ARTICLES

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Early 'visual' cortex activation correlates with superior verbal memory performance in the blind

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The visual cortex may be more modifiable than previously considered. Using functional magnetic resonance imaging (fMRI) in ten congenitally blind human participants, we found robust occipital activation during a verbal-memory task (in the absence of any sensory input), as well as during verb generation and Braille reading. We also found evidence for reorganization and specialization of the occipital cortex, along the anterior–posterior axis. Whereas anterior regions showed preference for Braille, posterior regions (including V1) showed preference for verbal-memory and verb generation (which both require memory of verbal material). No such occipital activation was found in sighted subjects. This difference between the groups was mirrored by superior performance of the blind in various verbal-memory tasks. Moreover, the magnitude of V1 activation during the verbal-memory condition was highly correlated with the blind individual's abilities in a variety of verbal-memory tests, suggesting that the additional occipital activation may have a functional role.

"The traditions cited by Rabbi Sheshet are not subject to doubt as he is a blind man." –Talmud Yerushalmi, *tractate Shabat 6b*

Perceiving the world in total absence of vision must often be based on verbal descriptions of events (for instance, following a basketball game on the radio). The absence of visual cues may augment the reliance on memory (as in recalling where you left your keys when they are hidden from view). Congenitally blind people are therefore likely to depend more on memory in general, and on verbal memory in particular, to interact with the world. Indeed, some studies indicate that the congenitally blind have superior verbal-memory abilities[1–4]. Anecdotally, in ancient times the blind often served as a 'living database' of the interpretations of the bible, which were passed from generation to gener-ation by word of mouth, and a quotation of a source by a blind person was considered the most reliable (quoted above). Previous studies showed that the 'unemployed' occipital cortex in the blind undergoes a radical form of plasticity to be putatively involved in non-visual tasks. Here we tested the possibility that this cortical structure may also be recruited to support the allegedly superior verbal-memory abilities of the congenitally blind.

The areas devoted to vision constitute a substantial part of the primate cortical sheet (20–25% of the primate brain[5]), and a principle of division of labor exists where different subregions process different aspects of visual information[6]. In the past, it was thought that loss of vision renders these regions useless, but several years ago it was shown that the occipital cortex of the blind is activated when they read Braille[7]. This was confirmed[8–10] and interpreted as a form of cross-modal plasticity[11,12] leading to an adaptive recruitment of the occipital cortex for tactile processing. Two recent studies, however, show occipital activation during auditory verb generation[13] and speech comprehension[14] tasks, suggesting this cortex might be engaged in linguistic processing. Yet other groups report that in the blind, non-verbal auditory tasks[15–17] and an auditory-triggered imagery task[18] also activate this cortex.

These findings give rise to at least two alternatives: (i) that the occipital cortex of the blind has a general-purpose function, activated by all these different tasks and sensory modalities or (ii) that different anatomical regions within the occipital cortex of the blind may acquire new specialized functional characteristics (much like the 'division of labor' in the sighted brain). To address these issues, we assessed fMRI activation in the cortex of congenitally blind subjects during Braille reading and auditory verb-generation tasks, as well as a new verbal-memory task that requires retrieval of abstract words from long-term memory without any sensory stimulation.

We found that extensive occipital regions in the blind, including the primary visual cortex (V1), were activated during both the verbal-memory and verb-generation tasks. Such activation was not found in the sighted. This was mirrored by superior verbal memory abilities of the blind as a group as well as a strong positive correlation between the blind individual's verbal-memory skills and the magnitude of that individual's V1 activation during the verbal-memory epoch. We also found evidence for topographical specialization in the occipital cortex of the blind: whereas anterior regions showed preference for tactile Braille reading, the posterior regions were more active during the verbal-memory and verb-generation tasks.

RESULTS

We investigated the patterns of cortical activation in ten congenitally blind subjects (**Supplementary Table 1**) under six different conditions.

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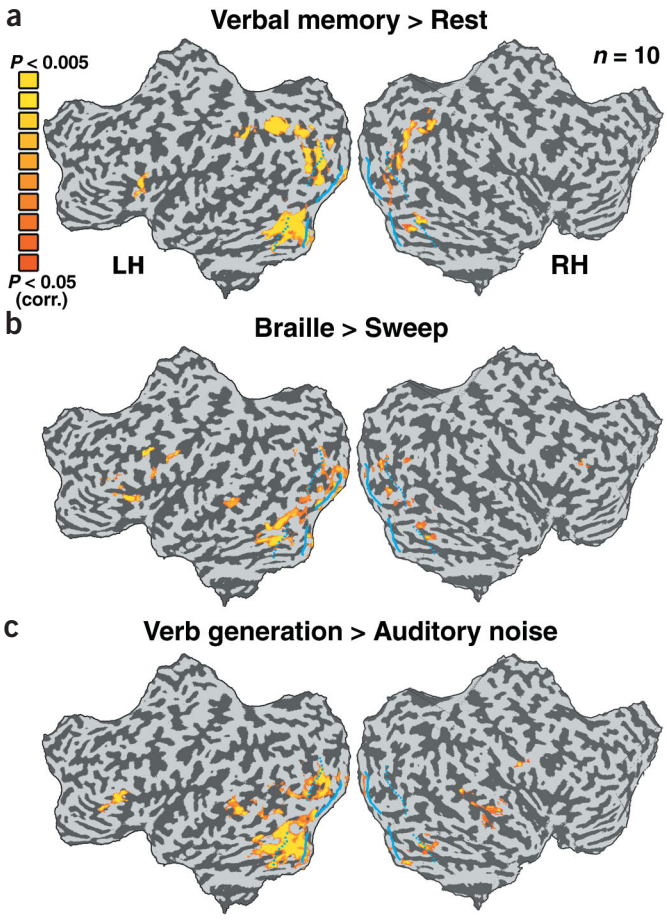

Figure 1 Robust posterior occipital activation during verbal-memory, Braille and verb-generation tasks in the congenitally blind. (**a**–**c**) Statistical parametric maps of activation in the congenitally blind ($n = 10$) using a random effect GLM analysis. The data are presented on a full Talairach–normalized unfolded brain of the left (LH) and right (RH) hemispheres. Color scale denotes significance (corrected for multiple comparisons). The blue continuous line indicates the approximate V1/V2 border; the dotted line denotes the estimated anterior border of retinotopic areas in the sighted. (**a**) the verbal-memory (VM) versus rest contrast, showing robust and highly significant activation in the occipital cortex (mainly in the left hemisphere), including the calcarine sulcus. Activation was also found in the left inferior prefrontal cortex and the parietal regions bilaterally. (**b**) A map showing differential activation during Braille reading versus the tactile sweep. The posterior occipital activation is less prevalent and more evenly distributed between the two hemispheres. Highly significant activation is found in LOC (anterior to the ventral dashed blue line). (**c**) Voxels preferentially activated during auditory verb generation (VG) versus the auditory noise (AN). Again, robust activation was present in the left occipital regions including the calcarine sulcus.

