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Negative BOLD in Sensory Cortices During Verbal Memory: A Component in Generating Internal Representations?

Haim Azulay · Ella Striem · Amir Amedi

Abstract People tend to close their eyes when trying to retrieve an event or a visual image from memory. However the brain mechanisms behind this phenomenon remain poorly understood. Recently, we showed that during visual mental imagery, auditory areas show a much more robust deactivation than during visual perception. Here we ask whether this is a special case of a more general phenomenon involving retrieval of intrinsic, internally stored information, which would result in crossmodal deactivations in other sensory cortices which are irrelevant to the task at hand. To test this hypothesis, a group of 9 sighted individuals were scanned while performing a memory retrieval task for highly abstract words (i.e., with low imaginability scores). We also scanned a group of 10 congenitally blind, which by definition do not have any visual imagery per se. In sighted subjects, both auditory and visual areas were robustly deactivated during memory retrieval, whereas in the blind the auditory cortex was deactivated while visual areas, shown previously to be relevant for this task, presented a positive BOLD signal. These results suggest that deactivation may be most prominent in task-irrelevant sensory cortices whenever there is a need for retrieval or manipulation of internally stored representations. Thus, there is a task-dependent balance of activation and deactivation that might allow maximization of resources and filtering out of non relevant information to enable allocation of attention to the required task. Furthermore, these results suggest that the balance between positive and negative BOLD might be crucial to our understanding of a large variety of intrinsic and extrinsic tasks including high-level cognitive functions, sensory processing and multisensory integration.

Keywords Multisensory integration · Negative BOLD · Intrinsic processing · Crossmodal brain plasticity · Verbal memory · Crossmodal deactivation

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Introduction

People tend to close their eyes or look upward in an unfocused manner when trying to retrieve old or barely recallable items from memory. Interestingly, blind individuals (with a complete absence of vision) seem to have superior memory capabilities (Tillman and Bashaw 1968; Smits and Mommers 1976; Pozar 1982; Pring 1988; Hull and Mason 1995; Röder et al. 2001; D'Angiulli and Waraich 2002; Raz et al. 2007) including verbal memory capabilities (Tillman and Bashaw 1968; Smits and Mommers 1976; Pozar 1982; Pring 1988; Hull and Mason 1995; Amedi et al. 2003; Raz et al. 2007). Similarly, people find it much easier to visually mentally imagine a visual object with their eyes closed (Spanos and Stam 1979). However the brain mechanisms for this phenomenon remain debated and poorly understood.

For many years a large body of work emphasized the overlap in the neural substrates supporting perception and

mental imagery, especially in the visual modality (Ishai and Sagi 1995; Kosslyn et al. 1999; Ishai et al. 2000; Kreiman et al. 2000; O'Craven and Kanwisher 2000; Mechelli et al. 2004). For instance, one can predict whether an imagined object during an fMRI scan is a face or a house based on the magnitude of activity in the relevant object-specific areas (O'Craven and Kanwisher 2000). However, in a recent study (Amedi et al. 2005a) we showed that while the unisensory cortex involved in imagery may indeed be activated in similar ways during perception and imagery, other sensory cortices are active in very different ways during these two states. In particular, during imagery of visual objects, auditory and somatosensory cortices show a clear deactivation (Amedi et al. 2005a), while there is much smaller deactivation during perception (Laurienti et al. 2002; Mozolic et al. 2008). It may be that the nature of unisensory imagery requires that the "blooming, buzzing confusion" of the multisensory information input from the outside world is shut off so that one can focus the "mind's eye" on visual mental imagery. In fact, we found correlations between the magnitude of deactivation and the vividness of visual imagery across individuals (Amedi et al. 2005a). However, the process of focusing on internally stored information is not unique to visual mental imagery. Is robust crossmodal deactivation unique to visual mental imagery or is it a special case of a more general phenomenon covering any intrinsic, internally stored information which would be applicable to deactivations in other sensory cortices?

One way to examine this question is by looking at the neural correlates of auditory or tactile mental imagery which could generalize the deactivation phenomenon to mental imagery in other sensory modalities and other sensory cortices. An even more remote intrinsic task is memory retrieval involving verbal (verbal memory, VM) rather than sensory items. VM also requires focusing on stored internal representations, which might also require the blocking of ongoing irrelevant sensory processing (Kenet et al. 2003; Mantini et al. 2007; Bianciardi et al. 2009; Nir et al. 2008; Wang et al. 2008).

Here we scanned normally sighted subjects, using fMRI, while they performed verbal memory retrieval of highly abstract words. If deactivation is specific to visual imagery, we should not find comparable sensory cortex deactivation during VM for highly abstract words. However, if the more general 'silencing of irrelevant input' hypothesis is correct, we should find auditory cortex deactivation for VM as well. We also expect to find additional deactivation in other non-relevant sensory cortical structures such as visual retinotopic areas.

