al.*, 1998; Roder *et al.*, 1999) and a corresponding cortical reorganization (e.g. Roder *et al.*, 1999; Weeks *et al.*, 2000) were also found in blind humans.

Early-onset blind show on average better performance in various verbal-memory tasks compared with sighted peers (e.g. Tillman and Bashaw, 1968; Smits and Mommers, 1976; Pozar, 1982; Hull and Mason, 1995; Roder *et al.*, 2001, Amedi *et al.*, 2003), suggesting compensatory mnemonic performance (Roder and Rosler, 2003). Indeed, improved verbal-memory performance (compared to sighted peers) was found (on average) in the group of blind subjects we retested here (using various memory tests taken from the Wechsler Memory Scale: WMS — 3rd edn). Superior performance for the blind in these tests was seen in comparison to a group of sighted controls matched for age, sex and education on a subject–by–subject basis (Student's *t*-test, $P < 0.005$). Furthermore, average superior performance in the blind (as a group) was also found in a long–term recognition memory test (corresponding to the WPL recognition in the present experiment) administered 6 months after scan 1 (80.1 ± 3.9 versus 68.6 ± 5.6% of correct responses for the blind and sighted subjects respectively, $P < 0.05$, Student's *t*-test; see Amedi *et al.*, 2003). In the current study, we also show a correspondence between the BOLD signal in the occipital cortex of the congenitally blind subjects and their online memory performance level (on a subject-by-subject basis).

What might be the causes for the improved memory performance and the associated changes in the cortical representation in the blind? It seems plausible that these changes may result from a lifetime practice, used to overcome the limitations caused by the absence of vision. For example, in order to independently manage in their daily life, the blind need to keep in memory vast amounts of information that we get directly from vision (such as the list of the grocery products placed in each row in your supermarket).

There are some indications that extensive memory training can result in cortical reorganization (Maguire *et al.*, 2003; Olesen *et al.*, 2004). However, unlike the case of congenitally blind, memory activation in these subjects did not extend into early visual regions, suggesting that an absence of the original input (i.e. visual deprivation) is necessary for the recruitment of early visual areas for other functions.

Compensatory adjustment in the visual cortex of blind was discussed in relation to their superior performance in the remaining senses, such as finer tactile acuity (e.g. Pascual-Leone and Torres, 1993; Van Boven *et al.*, 2000; Goldreich and Kanics, 2003) or better auditory skills, such as sound localization (e.g. Muchnik *et al.*, 1991; Lessard *et al.*, 1998; Roder *et al.*, 1999; Weeks *et al.*, 2000; for superior performance in other auditory skills, see Miller, 1992; Gougoux *et al.*, 2004). We suggest that compensatory adjustment may also extend to non-sensory cognitive functions, such as memory, which is likely to be vital for normal function following blindness. However, in order to establish a compensatory adjustment in the visual cortex of blind, it will be necessary to show that transient disruption of the occipital cortex function impairs memory abilities. This might be performed nowadays using TMS, as was done for Braille reading (Cohen *et al.*, 1997) and verb generation (Amedi *et al.*, 2004). (For a review on TMS, see Pascual-Leone *et al.*, 2000.) The prediction is that TMS to the occipital cortex of congenitally blind during memory tasks would hamper their memory performance level.

Notes

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References

Amedi A, Raz N, Pianka P, Malach R, Zohary E (2003) Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci 6:758–766.

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG (2004) Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci 7:1266–1270.

Arno P, De Volder AG, Vanlierde A, Wanet-Defalque MC, Streel E, Robert A, Sanabria-Bohorquez S, Veraart C (2001) Occipital activation by pattern recognition in the early blind using auditory substitution for vision. Neuroimage 13:632–645.

Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. J Neurosci 16:4207–4221.

Buchel C, Price C, Friston K (1998a) A multimodal language region in the ventral visual pathway. Nature 394:274–277.

Buchel C, Price C, Frackowiak RS, Friston K (1998b) Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 121:409–419.

Burton H, Snyder AZ, Conturo TE, Akbudak E, Ollinger JM, Raichle ME (2002a) Adaptive changes in early and late blind: a fMRI study of Braille reading. J Neurophysiol 87:589–607.

Burton H, Snyder AZ, Diamond JB, Raichle ME (2002b) Adaptive changes in early and late blind: a fMRI study of verb-generation to heard nouns. J Neurophysiol 88:3359–3371.

Burton H, Diamond JB, McDermott KB (2003) Dissociating cortical regions activated by semantic and phonological tasks: a FMRI study in blind and sighted people. J Neurophysiol 90:1965–1982.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J Honda M, Sadato N, Gerloff C, Catala MD, Hallett M (1997) Functional relevance of cross-modal plasticity in blind humans. Nature 389:180–183.

De Volder AG, Toyama H, Kimura Y, Kiyosawa M, Nakano H, Vanlierde A, Wanet-Defalque MC, Mishina M, Oda K, Ishiwata K, Senda M (2001) Auditory triggered mental imagery of shape involves visual association areas in early blind humans. Neuroimage 14:129–139.

Engel SA, Glover GH, Wandell BA (1997) Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex 7:181–192.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 33:636–647.

Friston KJ, Holmes AP, Worsley KJ (1999) How many subjects constitute a study? Neuroimage 10:1–5.

Gizewski ER, Gasser T, de Greiff A, Boehm A, Forsting M (2003) Cross-modal plasticity for sensory and motor activation patterns in blind subjects. Neuroimage 19:968–975.