These included a verbal-memory task (VM) in which subjects covertly recalled lists of previously learned abstract words, a verb-generation condition (VG) in which subjects covertly retrieved a compatible verb to a heard noun[19] (*e.g.*, "read" for "book") and an auditory noise condition (AN) that was designed to match the basic auditory components of the heard words in VG. During AN, subjects performed a one-back task, judging if the current auditory noise was identical to the previous one. There was also a Braille condition in which subjects covertly read abstract words, a corresponding sweep condition in which they swept their fingers on a meaningless array of Braille signs, and finally a rest condition that served as a hemodynamic baseline.

Data were analyzed at several levels: group analysis of the blind population (**Figs. 1** and **3**), differential activation of the blind versus sighted groups (**Fig. 2**), analysis of the activation pattern and time course within subjects (**Figs. 4**, **5** and **6a**) and correlation of the blind individuals' activation in V1 during VM with their performance on various verbal-memory tasks (**Figs. 6b** and **7**).

We used a random effect general linear model (GLM)[20] to analyze the group results of the cortical activation in the blind (**Fig. 1**; activation maps are presented on a full Talairach-normalized[21] unfolded brain). In the VM versus rest condition (**Fig. 1a**), the most conspicuous activation was in the left occipital and occipitotemporal cortex. The occipital activation stretched along the ventral 'visual' retinotopic pathway and included the left calcarine sulcus, corresponding to V1. Several significant clusters were identified in the right occipital cortex, but to a much lesser extent. Robust and significant activation was also found in left inferior prefrontal cortex and in parietal regions, bilaterally. Activation was also present in the dorsolateral prefrontal and in the left medial temporal regions (not shown in **Fig. 1**), when analyzing the data from a sub-group of blind subjects in which these regions were scanned ($n = 7$ or 8, respectively; see Methods and **Supplementary Table 1** online). The Braille versus sweep contrast (**Fig. 1b**) revealed a more bilateral activation in the posterior occipital cortex. Highly significant clusters were also found in the regions corresponding to the non-retinotopic lateral occipital complex[22] (LOC). Finally, lateralized posterior occipital and calcarine activations were found when contrasting the verb generation with the auditory noise condition (**Fig. 1c**). In addition, other memory-related regions were activated (**Supplementary Table 3**). Note that the activation maps presented in both the first and third contrast (**Fig. 1a**,**c**) were obtained using non-tactile conditions, and yet overlapping activations were found in occipital areas, including highly significant activation in the left V1.

Another feature of these two maps (**Fig. 1a**,**c**) is their laterality, which was confirmed by analysis of variance (ANOVA) testing for task (condition) × hemisphere interactions (Methods). The condition factor, hemisphere factor, and the condition × hemisphere

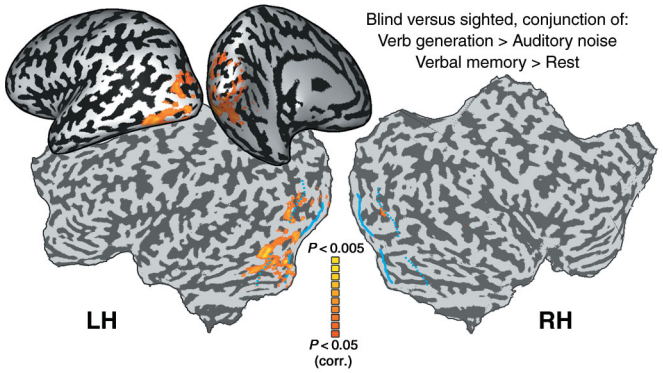

Figure 2 Differences in the fMRI activation patterns between blind and sighted groups. The two hemispheres of a Talairach-normalized unfolded brain are shown as well as a lateral and medial-ventral inflated view of the left hemisphere. The figure delineates significant voxels conjunctively active during both VM (vs. rest) and VG (vs. AN) compared to the sighted group ($P < 0.05$ corrected) using a random effect GLM analysis. The regions that show dramatic plasticity in the blind are mainly in the left occipital cortex, including early 'retinotopic' regions (blue lines as in **Fig. 1**).