Additionally, we scanned a group of congenitally blind individuals on the same task. The advantage of using blind individuals for the current investigation is twofold: (1) The congenitally blind do not have any prior visual experience and thus cannot use visual imagery per se. (2) Since we previously showed that visual cortex is functionally relevant to VM for the blind (Amedi et al. 2003; Raz et al. 2005), we expect to find no VM deactivation at all, as predicted by the visual imagery hypothesis. However, we also expect to find VM deactivation in the auditory but not in the visual cortex if the second, more general deactivation of non-relevant sensory extrinsic areas during internal representation retrieval hypothesis is correct.

Methods

Subjects

Ten fully congenitally blind subjects and nine normally sighted subjects without neurological or psychiatric problems participated in the experiment. Sighted subjects included 4 women and 5 men, aged 27–50; six were right handed and three left handed as assessed by the Oldfield Handedness Questionnaire. The blind subjects included 5 women and 5 men, aged 19–51; nine of whom were right handed and one left handed as assessed by the Oldfield Handedness Questionnaire (see also Table 1). The blind subjects were examined by an ophthalmologist to assess the cause of blindness and presence of any light perception. All ten blind 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 (see Table 1). One subject could only report the presence of a strong light, but could not localize it or recognize any pattern. The Tel–Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject.

Functional MRI Acquisition

The fMRI measurements were conducted in a whole-body, 1.5-T Signa Horizon LX8.25 scanner (General Electric). 3D anatomical volumes were collected using a T1 SPGR sequence. The fMRI protocols were based on multi-slice gradient echoplanar imaging and a standard head coil. The functional data were obtained under the optimal timing parameters: TR = 3 s, TE = 55 ms, FA = 90°, imaging matrix = 80 × 80, FOV = 24 cm^2. The 17 slices with a slice thickness of 4 mm and a 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, and the location and angle of the slices).

Table 1 Characteristics of blind participants

Subject	Age & sex	Cause of blindness	Light perception	Handedness	Preferred hand for Braille reading	Braille reading since (age)
FM	20 F	Microphthalmia	None (prosthesis)	Right	Right	5
TT	45 M	Retinopathy of prematurity	None	Right	Right	7
TU	51 F	Leber congenital amaurosis	None	Right	Right	6
NN	32 M	Retinopathy of prematurity	Faint	Right	Right	6
TF	30 F	Rubella	None	Right	Left	6
VN	31 M	Retinopathy of prematurity	None	Right	Left	6
PC	28 M	Retinopathy of prematurity	None (prosthesis)	Right	Left	6
OT	19 F	Retinopathy of prematurity	None	Right	Left	5
HB	27 M	Retinopathy of prematurity	None	Right	Left	6
TB	27 F	Retinopathy of prematurity	None	Left	Left	6

Experimental Setup

The visual stimuli were generated on a PC and projected via an LCD projector (Epson MP 7200) onto a tangent screen located inside the scanner and in front of the subject. 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

The verbal memory (VM) task was conducted in both blind and sighted groups identically. In the VM condition we used a block design. All epochs lasted 12 s followed by 9 s of rest. During each epoch, all subjects (sighted and blind) were asked to recall nine words from one of four lists, which had been learned in advance (1 week before the scan). A short ($\sim$1 s) auditory instruction was given at the start (stating which list which should be recalled: "list A", "list B", "list C" or "list D") and the end (the word "stop") of all epochs. The words were presented aurally to both groups during the initial learning stage of the lists. Each list contained nine abstract words (low imaginability 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 a given epoch period. This was the threshold which we required on all lists before the scan could begin. We controlled for this threshold before scheduling a scan but also while subjects lay in the scanner just before the scan. Performance was tested for each subject in the scanner before and after each scan, but not during scan time itself, as the recall was silent to avoid confounds involving motor, head or hand movement and the physical articulation of words.

Behavioral Data

Performance assessed after the scan confirmed that all subjects had nearly perfect results (99 $\pm$ 2% SD for recall of words from the lists, no statistical difference between the sighted and blind groups, Student's t-test $P > 0.34$).

The rationale for generating ceiling performance in both groups was to try to equalize performance between the blind and sighted individuals since blind people, as a group, tend to have superior verbal memory capabilities (Tillman and Bashaw 1968; Smits and Mommers 1976; Pozar 1982; Pring 1988; Hull and Mason 1995; Amedi et al. 2003; Raz et al. 2007). Thus, we attempted to achieve perfect performance in both the blind and sighted participants through extensive training on the lists until retrieval was optimal. To make sure that all participants were similarly engaged in the task during the scan, they were instructed to finish retrieving the list before the 12-s period ended (signaled by the auditory stop cue), and should continue re-retrieving the words from the list from the start until the auditory end cue. Therefore, while there may be differences between blind and sighted populations in general with regard to mnemonic abilities, the performance and engagement on the specific VM task during the scan was comparable for both groups.