Goldreich D, Kanics IM (2003) Tactile acuity is enhanced in blindness. J Neurosci 23:3439–3445.

Gougoux F, Lepore F, Lassonde M, Voss P, Zatorre RJ, Belin P (2004) Neuropsychology: pitch discrimination in the early blind. Nature 430:309.

Green DM, Swets JA (1966) Signal detection theory and psychophysics. New York: Robert E. Krieger.

Hamilton RH, Pascual-Leone A (1998) Cortical plasticity associated with Braille learning. Trends Cogn Sci 2:168–174.

Herron JE, Henson RN, Rugg MD (2004) Probability effects on the neural correlates of retrieval success: an fMRI study. Neuroimage 21: 302–310.

Hull T, Mason H (1995) Performance of blind children on digit-span tests. J Vis Impair Blind 89:166–169.

Kahn I, Davachi L, Wagner AD (2004) Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. J Neurosci 24:4172–4180.

Kujala T, Huotilainen M, Sinkkonen J, Ahonen AI, Alho K, Hamalainen MS, Ilmoniemi RJ, Kajola M, Knuutila JE, Lavikainen J Salonen O, Simola J, Standertskjöld-Nordenstam CG, Näätänen R (1995) Visual cortex activation in blind humans during sound discrimination. Neurosci Lett 183:143–146.

Lambert S, Sampaio E, Mauss Y, Scheiber C (2004) Blindness and brain plasticity: contribution of mental imagery? An fMRI study. Brain Res Cogn Brain Res:20:1–11.

Lessard N, Pare M, Lepore F, Lassonde M (1998) Early-blind human subjects localize sound sources better than sighted subjects. Nature 395:278–280.

Maguire EA, Valentine ER, Wilding JM, Kapur N (2003) Routes to remembering: the brains behind superior memory. Nat Neuorsci 6:90–95.

Miller L (1992) Diderot reconsidered: visual impairment and auditory compensation, J Vis Impair Blind 86, 206–210.

Muchnik C, Efrati M, Nemeth E, Malin M, Hildesheimer M (1991) Central auditory skills in blind and sighted subjects. Scand Audiol 20:19–23.

Noppeney U, Friston KJ, Price CJ (2003) Effects of visual deprivation on the organization of the semantic system. Brain 126:1620–1627.

Olesen PJ, Westerberg H, Klingberg T (2004) Increased prefrontal and parietal activity after training of working memory. Nat Neurosci 7:75–79.

Pascual-Leone A, Torres F (1993) Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 116:39–52.

Pascual-Leone A, Walsh V, Rothwell J (2000) Transcranial magnetic stimulation in cognitive neuroscience-virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 10:232–237.

Pozar L (1982) Effects of long-term sensory deprivation on recall of verbal material. Studia Psychol 24:311.

Rauschecker JP (1995) Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci 18:36–43.

Roder B, Rosler F (2003) Memory for environmental sounds in sighted, congenitally blind and late blind adults: evidence for cross-modal compensation. Int J Psychophysiol 50:27–39.

Roder B, Teder-Salejarvi W, Sterr A, Rosler F, Hillyard SA, Neville HJ (1999) Improved auditory spatial tuning in blind humans. Nature 400:162–166.

Roder B, Rosler F, Neville HJ (2001) Auditory memory in congenitally blind adults: a behavioral–electrophysiological investigation. Brain Res Cogn Brain Res 11:289–303.

Roder B, Stock O, Bien S, Neville H, Rosler F (2002) Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci 16:930–936.

Ross DA, Olson IR, Gore JC (2003) Cortical plasticity in an early blind musician: an fMRl study. Magn Reson Imaging 21:821–828.

Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, Hallett M (1996) Activation of the primary visual cortex by Braille reading in blind subjects. Nature 380:526–528.

Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M (1998) Neural networks for Braille reading by the blind. Brain 121:1213–1229.

Sadato N, Okada T, Honda M, Yonekura Y (2002) Critical period for cross-modal plasticity in blind humans: a functional MRI study. Neuroimage 16:389–400.

Smits BW, Mommers MJ (1976) Differences between blind and sighted children on WISC verbal subtests. N Outlook Blind 70:240–246.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. New York: Thieme.

Tillman MH, Bashaw WL (1968) Multivariate analysis of the WISC scales for blind and sighted children. Psychol Rep 23:523–526.

Tulving E (1972) Episodic and semantic memory. In: Organization of memory (Tulving E, Donaldson W, eds), pp. 381–403. New York: Academic Press.

Van Boven RW, Hamilton RH, Kauffman T, Keenan JP, Pascual-Leone A (2000) Tactile spatial resolution in blind Braille readers. Neurology 54:2230–2236.

Veraart C, De Volder AG, Wanet-Defalque MC, Bol A, Michel C, Goffinet AM (1990) Glucose utilization in human visual cortex is abnormally elevated in blindness of early onset but decreased in blindness of late onset. Brain Res 510:115–121.

Wanet-Defalque MC, Veraart C, De Volder A, Metz R, Michel C, Dooms G, Goffinet A (1988) High metabolic activity in the visual cortex of early blind human subjects. Brain Res 446:369–373.

Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, Hallett M, Rauschecker JP (2000) A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci 20:2664–2672.

Wheeler ME, Buckner RL (2003) Functional dissociation among components of remembering: control, perceived oldness, and content. J Neurosci 23:3869–3880.