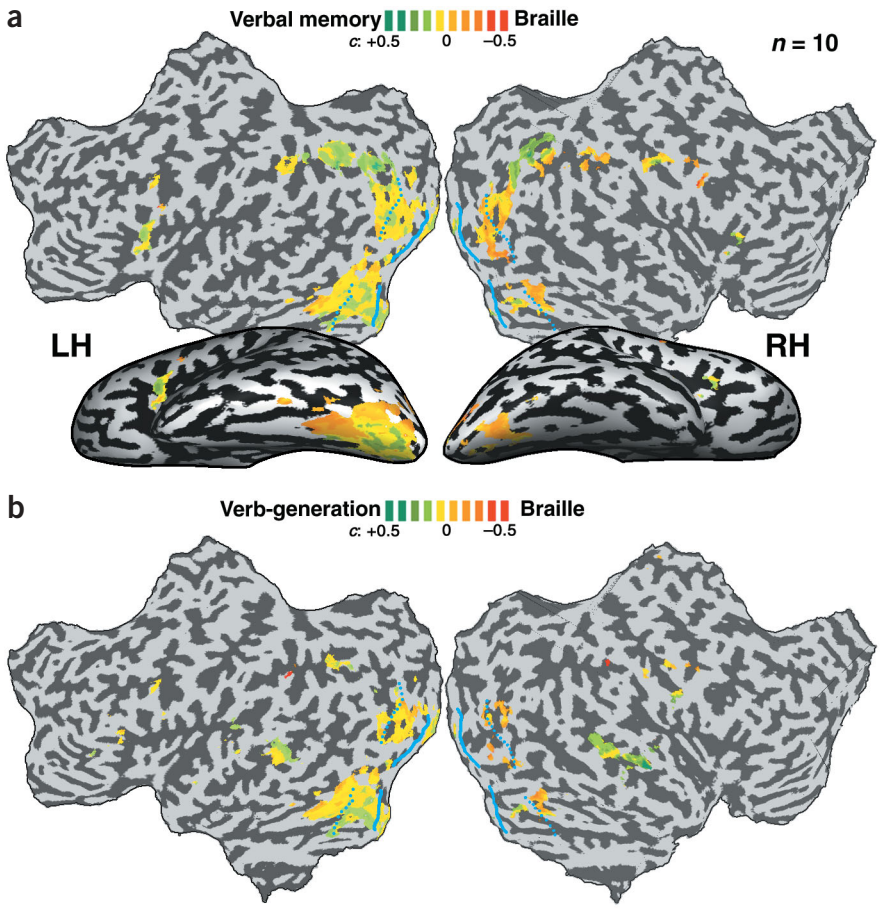

Figure 3 Indication for a novel functional organization in the occipital cortex of the blind. Results of across subjects ($n = 10$) random effect GLM analysis are presented on a Talairach-normalized unfolded brain, as well as a ventral view of each inflated hemisphere. The highlighted voxels are those for which the variance explained by two predictors was significant ($P < 0.05$, corrected). The two predictors were VM and Braille (**a**) and VG and Braille (**b**). Color scale denotes the relative preference of the voxel to one of the two conditions. Voxels showing preference for VM (**a**) or VG (**b**) appear in green ($c > 0$), and those with Braille preference ($c < 0$) are in red. (**a**) The left posterior ventral occipital 'retinotopic' regions (located posterior to the dotted line) showed preference for the VM, although it contained no sensory input. This preference was also evident in the left calcarine sulcus. LOC, located anterior to the retinotopic regions (as well as the right posterior occipital regions) showed the reverse pattern of preference. (**b**) The relative weights of the VG and tactile based Braille reading showed similar general preferences as in (**a**) across the occipital and occipito–temporal regions.

interaction term were all significant (respectively, $F_{4,90} = 9.632$, $P < 0.001$; $F_{1,90} = 4.532$, $P < 0.005$; and $F_{4,90} = 4.931$, $P < 0.005$). Paired *t*–tests showed significant left occipital dominance in the VG and VM conditions ($P < 0.005$). Significant (but much weaker) left-hemisphere preference was also found during the Braille condition ($P < 0.05$; see also **Supplementary Fig. 1**).

For comparison, we carried out a similar experiment (excluding the Braille and sweep conditions) in seven blindfolded sighted individuals. Activation during VM and VG was generally found in similar regions as in the blind (and in general accordance with previous reports[23–26] (**Supplementary Tables 2** and **4**), apart from the lack of robust occipital activations in the sighted. This difference is conspicuous in the differential activation map of the blind versus sighted using random effects GLM analysis (**Fig. 2**). The highlighted voxels are those showing significantly greater activation in the blind (compared with the sighted group) during both tests (VM vs. rest and VG vs. AN; using conjunction analysis; $P < 0.05$, corrected). A constellation of regions stretching from the calcarine sulcus to the occipitotemporal cortex (V1 to LOC) was significantly more activated in the blind during both VM and VG tasks. No area was more active during both tasks in the sighted compared to the blind. This suggests that total visual deprivation caused by congenital blindness leads to a radically different organization of the occipital cortex, such that it becomes activated during tasks requiring retrieval of words from long-term memory.

To investigate the possible functional specializations of the two occipital hemispheres of the blind, we assessed the relative weight of different experimental conditions for each Talairach-defined voxel. We mapped the activated regions in the two conditions involving covert naming of abstract words—recalled from memory (VM) or based on touch (Braille) (**Fig. 3a**). The most striking feature of the maps is that the left posterior ventral occipital regions (corresponding to retinotopic regions) showed clear preference for the VM condition. In contrast, the more anterior object related areas (LOC) and the right posterior occipital regions showed preference for the Braille condition. A similar picture was seen when the same analysis was applied for the VG and Braille conditions (**Fig. 3b**). The VG preference is probably related to the verb-generation task rather than to the auditory components *per se*, as no such preference was found in the auditory noise versus Braille analysis.

To quantitatively assess the suggested topographical specialization in the occipital cortex, we analyzed the time course of the activation in three regions of interest (ROI) located within the occipital cortex (V1, extrastriate regions and LOC) on a subject-by-subject basis. This was accomplished by using a single-subject GLM analysis[27], with Braille and VM (**Fig. 4a**) or Braille and VG (**Fig. 4b**) as the relevant predictors. There was a striking shift in the regions' preference along the posterior–anterior axis within the left hemisphere. Whereas V1 showed clear preference for VM over Braille, LOC showed the opposite tendency (**Fig. 4a**). The right hemisphere showed preference for Braille in both the extrastriate retinotopic regions and LOC (however, far fewer clusters were found in the right hemisphere; **Fig. 3**). A very similar pattern of preference emerged for the VG and Braille conditions (**Fig. 4b**). These results suggest a specialization within the occipital cortex of the congenitally blind, such that left posterior regions (including V1) show preference for conditions requiring memory of verbal materials (*i.e.*, VM and VG), and the more anterior regions show preference for the tactile based Braille reading.

Next, we focused on the primary visual cortex (comparing it with other primary sensory regions) by testing whether its pattern of response is driven by sensory-specific elements or by verbal elements irrespective of the input modality. To that end, we used a GLM test searching for voxels showing activation in all four conditions involving