Data Analysis

Data analysis was conducted on BrainVoyager QX 1.10 software packages (Brain Innovation, Maastricht, The Netherlands). This included preprocessing stages and general linear analysis (GLM). Preprocessing included head motion correction, slice scan time correction, and high-pass temporal filtering in the frequency domain to remove drifts and to improve the signal-to-noise ratio, and spatial smoothing (Gaussian kernel of 6.0 mm FWHM). To compute statistical parametric maps we applied a GLM

with predictors convoluted with a typical hemodynamic response function (using parameters as in Boynton et al. 1996). Across-subject statistical parametric maps were calculated by using hierarchical random-effects model analysis (Friston et al. 1999) after transformation into Talairach space (Talairach and Tournoux 1988). We used a statistical threshold criterion of $P < 0.05$ corrected for multiple comparisons using a cluster-size threshold adjustment, based on a Monte Carlo simulation approach extended to 3D data sets using the threshold size plug-in BrainVoyager QX (Forman et al. 1995; for more details on implementation see Amedi et al. 2005b, 2007). This cluster threshold estimator takes input regarding the functional voxel size (3 mm³ for 3D BrainVoyager QX data), the total number of significant voxels within a map, and the estimated smoothness of a map and performs Monte Carlo simulations (1,000 iterations) to estimate the probability of clusters of a given size arising purely by chance. Because the minimum cluster size for a corrected P value (0.05) is estimated separately for each map, the cluster sizes can differ for different comparisons.

Single-Subject 3D Brain Volume Data Acquisition and Cortex Reconstruction

3D VMR (Volume Magnetic Resonance) data acquisition was used for surface reconstruction. This procedure included the segmentation of the white matter by using a grow-region function. The cortical surface was then inflated and unfolded, cut along the calcarine sulcus, and flattened. The obtained activation maps (Figs. 1 and 3) were superimposed on the inflated and unfolded cortex of a single subject.

Time Course and Percent Signal Change Analysis

Beyond statistical parametric maps, activation was sampled (for demonstrative purposes) from various regions of interest (ROIs) in all single subjects for verbal memory versus rest using the group peak activation cluster and regardless of whether the voxel was peak maximum or minimum. For this procedure we used the smoothed data so that each peak would reflect activation in its immediate vicinity in a Gaussian manner. Then we averaged the percent signal change at the time of peak hemodynamic response (TRs 3–5) and standard errors were calculated for each group. The magnitude of activation was sampled from three ROIs in each hemisphere based on known anatomical markers (Fig. 2): (1) Peak VM in Heschl's gyrus (HG ROI: which roughly corresponds to Brodmann's area 41/42, early/primary auditory cortex); (2) Peak VM activation or deactivation that fell between pars triangularis (PTR) anteriorly and pars opercularis (POP) posteriorly in inferior
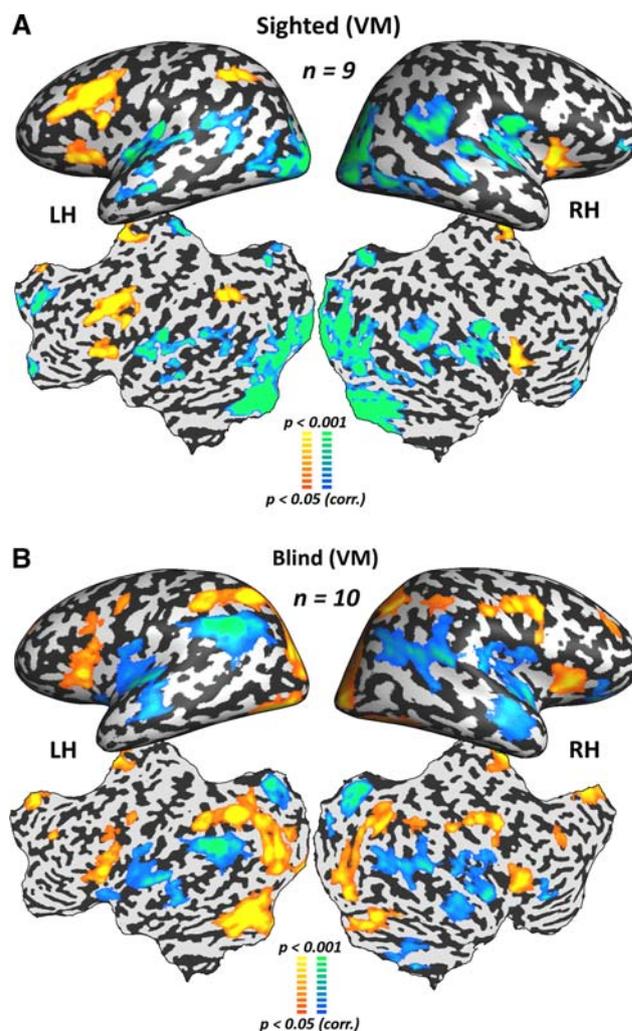
Fig. 1 Verbal memory positive and negative BOLD in sighted and blind. Statistical parametric maps of activation for the verbal memory versus rest contrast using a random effect GLM analysis. Group results are presented on a full Talairach-normalized inflated and unfolded brain of the left (LH) and right (RH) hemispheres. Color scale denotes significant activations (red to yellow) and significant deactivation (blue to green) (corrected for multiple comparisons, see Methods). a The verbal memory versus rest contrast in sighted subjects ($n = 9$) showed robust and highly significant deactivations both in early auditory regions and in early visual areas including the occipital cortex stretching along the ventral visual retinotopic area together with the calcarine sulcus, corresponding to V1. Marked activation is shown in the left prefrontal and left parietal regions and in inferior prefrontal bilaterally. b Statistical parametric maps of activation in the congenitally blind group ($n = 10$). Primary auditory cortex shows robust deactivations bilaterally during verbal memory task. In contrast, the visual cortex, which is known to be involved in verbal memory tasks and speech in the blind, showed marked positive activations in the occipital area corresponding to V1 and in ventral and dorsal retinotopic areas bilaterally. As in the sighted group marked activation was shown in the left prefrontal and inferior prefrontal bilaterally

prefrontal cortex (POP/PTR ROI: in areas corresponding to Broca's area); (3) peak VM activation or deactivation in calcarine sulcus/cuneus gyrus which roughly corresponds
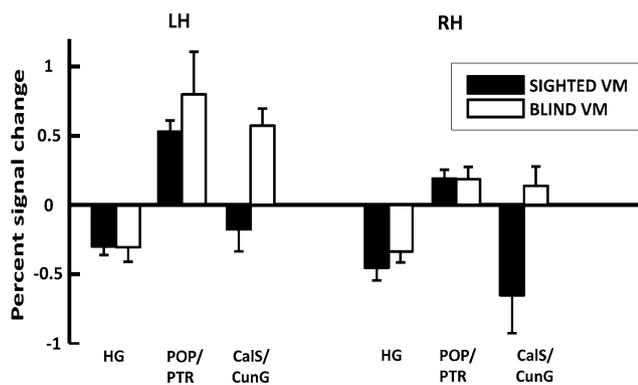
Fig. 2 Magnitude of activation in several regions-of-interests (ROIs). Average percent signal change is shown for VM condition versus rest as measured by peak activations in six defined ROIs corresponding to bilateral A1 (Heschl's gyrus: HG), bilateral prefrontal (inferior frontal sulcus: pars triangularis, PTR, and pars opercularis, POP), bilateral V1 (calcarine sulcus/cuneus gyrus) in sighted and blind groups ($n = 9$ and $n = 10$, respectively). Demonstrable deactivations in both the auditory and visual cortices bilaterally were observed in the sighted group together with significant activations in the prefrontal regions with marked preference for the left hemisphere. In the blind group primary auditory cortex showed significant deactivation as opposed to noticeable activations in the primary visual cortex ROI corresponding to ventral visual retinotopic areas. Significant activation in the left prefrontal region was observed

to Brodmann's area 17 (CalS/CueG ROI: early/primary visual cortex).

Functional Localizers

In the SCR (scrambled visual images) condition, subjects viewed visual noise composed of highly scrambled images of visual objects presented at a 1 Hz rate (while fixating, and with no further instruction). This SCR condition was scanned in all sighted subjects and its activation was used to define posterior occipital cortex/retinotopic visual areas (Fig. 3). This was done using the same block design (12 s stimulation and 9 s of rest) as in the main experiment.