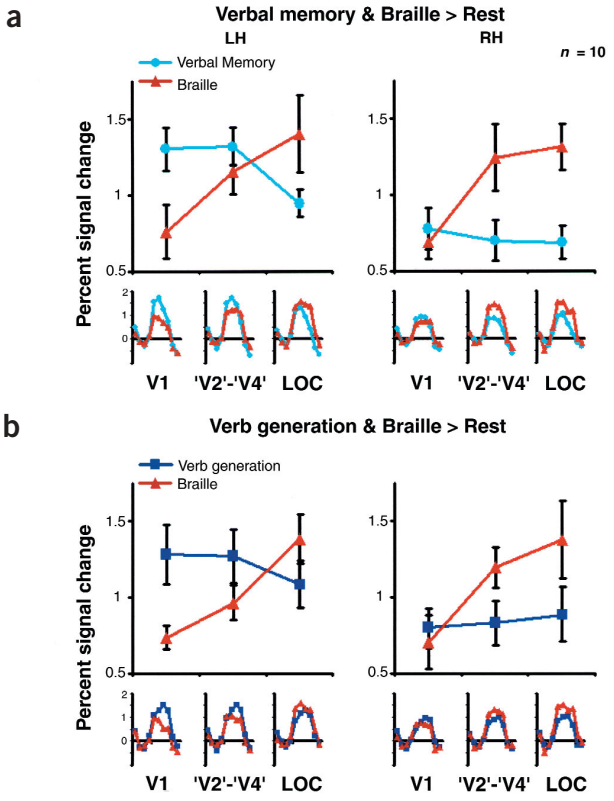

Figure 4 The preference of regions within the occipital cortex of the blind. We define three ROIs along the anterior–posterior axis of the occipital cortex: the calcarine sulcus (corresponding to V1), the extrastriate retinotopic areas (corresponding to 'V2'–'V4') and the non-retinotopic LOC in each of the two hemispheres. The time course of activation was constructed by pooling voxels showing activation above a liberal threshold ($P < 0.005$ uncorrected; to allow collection from all ROIs in all ten blind subjects) within each of the three ROIs in each subject, and then averaging across subjects. (**a**) The statistical test searched for voxels activated by both Braille and VM compared to rest. Thus, no a priory bias was introduced in favor of activation in one of the two conditions. For each ROI we present the average percent signal change for VM and Braille conditions in the upper panel and the average time course of activation below. In the left hemisphere, a dramatic shift in the regions' preference can be seen along the posterior–anterior axis: while V1, which is located posteriorly, shows clear preference for VM, the more anterior LOC shows preference for the tactile Braille condition. The extrastriate retinotopic regions, located between these two ROIs showed an intermediate pattern. In the right hemisphere the extrastriate retinotopic areas and LOC ROIs show preference for the Braille condition, although much fewer voxels (~4× less) were found in the right ROIs. (**b**) The same analysis was preformed for the VG and Braille conditions, showing the same general trend.

sensory input (VG, AN, Braille and sweep conditions) with respect to the rest condition. These predictors were selected to create a balance between the auditory and tactile conditions (as well as a balance between conditions containing verbal elements and those that do not). Time courses from primary sensory regions were analyzed for each subject and then averaged across subjects. The activation profile and time course of the left-hemisphere V1 clusters during the VG and Braille conditions elicited a robust response, whereas much weaker activation was found during the AN and sweep conditions (**Fig. 5a**). In contrast, activation in the primary auditory cortex (A1) was specific to the two auditory conditions, and in the primary somatosensory cortex, (S1) it was specific to the two tactile conditions (**Fig. 5b**).

To characterize the dominant factors in each ROI, we used a two-way ANOVA, including a modality variable (tactile for Braille and sweep; auditory for the VG and AN) and a verbal input variable (positive in VG and Braille, negative in AN and sweep) as independent factors. This analysis revealed that the significant factor explaining variance in activation level across conditions in left V1 was the presence of verbal elements ($F_{1,36} = 13.9$, $P < 0.005$) rather than the modality type. This conclusion was further supported by the fact that VM also vigorously activated left V1 (**Fig. 5a**). This robust activation was present, although the VM condition was not included as a predictor in the test used to select the significant voxels (thus putting it in disadvantage compared to the other conditions). The opposite picture was evident in the two intact primary sensory regions, where the only significant factor was the modality type (bilateral A1: $F_{1,36} = 54.9$, $P < 0.001$; contralateral S1: $F_{1,36} = 10.1$, $P < 0.005$).

Thus far we have shown that the primary visual cortex of the blind has a preference for tasks requiring the use of verbal memory. This may indicate that V1 is engaged in verbal mnemonic function. A necessary (though not sufficient) step to conclude that V1 has a functional role in verbal-memory processing is to show that the degree of V1 activation is correlated with the subject's verbal-memory abilities. Although some V1 activation was seen during VM in all blind subjects, wide variation existed in both the spatial extent and significance level of the activation within subjects (**Fig. 6a**). We therefore analyzed within-subject covariation of V1 activity during VM in various verbal-memory tasks, starting with long-term memory of the lists of words (**Fig. 6b**). Performance was measured as the percentage of words that were correctly identified as belonging to the original

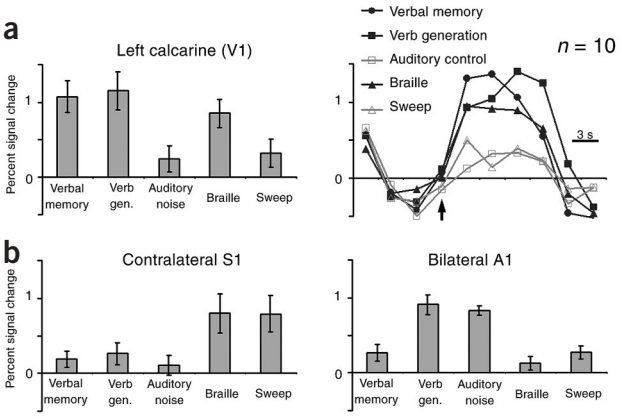

Figure 5 Comparing the activation pattern in three primary sensory regions. We define three ROIs corresponding to left V1, contralateral S1 (primary somatosensory cortex) and bilateral A1 (primary auditory cortex). The time course of activation was constructed by pooling voxels showing activation above a liberal threshold within each ROI ($P < 0.005$ uncorrected) using all the sensory conditions (VG, auditory control, Braille and sweep) versus rest test. Thus, no *a priori* preference was given to any of the sensory conditions over the others. (**a**) Histograms of the average percent signal change (left) and averaged time course of activation in left V1 (right; arrow indicates the beginning on an epoch). Error bars denote standard errors of the mean. The data indicate that verbal elements rather than sensory specific elements are driving the activation in the left calcarine sulcus. In agreement with this, the VM, not included in the statistical test (thus creating some bias against it) also strongly activated the left V1. (**b**) In sharp contrast, the results of the same analysis in the two intact primary sensory regions showed clear modality specificity (tactile preference in S1, auditory in A1) and negligible verbal-memory activation.