In order to define the early auditory cortex functionally, we also invited five of the nine original sighted subjects to an additional scan. The auditory cortex localizer was tested using a block-design paradigm with two main conditions: "pure tones" and rest. The pure tone blocks contained 24 tones presented at 2 Hz. The duration of each tone was 350 ms, with linear onset and offset ramps of 5 ms. Three block types were created, each containing tones in a different frequency range: low (200–300 Hz), medium (800–1200 Hz), and high (3200–4800 Hz). As pure tones were only used to define early auditory cortex in general and not to assess tonotopic organization, we combined all these blocks into one predictor (PT). Specifically, we used a combination of functional and anatomical markers. We took all the voxels located in Heschl's gyrus and its vicinity
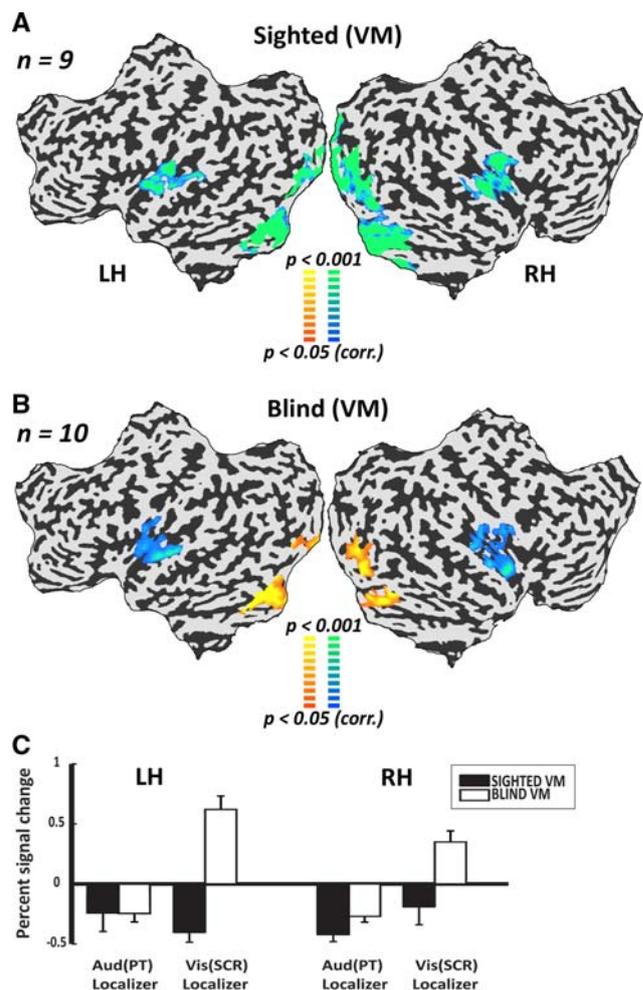
Fig. 3 Verbal memory BOLD signal in early visual and auditory sensory areas. Statistical parametric maps of activation during VM using a random effect GLM analysis for the early sensory cortex. Group results are presented on a full Talairach-normalized unfolded brain of the left (LH) and right (RH) hemispheres. Color scale denotes significant activations (red to yellow) and significant deactivation (blue to green) (corrected for multiple comparisons, see Methods). The verbal memory versus rest contrast is shown only for primary auditory cortex (areas in the temporal lobe activated by pure tones, PT, see Methods for further explanation), and retinotopic visual cortex (occipital areas activated by visual noise stimuli, SCR). **a** In sighted subjects ($n = 9$) early auditory and visual cortex show highly significant deactivations. **b** In the blind subjects ($n = 10$) early auditory cortex shows deactivation to the VM task, while retinotopic visual cortex shows significant activation. **c** Average percent signal change is shown for the VM condition versus rest as measured in the bilateral entire functionally defined early auditory cortex (PT localizer) and retinotopic visual cortex (SCR localizer) in the sighted and blind groups ($n = 9$ and $n = 10$, respectively). The deactivation–activation pattern demonstrated in sections **a** and **b** is evident in these early sensory cortices

that were significantly activated by pure tones, signifying that they indeed corresponded to the early auditory cortex (Kaas et al. 1999; Wessinger et al. 2001). Both functional localizers (SCR, PT) were used to display activation (or

deactivation) during VM only in early sensory cortices (Fig. 3a, b). We then used these masks to sample the individual time course and percent signal change for each subject. The averages and standard errors of the mean (SEM) are presented in Fig. 3c.

Results

Negative and Positive BOLD During the VM Task in the Sighted Group

To characterize the pattern of activity in the VM task, we measured brain activity, as indexed by the fMRI blood-oxygen-level-dependent (BOLD) signal, while sighted participants performed a verbal memory task of highly abstract words (VM). By contrast with rest, the VM task showed marked (positive) activation in the inferior frontal gyrus bilaterally (with a preference for the left hemisphere) as well as some other typical brain areas (such as the parietal and parahippocampal areas) (Fig. 1a). All activations were typically lateralized to the left side as previously described (Petrides et al. 1993; Fiez 1997; Gabrieli et al. 1998). More importantly, we found robust and highly significant deactivation in the bilateral auditory cortex, as was reported for visual mental imagery (Amedi et al. 2005a). However, in contrast to the findings in the study on visual mental imagery we also observed a highly significant bilateral deactivation in large-scale posterior occipital cortex areas (Fig. 1a).