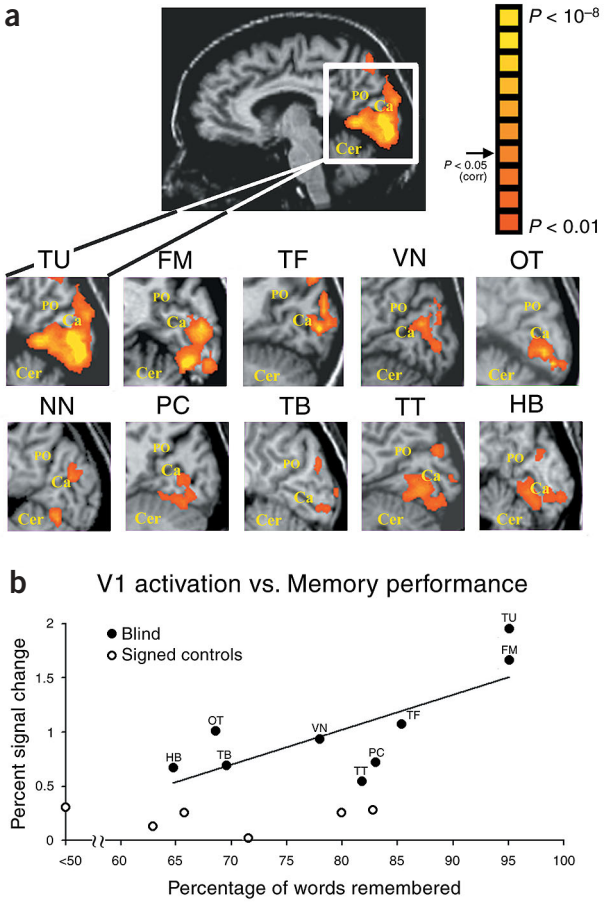

Figure 6 The blind subjects' V1 activation during verbal-memory is correlated with their word recognition performance ~6 months later. (**a**) Subject-by-subject activation in the calcarine sulcus for the VM versus rest test. The active voxels are ones above a fixed liberal threshold ($P < 0.01$, uncorrected). Great variation in the degree of calcarine (and occipital) activation is seen among the congenitally blind. This variation is seen in both the volume of activation and the activation significance level (as indicated by the color scale). The black arrow in the significance scale denotes the usually used threshold ($P < 0.05$, corrected). Ca, calcarine sulcus; PO, parieto-occipital sulcus; Cer, cerebellum. (**b**) A scatter diagram showing the calcarine activation observed in the individual subjects versus their memory performance. Calcarine activation was measured by the BOLD signal intensity during VM. Subjects were tested approximately 6 months after the scan on a verbal-memory recognition test (identifying the words memorized in the original fMRI scan). Positive and statistically significant correlation is found between long-term memory performance and the VM elicited activation in the calcarine sulcus (black circles; Pearson's $r = 0.74$). Open circles denote the sighted controls' data ($n = 6$), showing on average worse memory performance, non-significant calcarine activation, and no correlation between the two.

list 6 months after the scan. The activation elicited by recalling these words during the scan (in VM) was assessed in each subject by the BOLD (blood oxygenation level–dependent) signal intensity of the peak calcarine voxel in a smoothed volume. Statistically significant and highly positive correlation was found between long-term memory performance and the V1 BOLD signal during VM (Pearson's $r = 0.74$, $P < 0.05$; **Fig. 6** and Methods).

The comparison to the sighted group is illuminating. Blind subjects performed significantly better than sighted in the long-term recognition test (80.1 ± 3.9% versus 68.6 ± 5.6% correct, $P < 0.05$, Student's *t*-test). Furthermore, six of the ten blind subjects had significant V1 activation, and none of the sighted subjects had significant V1 activation. Finally, no correlation was observed between performance level and the V1 activation in sighted controls (Pearson's $r = -0.15$).

To check for similar correlation between verbal-memory induced V1 activation and general verbal-memory abilities, we tested each of the blind subjects on the auditory verbal subtests of the Wechsler Memory Scale (WMS 3rd edition[28]). The tests provide two standardized scores, for immediate and delayed (30 min) memory performance, which can be compared to performance of the general sighted population. We added a third measurement, performed 9 days after the original test (without any renewed exposure), to assess longer-term memory. Nine of the ten blind subjects performed above the sighted population average. In fact, the blind group's average performance was 1.36 and 1.49 standard deviations (s.d.) above the population average, for immediate and short delay memory tests, respectively. It was also significantly superior, in comparison to a group of ten sighted controls matched for age, sex and education on a subject-by-subject basis; Student's *t*-test, $P < 0.005$). Furthermore, among the blind, the magnitude of the calcarine activation was positively and significantly correlated with memory performance in the Wechsler immediate (**Fig. 7a**) and long-term (**Fig. 7b**) tests as well as the delayed version of the Wechsler test and the classical digit span test (Pearsons' $r = 0.81, 0.79, 0.65$ and 0.64, respectively; $P < 0.05$ in all cases). The observed correlations were specific to tasks requiring the use of memory for verbal material. Somewhat weaker positive correlations were found between verbal-memory performance and the activation during VG ($r = 0.61, 0.56, 0.57$ with the immediate, delayed and long-term versions of the Wechsler test). No correlation was found between V1 activation during the auditory noise one-back task (which required the use of nonverbal working memory) and performance in the Wechsler memory tests (Pearson's $r < 0.2$ in all tests), suggesting that the activation may be specific for verbal memory processes. Negligible correlation was seen between the subjects' verbal memory abilities and the magnitude of VM activation in a cortical area, which was significantly activated by this task (the intraparietal sulcus, either hemisphere). This indicates that the observed correlation in V1 was not a global cortical phenomenon. Finally, no significant correlations were found between V1 activation level during VM and the subjects' years of education or total IQ (measured by the Wechsler Adults Intelligence Scale, WAIS–3).

DISCUSSION

To summarize, we report here that blind subjects have unique occipital fMRI activation during performance of tasks that require memory of verbal material. Specifically, activation was found in V1 of the blind during a verbal memory task in the absence of any sensory input and in poor imagery conditions (using abstract words). Furthermore, we found strong positive correlation between the blind individual's verbal-memory skills and the magnitude of that individual's V1 activation during verbal memory. The implications of these results are discussed in light of the fact that the congenitally blind (as a group) have superior verbal-memory abilities compared to sighted peers. We also found differences in the functional preferences of regions along the occipital posterior–anterior axis, suggesting a novel topographical specialization in the occipital cortex of the blind. Before discussing these issues in depth, we will address confounding factors that may have contributed to the occipital activation during verbal-memory and verb-generation tasks.

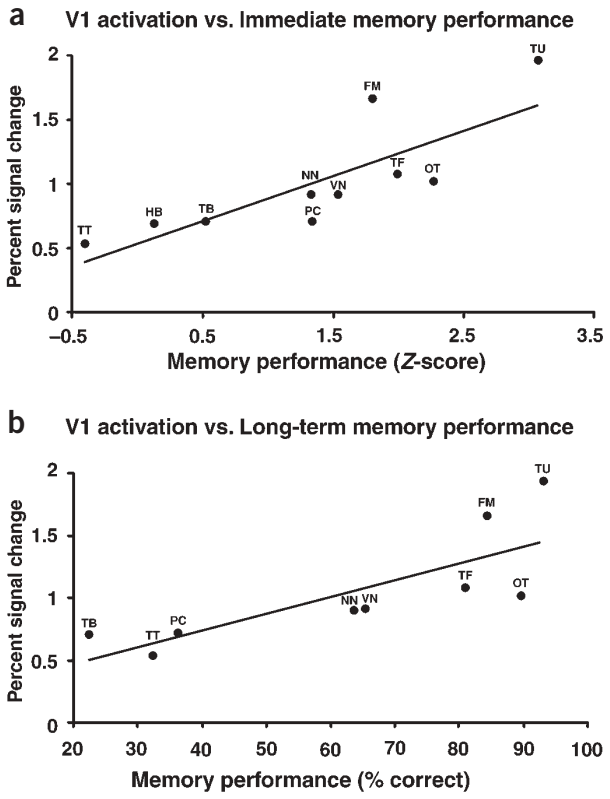

Figure 7 The magnitude of calcarine activation in the blind is correlated with performance level in the standardized Wechsler verbal-memory tests. Scatter diagrams showing the calcarine activation level of each blind subject during VM, plotted against performance in the Wechsler verbal-memory test. Scores given in *Z*–score, normalized according to the general population results (thus $Z = 0$ denotes the average score of the sighted population). As in **Fig. 6**, activation is measured by the BOLD signal intensity during VM. Scores are given as percent of correct responses in **b** because long-term assessment of performance (testing 9 d after presentation) is not part of the standardized Wechsler test. Both immediate (**a**) and long-term (**b**) performance level are highly correlated with the magnitude of the calcarine activation (immediate memory, Pearson's $r = 0.81$; long-term memory, $r = 0.79$).

Possible confounding factors

The observed activation could be a result of differences in arousal or attention demands. The task we used during AN, however, was especially demanding as it required a continuous comparison between the current auditory noise and the previous one. In fact, performance level during this condition was somewhat lower than during VG and VM, suggesting it was indeed challenging. Thus, the significantly greater responses in the V1 ROI during the VG and VM conditions compared to AN (**Fig. 5a**) are unlikely to arise from arousal effects. The role of arousal and attention could also be assessed by comparing the magnitude of activation in the AN to that of the sweep condition, which did not require any discrimination. No clear preference for the AN over the sweep was found in the V1 ROI (**Fig. 5a**).

It could also be speculated that the occipital activations were a result of release from inhibition, which might occur in the blind. There are some suggestions for inhibition of early visual cortex during auditory or tactile processing in sighted people[7]. If this inhibition is less effective in the blind, it might explain the occipital activations during the auditory VG. Still, it does not explain the differential activation in this condition compared to the matched AN condition, and it certainly does not explain the activation during VM that lacked sensory input. Finally, the strong correlation between the V1 activation and verbal-memory capabilities argues against such an explanation.

Another possibility is that the reported activation in VM resulted from imagery processes, but because subjects were congenitally blind, visual imagery is highly unlikely. The use of abstract words also diminished the possibility of tactile object imagery. This leaves the possibility of tactile imagery of the Braille dot structure of the remembered words. However, while it is generally accepted that imagery is significantly less effective in generating fMRI activation than perception of the comparable physical stimulus[29–31], the activation in V1 during Braille (corresponding to the physical stimulus) was less prominent than during VM (**Figs. 3–5**). Moreover, preliminary evidence (Lanzenberger R. *et al. Human Brain Mapping Abstr.* **994**, 2001), indicates that there is no V1 activation during explicit tactile imagery of Braille dot patterns in blind subjects.

Functional preference within the occipital cortex of the blind

The findings that V1 is activated in the blind during Braille reading[7], and that transcranial magnetic stimulation (TMS) of the occipital regions induces errors in Braille reading[11], have been considered strong evidence for the functional involvement of visual cortex in fine tactile processing.

Our results enable a new perspective on the nature of Braille activation in the occipital cortex. First, although Braille reading activated the occipital regions bilaterally, only the right occipital regions showed clear preference for the Braille over the VG and VM conditions. Second, the most selective region for Braille (compared to the sweep or rest conditions) was found in LOC, bilaterally, anterior to the retinotopic ventral regions. Moreover, this region showed preference for Braille over the other non-tactile verbal conditions (**Figs. 3** and **4**). A region within LOC in the sighted (termed LOtv) is active during both visual[22,31] and haptic[31,32] object presentation, and is probably involved in the analysis of geometrical shape of objects[32,33]. Since Braille requires specialization in fine pattern/shape recognition, it is plausible that LOtv serves as a tactile 'anchor' for the development of the Braille responses in the retinotopic visual regions of the blind. The posterior declining gradient of Braille preference in the left occipital cortex is in accordance with this anchor hypothesis. Another option is that the plasticity is mediated via the parietal cortex[7], as tactile processing of gratings and orientation has been reported in the parieto-occipital cortex of the sighted[34].

We further suggest that different anatomical regions within the occipital cortex of the blind acquire new specialized functional characteristics (much like the principle of division of labor in the visual cortex of sighted). This specialization was seen in the different preferences of regions along the anterior–posterior axis. Specifically, the anterior regions located in LOC showed preference for the tactile Braille condition (in both hemispheres), whereas left V1 showed preference for VM and VG. It could be speculated that this gradient may reflect 'reverse hierarchical' organization. Visual processing in the sighted brain is typically described in hierarchical terms. Cortical responses in V1 are generally governed by the physical aspects of the stimulus. The responses gradually change to reflect a more abstract representation in the anterior object-related LOC[35] (that is mirrored by relative invariance to the object defining cue, size, position, viewpoint[36] or even modality[31–33]). Interestingly, in total absence of visual input, this hierarchy seems to be reversed. Thus, early retinotopic regions process more 'abstract' aspects (such as verbal-memory) while the anterior regions are more 'sensory' (showing robust tactile[10] and potentially also auditory activation, as reported previously[15–17]).

Correlation of verbal memory abilities and fMRI signal

The present results strongly support the notion that congenitally blind people generally have superior verbal-memory abilities (for both immediate and long-term intervals)[1–4]. Our finding that as a group they showed extra activation in the occipital cortex (compared to sighted) during performance of verbal-memory tasks suggests that verbal-memory processing in this region may account for their superior abilities. This suggestion is further supported by the strong positive correlation between the individual's calcarine activation during VM and the same individual's performance in various verbal-memory tasks (**Figs. 6** and **7**). These correlations were most dramatic in V1, were specific to tasks involving verbal-memory, and could not be explained by the subjects' IQ or education.

Correlation between performance and fMRI activation has previously been reported in sighted subjects (*e.g.*, correlations between visual object recognition performance and the fMRI elicited activation in LOC[37]). Furthermore, training improves performance and is mirrored by a greater fMRI activation level and enlarged volume of activation (in LOC[37] and primary motor cortex[38], respectively). A recent study of sighted individuals having superior memory abilities[39] reports enhanced fMRI activation in unique regions as well as in regions that were also activated in a control group (during performance of visual memory tasks). Interestingly, the retinotopic areas in the occipital cortex were not active in these individuals (after accounting for the visual input component). This might indicate that visual deprivation is necessary for the development of verbal-memory activation in visual cortex. In accordance with this notion, the superior memory performance in blind subjects was shown to be dependent on the degree of visual impairment: only blind subjects that have no perception of visual form show superior verbal-memory performance compared to sighted matched controls[4]. Thus, residual functioning of the visual cortex might prevent or reduce this kind of reorganization.