Negative and Positive BOLD During the VM Task in the Blind Group

In the congenitally blind group (who have no visual recollections) robust activation was found in the prefrontal cortex (Fig. 1b), similar to the finding in the sighted. Furthermore, strong deactivation was found in auditory areas as in the sighted group. However, in the visual cortex the blind group showed significant activation rather than deactivation, probably since the area *is relevant* for memory functions (Fig. 1b; see also Discussion). Thus, even if the positive pattern of activation (in the occipital lobe) was modified due to brain plasticity, a deactivation of non-relevant areas (i.e., auditory cortex) was still present.

Time Courses in Different Regions of Interest (ROIs)

For demonstrative purposes we assessed the magnitude of activation and deactivation patterns in various regions of interest (ROIs), taken from the peak prefrontal (PTR/POP ROI, auditory (HG ROI) and visual (CalS/CueG ROI) areas of both hemispheres (Fig. 2). This procedure was repeated

in both the sighted and blind individuals. The results as averaged across the entire set of subjects were highly consistent with the statistical parametric maps reported at the group level. Specifically, the percent signal change from the prefrontal cortex showed robust activation in both groups (with left hemisphere preference). The auditory peak showed clear VM deactivation in both groups. Finally, VM activated visual areas bilaterally in the blind group (with similar left hemisphere preference) whereas the sighted showed the opposite effect, with clear VM deactivation (Fig. 2).

Activation Pattern for VM in the Early Sensory Cortices

In order to specifically test the deactivation hypothesis in the early sensory cortices, we used a pure-tone (PT) functional localizer to define the early auditory cortex (Kaas et al. 1999; Wessinger et al. 2001) and a visual SCR localizer to define the visual retinotopic cortex (i.e., early visual cortex, see Methods). Figure 3 depicts the VM activation seen in the sighted and blind groups (Fig. 3a, b), only in regions defined by these functional localizers. It demonstrates that indeed the deactivation–activation pattern of these cortices exists in early sensory cortex, and that the blocking of sensory inputs is not only specific to high-order processing regions (Fig. 3a). Thus, the early auditory cortex of both groups was deactivated, but the early visual cortex was deactivated in the sighted group and activated in the blind group. It is important to emphasize that this pattern was highly consistent at the group level across these localizers as *all* the significantly active group level voxels in early auditory cortex showed negative BOLD in both groups (i.e., there were no positive significantly active voxels). Similarly, all the significantly active visual cortex voxels showed negative BOLD in the sighted and positive BOLD in the blind. Additionally, to verify this, we sampled the individual time-course of the entire functional auditory and visual masks in both groups, regardless of their functional activity during VM. The average percent signal change (Fig. 3c) shows that the early auditory and visual cortices in the sighted and the auditory cortex in the blind do indeed respond with marked deactivation to the VM task.

Discussion

Summary of Results

We report here that in sighted subjects both auditory and visual areas are deactivated during memory retrieval, while in the blind only the auditory cortex, which is irrelevant to

the task, is deactivated (in contrast to visual areas, which we and others have shown to be functionally relevant in the blind for language and verbal memory). These results suggest that deactivation may also be present in sensory cortices outside the default-mode areas, whenever there is a need for retrieval or manipulation of internally stored representations. In these cases, we suggest that any sensory cortex which is irrelevant to the specific task will be deactivated. Furthermore, these results suggest that the balance between positive and negative BOLD might be highly relevant for our understanding of a large variety of intrinsic and extrinsic tasks including high-level cognitive functions, sensory processing and multisensory integration.

Robust Sensory Cortices Deactivation on Intrinsic Tasks

We previously showed (Amedi et al. 2005a) that visual imagery deactivates the auditory cortex in sighted subjects. Two possible hypotheses were suggested to account for these results: the first is that deactivation could stem from the highly unisensory nature of visual mental imagery, as compared to the multimodal nature of normal perception (Amedi et al. 2005a). Visual perception is inextricably associated with a multisensory experience of the object (Stein and Meredith 1993; Driver and Spence 1998; Pascual-Leone and Hamilton 2001; Amedi et al. 2005c; Beauchamp 2005; Pascual-Leone et al. 2005), whereas unisensory visual imagery (as examined in Amedi et al. 2005a) was characterized by isolated activation of visual cortical areas with concurrent deactivation of sensory inputs that could potentially disrupt the image created by the mind's eye. In this case, the deactivation of the auditory cortex may be unique to visual imagery, and not come into play in other non-sensory tasks.