Our results indicate that instead of a drastic reshuffling of the memory circuitry, the blind seem to have an additional memory–related region, located in the occipital cortex. How this reorganization is accomplished is still a mystery. The reorganization might be based on existing anatomical connections between visual cortex and classical memory areas. Reciprocal connections between medial temporal regions and V1 are found in the primate brain, either directly or via the inferotemporal cortex[40,41] (which was also robustly active in our blind group during VM). The visual cortex is interconnected with prefrontal regions as well, via reciprocal connections of both regions with the inferotemporal cortex[42]. Some of these projections to the visual cortex are much more extensive in the newborn, but attenuate gradually[43]. In congenital blindness, these feedback pathways might be enhanced due to the lack of competition from visual input, giving rise to the functional plasticity reported here.

The possible role of occipital cortex in verbal memory

We suggest that the occipital cortex activation during VM and VG is related to memory processes involving verbal material. One interpretation of the results is that the degree of occipital activation is an indicator of the level of occipital cortex engagement in memory processing. Thus, individuals using this cortex more extensively in memory processing will show greater occipital activation during a verbal memory task, even when retrieval performance is the same (in our case, due to training). A similar effect was previously reported in sighted superior memorizers[39] who showed extra activation in a variety of cortical regions during memory tasks compared with controls. Importantly, this difference was maintained even when performance was matched between the groups. Our results are in line with the hypothesis that the recruited cortical mass underlies improved mnemonic skills, as the magnitude of the additional occipital activation was highly correlated with the subject's performance in the standard Wechsler verbal memory tests.

The variation in occipital activation might reflect differences in the efficacy of encoding of the words into long-term memory during the scan (*i.e.*, the chance that they will be maintained for longer periods). The strong correlation between the blind individuals' V1 activation during VM and recognition performance of the words from the list 6 months later supports this encoding depth hypothesis. Note that activation was also found during VG, a task that generates effective encoding of the newly presented nouns[44]. Thus, in addition to semantic memory processing, the activation during VG may be related to episodic encoding of the presented nouns. As was shown recently, the fMRI signal in the left prefrontal and temporal cortex of sighted people is greater during encoding of words that are later successfully retrieved than for those forgotten later[45,46]. The encoding hypothesis predicts that a similar effect would be found in retinotopic regions of the congenitally blind.

Another possible interpretation is that activation is due to the processing of the semantic content of the retrieved words. According to this view, the activation reflects the outcome of successful word retrieval, rather than contributing directly to the memory process. While this interpretation fits well with some of our results, it is inconsistent with a number of findings. First, no differential activation for words versus non-words was found previously in the occipital cortex of congenitally blind[7,8], as the semantic processing hypothesis would predict. In addition, in our study the semantic content (the number of words processed) during VM was practically the same among the subjects, as retrieval level (as assessed immediately after the scan) was identical and perfect in all the subjects but one. Thus, the great variation in calcarine activation during VM, as well as the strong correlation between this activation and the subject's verbal memory abilities, cannot be explained by variability in semantic content between subjects.

The putative function of the right occipital regions in the blind is unclear. Whereas activation during VM was clearly left-lateralized, some significant clusters were also found in the right occipital cortex, suggesting it might be involved in verbal memory in some cases (*e.g.*, two subjects showed a balanced pattern of activation). Still, the right hemisphere might also be engaged in nonverbal memory (**Supplementary Fig. 1**).

We suggest that the greater reliance of the blind on verbal memory leads to practice-induced reorganization of the 'visual' cortex, when deprived of its original input, such that it becomes involved in verbal-memory processes. If the occipital cortex of the congenitally blind is reorganized to serve as an 'extra' memory region, then damage to the occipital cortex might impair their superior memory abilities. This can now be tested by inducing virtual transient lesions in the occipital cortex of the blind using TMS (for review, see ref. 47) during performance of verbal-memory tasks. The prediction is that TMS would hamper performance, especially in individuals who show exquisite memory capabilities.

METHODS

Subjects. Ten blind and seven sighted native Hebrew speakers participated in the experiment. The Tel–Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject. An expert examined the blind subjects to assess the cause of blindness and presence of any light perception. All ten subjects were congenitally blind, had major retinal damage, and their blindness was not due to a progressive neurological disease. Nine of the subjects did not have any form of light perception (**Supplementary Table 1**). The last subject (NN) could only report the presence of a strong light, but couldn't localize it or recognize

any pattern. Handedness of subjects was assessed using the adapted version of the Edinburgh test. Sighted controls were four women and three men, matched for age, gender and handedness. Their years of formal education were significantly greater than the blind participants (18.7 ± 2.8 vs. 13.5 ± 2.6, respectively). Sighted subjects were blindfolded throughout the scan.

Functional MRI acquisition. The BOLD fMRI measurements were performed in a whole-body, 1.5–T Signa Horizon LX8.25 scanner (General Electric). The fMRI protocols were based on a multi-slice gradient echoplanar imaging and a standard head coil. The functional data were obtained under the optimal timing parameters: T*R* = 3 s, TE = 55 ms, FA = 90°, imaging matrix = 80 × 80, FOV = 24 cm^2. The 17 slices with slice thickness 4 mm and 1 mm gap were oriented in the axial or oblique position, for optimal coverage of the occipital cortex. The scan covered the whole brain except the most dorsal tip and/or the most ventral tip (depending on the brain size of each individual, the location and angle of the slices).

Experimental setup. During the whole experiment, the subjects had their right hand on a custom-made table, keeping their hand still during the non-tactile conditions (thus minimizing hand movements), and scanning Braille signs during the tactile conditions. The Braille stimuli were attached to PVC boards, which were placed on the table. The auditory stimulus sequences were recorded, digitized and played on a CD player. The auditory signals were transferred binaurally to the subjects through a pneumatic device of silicone tubes into commercially available noise shielding headphones (Slimline noise guard headset, Newmatic Sound System) at a level of 86–89 dB SPL.

Stimuli and experimental protocol. Six different experimental conditions were used in a block design. All epochs lasted 12 s followed by 9 s of rest. Each epoch was repeated five times using different stimuli. A short (~1 s) auditory instruction was given before the beginning and at the end of all epochs. All stimuli presented during the scan were novel (subjects were trained on an alternative set of stimuli). In the VM condition, subjects recalled words from four lists, which were learned in advance (one week before the scan). Each list contained nine abstract words (imageability score of 100–350 according to the MRC psycholinguistic database (www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). All subjects (blind and sighted) could name at least eight out of the nine words from each list during an epoch period. During VG, subjects covertly generated a compatible verb to a heard noun. The nouns were of everyday objects presented every 2 s. The AN condition contained six noise sounds within each block. Each noise sound matched a corresponding presented word (by creating Gaussian noise stimulus with the average power spectrum across all words in the corresponding VG block that was then multiplied by each word's temporal envelope[32,48]). This procedure created a noise sound that matched the word sound in its duration, average amplitude and temporal envelope. Each AN epoch had the same average spectral composition as the corresponding VG epoch. Each AN (and VG) block contained 0–2 repeated stimuli, and subjects were instructed to covertly judge in the AN block if the current noise matched the previous noise within the same block ('one-back' task). During the Braille epoch, a board containing 30 abstract words (mean word length, 4.9 letters; imageability score, 100–350 as in VM) was presented to the subjects in a fixed location. Subjects were instructed to covertly read the words. In the tactile sweep condition, subjects swept their reading finger over a surface homogenously covered by a full six-dot Braille sign (which is meaningless). They were instructed to maintain the same sweep speed as in reading Braille. No response was required. Finally in the rest period subjects lay still in the scanner.

Behavioral performance in all tasks was assessed immediately after each scan. Performance level for AN (88 ± 6% (s.d.) correct for same/different judgments) was lower than for VG (98 ± 2% correct retrieval of verbs to nouns) and VM (99 ± 2% for recall of words from the lists), emphasizing that the AN condition was demanding. In the Braille condition, subjects read on average 10.4 words (± 2.4 s.d.). No significant differences were found between the blind and the sighted subjects in performance levels of the tasks used in the scan (Student's *t*-test: $P > 0.63$, $P > 0.92$ and $P > 0.34$ for VG, AN and VM, respectively).

Data analysis. Data analysis was performed using the Brain Voyager 4.95 software package (Brain Innovation). Before statistical analysis, head motion correction and high-pass temporal smoothing in the frequency domain were applied to remove drifts and to improve the signal-to-noise ratio. A general linear model (GLM) approach was used to generate statistical parametric maps. Across-subject statistical parametric maps were calculated using hierarchical random effects model analysis[20] allowing a generalization of the results to the population level. This was done after the voxel activation time courses of all subjects were transformed into Talairach space, *Z*–normalized and concatenated. Significance levels were calculated, taking into account the probability of a false detection for any given cluster[49] by a Monte Carlo simulation (using the AlphaSim software, 2000, written by B.D. Ward, Medical College of Wisconsin) using the combination of individual voxel probability threshold and a minimum cluster size of seven functional voxels. The minimum significance level, corrected for any given cluster, was $P < 0.05$.

The activation time course of individual subjects was obtained from statistically significant clusters in each region of interest (ROI) by using a fixed GLM approach with correction for multiple comparisons. The average signal intensity was also calculated for each subject and then averaged across subjects. Voxels in the V1 ROI (**Figs. 4–7**) were collected according to an anatomical marker: the calcarine sulcus including its upper and lower banks. The retinotopic borders displayed on the Talairach-normalized brain of the blind were estimated using the rotating wedge technique[50] on one of the sighted subjects. 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 retinotopic borders were also used for collecting significant voxels in the extrastriate retinotopic ('V2'–'V4') ROI. The LOC ROI was defined according to a specific localizer mapping in nine sighted subjects[31] (differential activation for objects versus scrambled objects). The Talairach-normalized volumetric time course of the sighted group was superimposed on each blind subject's Talairach-normalized brain. Significant cluster selection for the S1 and A1 ROIs (**Fig. 5b**) was based on anatomical markers: the post-central gyrus for S1 and the transverse gyrus of Heschl and planum temporale for A1.

To assess the task (condition) × hemisphere interaction in the retinotopic regions (including V1), we defined the left and right hemisphere retinotopic ROIs in Talairach space (see above). Then, the average percent signal change in the two ROIs was computed for each subject and each condition. Finally, an ANOVA testing for a task × hemisphere interaction was performed.

The marked voxels in the two-color maps (group analysis presented in **Fig. 3**) are those for which the relevant predictors (VM and Braille in **Fig. 3a**; VG and Braille in **Fig. 3b**) explained a significant portion of the variance in the voxel's activation time course (using $P < 0.05$ corrected). The index for relative contribution (c) was assessed as follows:

$$c = \frac{R_{\text{extra (VG)}} - R_{\text{extra (Braille)}}}{R_{\text{extra (VG)}} + R_{\text{extra (Braille)}}}$$

R_{extra} is the square root of the extra variance explained by the two predictors (VG and Braille). So, for example,

$$R_{\text{extra (VG)}} = \sqrt{R^2_{\text{total}} - R^2_{\text{reduced by VG}}}$$

for the VG predictor and similarly for the Braille condition predictor. The same applies also for the VM versus Braille map (**Fig. 3a**).

Behavioral measurements. We assessed the subjects' verbal memory abilities (as well as other behavioral tests) following the fMRI scan. Performance was measured by (i) the percent of words remembered from the lists, used in VM during the scan and (ii) performance in the standard Wechsler Memory Scale (WMS 3rd edn.[28]; not to be confused with the Wechsler adults intelligence scale, WAIS). All the subjects could name the words from the list almost flawlessly immediately after the scan. Therefore, we tested subjects (both blind and sighted) approximately 6 months after their fMRI scan. A list containing 82 words was read to each subject; 36 were the original words they memorized for the scan and the rest were abstract distractors taken from the same database. Subjects had to indicate for each word whether it was part of the original list or not (recognition task). We could not perform this test on one blind and one sighted subject. Each of the blind subjects was tested on the auditory verbal-memory subtests of the

WMS. These include recalling details of a heard story and a pair-association recall test. Based on these two tasks, a standardized score is obtained, assessing the subject's verbal-memory performance in comparison to the population average (*Z*–score, in units of s.d. from the population average). In addition, we tested our subjects on the digit-span test (taken from the WAIS–3), which is another standardized measure of short-term verbal-memory performance.

Correlation between cortical activation and behavior. Correction for multiple comparisons in V1 (**Fig. 6a**) took into account the total number of voxels in the ROI. Assessment of the calcarine activation during VM (for correlation with performance level in **Figs. 6b** and 7) was based on the BOLD signal intensity in each subject (of the peak voxel in a smoothed volume within the calcarine sulcus, after convolution with a Gaussian kernel of 8 mm full width at half maximum).

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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