The second hypothesis put forward is that any use or reference to internal representations or stored information could require the inhibition of cortices that usually process extrinsic sensory stimuli, so as to focus on such internal representations. In the present study, we showed that engaging in an intrinsic verbal memory retrieval task generates a robust crossmodal deactivation of both auditory and visual cortices in sighted subjects, and a robust deactivation in the auditory cortex of congenitally blind subjects in addition to activation (positive BOLD) of the occipital "visual" cortex in these subjects. Thus, our current results clearly support this second hypothesis, and demonstrate that deactivation is a more general phenomenon which is likely to occur in many tasks involving internal representations, but perhaps also in other tasks, for instance those imposing very strong crossmodal attention demands (see below). It is important to realize, however, that some tasks might include inherent crossmodal imagery

components and in these tasks the balance between positive and negative BOLD might be completely different (for instance see: Zangaladze et al. 1999; Sathian and Zangaladze 2002; Zhang et al. 2004; Sathian 2005).

The current results clearly demonstrate that robust sensory cortices deactivation is also prevalent outside the default mode network in at least one more intrinsic task, and thus is not unique to the process of visual mental imagery. It might be argued that the present VM deactivation findings could to some extent be the result of visual imagery which may be a component of the memory retrieval task. We believe that this is highly unlikely for several reasons: (1) the memorized and retrieved words used in our study were highly abstract, with the lowest imaginability scores (see Methods); (2) visual imagery normally results in positive activation in visual cortex (Kosslyn et al. 1993, 1999; Ishai and Sagi 1995; Ishai et al. 2000; Kreiman et al. 2000; O'Craven and Kanwisher 2000; Klein et al. 2004; Lambert et al. 2004; Mechelli et al. 2004; including our previous study on mental imagery: Amedi et al. 2005a). However, here we found a significant deactivation in the visual cortex of the sighted, further supporting the view that visual mental imagery was not used during VM; (3) the group of congenitally blind subjects showed deactivation of the auditory cortex for the same VM task. Congenitally blind individuals do not have any visual experience and thus cannot apply visual imagery while performing such a task. Therefore our results clearly suggest that such deactivations of non-relevant sensory cortices is a more general phenomenon, which may be needed in particular for allocating attention to tasks involved in extracting and manipulating internal representations.

The Link Between Negative BOLD and Neuronal Activity

The fMRI positive BOLD signal is a physiological process associated with a corresponding change in neural activity (for a review see: Logothetis and Wandell 2004). Growing evidence suggests that the negative BOLD signal indicates less neural processing for a given task as compared to baseline (Shmuel et al. 2002, 2006), and does not result from a measurement artifact (Laurienti et al. 2002; Shmuel et al. 2002; Wade 2002).

Negative BOLD studies have repeatedly been shown to be extremely useful in the context of the "default mode network" or extrinsic–intrinsic network (Gusnard and Raichle 2001; Raichle et al. 2001; Shmuel et al. 2002, 2006; Greicius and Menon 2004; Laurienti 2004; Fox et al. 2005; Raichle and Mintun 2006; Golland et al. 2007; Raichle and Snyder 2007; Golland et al. 2008). This network of the posterior-medial, posterior-lateral, and ventro-

medial prefrontal cortex is deactivated by a large variety of goal-directed cognitive functions in various sensory modalities (Gusnard and Raichle 2001; Greicius and Menon 2004). A few studies have investigated negative BOLD signal outside the default mode network such as are the pioneering work by Kawashima and colleagues on visual deactivation during somatosensory tasks irrespective of whether subjects opened or closed their eyes (Kawashima et al. 1995), and works on cross-modal deactivation in sensory areas during attention-demanding multisensory perceptual tasks (Laurienti et al. 2002; Mozolic et al. 2008) or within the unisensory cortex for non-preferred stimuli (Amedi et al. 2005a; Shmuel et al. 2006). Thus, in contrast to the deactivation of the default mode network which is relatively task-independent (present on a large variety of tasks), deactivation in sensory cortex has generally been shown in the context of competing cross-modal stimulation and the need to allocate attention to one modality rather than to another (Kawashima et al. 1995; Lewis et al. 2000; Mazoyer et al. 2001; Laurienti et al. 2002; Baier et al. 2006; Hairston et al. 2008; Wermke et al. 2008; Peiffer et al. 2009). Here we show that deactivation in sensory cortices is dramatically robust during the manipulation of internally generated representations, such as in the case of verbal memory as shown here, or during mental imagery (Amedi et al. 2005a). Thus the study of deactivations could be a highly important tool for our understanding of sensory cortices and subcortical processes outside of the default mode network.

A Functional Role for Sensory Cortices Negative BOLD?

What is the functional role of the sensory cortex VM deactivations reported here? One attractive explanation for these results is that the deactivations are causally relevant and helpful in the retrieval of intrinsically stored information by reducing 'noisy' synaptic input from less relevant brain areas. This type of non-relevant cortical deactivation might be needed for perception (Kawashima et al. 1995; Lewis et al. 2000; Mazoyer et al. 2001; Laurienti et al. 2002; Baier et al. 2006; Hairston et al. 2008; Wermke et al. 2008; Peiffer et al. 2009), but naturally it is much more crucial for intrinsic tasks where the stored representations might be much more difficult to access than straightforward physical signals such as light or sound. While it is impossible to prove causality using fMRI (or any other purely recording technique), several findings support this view: (1) Deactivation exists only in areas that are not required for the task, e.g., auditory cortex in visual imagery, and auditory and visual cortices in VM which do not require visual processing. (2) The pattern of activation and deactivation in the blind also supports this view:

deactivation in the auditory cortex is accompanied by positive BOLD in the visual cortex of the blind. In congenitally blind subjects, due to extensive cross-modal plasticity (for several examples see: Sadato et al. 1996; De Volder et al. 1997; Röder et al. 2000; Burton et al. 2002; Pascual-Leone et al. 2005; Noppeney 2007; Collignon et al. 2009), the visual cortex is functionally relevant for verbal memory tasks (as well as for other types of tasks, for example auditory localization or tactile processing: Sadato et al. 1996; Weeks et al. 2000; Sathian and Zangaladze 2002; Gougoux et al. 2005; Ptito et al. 2005; Garg et al. 2007; Collignon et al. 2009). For instance we found that the early visual cortex is robustly activated and behaviorally correlated with verbal memory performance (Amedi et al. 2003; Raz et al. 2005). Thus as expected, we found robust deactivation only in auditory areas. (3) Deactivation appears to be particularly robust when the subjects need to block distracting sensory inputs which may interfere with the task. Due to the noisy scanner environment, there might be much more need to inhibit the loud auditory input than the relatively absent tactile input (the subjects lay still during the scan, so there was no external tactile input) in this experiment. Although we cannot conclude this directly from our results, the functionality of the sensory cortex deactivations may explain why we obtained much weaker deactivation in the somatosensory cortex relative to the auditory cortex in this and in a previous study (Amedi et al. 2005a) also showing a trend but not a significant deactivation. (4) Our previous results on visual imagery show that the magnitude of deactivation positively correlates with the vividness of visual mental imagery, supporting a functional role for deactivation at least for visual imagery (Amedi et al. 2005a). It would be interesting in future studies to look for such correlations by adding behavioral correlates to study deactivation for additional intrinsic-oriented tasks or even better, to use TMS to study these questions with causal interference methods. (5) Several findings in recent years also seem to support the functionality of cortical deactivation in suppressing intruding external stimuli which are irrelevant to task performance. Such studies connect task-dependent cross-modal deactivation to a top down focusing which enables allocating attention to the task at hand (Kawashima et al. 1995; Lewis et al. 2000; Drzezga et al. 2005; Baier et al. 2006; Tomasi et al. 2006; Alain and McDonald 2007; Hairston et al. 2008; Peiffer et al. 2009). Sensory cortices that are not relevant to the task undergo deactivation which is related to task difficulty (Hairston et al. 2008), thus maximizing the resources of the activated network by filtering out irrelevant information. In addition to cross-modal deactivation, this can be seen in sensory cortex deactivation recorded during cognitive tasks (Stevens et al. 2008) in healthy elderly subjects and in Alzheimer's disease (AD) patients

(Drzezga et al. 2005; Wermke et al. 2008). These studies also report that the deactivation level is correlated with cognitive task performance (i.e., the more deactivation the better the task performance).

An additional finding (Garg et al. 2007) demonstrated the relevance of deactivation in terms of attention shifts. Garg and colleagues examined the frontal and occipital cortical responses to an auditory attention orientation task, and showed that the visual cortex of blind subjects shows a transient deactivation following a cue and before the onset of the auditory stimulus. With the onset of auditory stimulus, however, subjects show a positive BOLD signal. In addition to its importance for highlighting the relevance of attention shifts, this study also suggests that the temporal dynamics of the balance between activation and deactivations as manifested in negative BOLD are important to revealing specific processing properties of the cortex.

Thus, taken together these findings suggest that deactivation of specific non-relevant brain areas is present in any case in which the signal-to-noise ratio of the perceptual input is low. This may be due to interfering sensory stimuli, the need to allocate attention to a competing task or (and perhaps particularly) for intrinsic tasks such as mental imagery or memory recall in which there is no 'real' (extrinsic) signal coming from the environment. More generally our results support the view that negative BOLD is an important component of normal brain activity as much as positive BOLD. By allocating attention away from task-irrelevant sensory modalities, mental imagery and memory retrieval tasks might benefit the most from such deactivations of sensory cortices.

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