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Adaptive Changes in Early and Late Blind: A fMRI Study of Braille Reading

H. BURTON^{1,3}, A. Z. SNYDER^{2,3}, T. E. CONTURO³, E. AKBUDAK³, J. M. OLLINGER³, and M. E. RAICHLER^{1,2,3}

¹Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri 63110

²Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri 63110

³Department of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110

Abstract

Braille reading depends on remarkable adaptations that connect the somatosensory system to language. We hypothesized that the pattern of cortical activations in blind individuals reading Braille would reflect these adaptations. Activations in visual (occipital-temporal), frontal-language, and somatosensory cortex in blind individuals reading Braille were examined for evidence of differences relative to previously reported studies of sighted subjects reading print or receiving tactile stimulation. Nine congenitally blind and seven late-onset blind subjects were studied with fMRI as they covertly performed verb generation in response to reading Braille embossed nouns. The control task was reading the nonlexical Braille string “#####”. This study emphasized image analysis in individual subjects rather than pooled data. Group differences were examined by comparing magnitudes and spatial extent of activated regions first determined to be significant using the general linear model. The major adaptive change was robust activation of visual cortex despite the complete absence of vision in all subjects. This included foci in pericalcarine, lingual, cuneus and fusiform cortex, and in the lateral and superior occipital gyri encompassing primary (V1), secondary (V2), and higher tier (VP, V4v, LO and possibly V3A) visual areas previously identified in sighted subjects. Subjects who never had vision differed from late blind subjects in showing even greater activity in occipital-temporal cortex, provisionally corresponding to V5/MT and V8. In addition, the early blind had stronger activation of occipital cortex located contralateral to the hand used for reading Braille. Responses in frontal and parietal cortex were nearly identical in both subject groups. There was no evidence of modifications in frontal cortex language areas (inferior frontal gyrus and dorsolateral prefrontal cortex). Surprisingly, there was also no evidence of an adaptive expansion of the somatosensory or primary motor cortex dedicated to the Braille reading finger(s). Lack of evidence for an expected enlargement of the somatosensory representation may have resulted from balanced tactile stimulation and gross motor demands during Braille reading of nouns and the control fields. Extensive engagement of visual cortex without vision is discussed in reference to the special

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Correspondence to: H. BURTON.

Address for reprint requests: H. Burton, Dept. of Anatomy and Neurobiology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110 (harold@touch.wustl.edu).

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demands of Braille reading. It is argued that these responses may represent critical language processing mechanisms normally present in visual cortex.

INTRODUCTION

A growing body of work suggests that blind individuals use areas of the cerebral cortex normally reserved for vision during Braille reading and other nonvisual tasks involving tactile discrimination. Initial evidence appeared in functional neuroimaging studies with positron emission tomography (PET) (Sadato et al. 1996, 1998) and experiments using transcranial magnetic stimulation (TMS) of occipital cortex (Cohen et al. 1997, 1999). Several questions remain especially concerning differences between early blind subjects, i.e., persons blind since birth or early childhood, versus persons who lost sight after having learned to read print. Specifically, occipital TMS disrupted Braille reading and tactile discrimination of embossed capital letters (Cohen et al. 1997, 1999). These effects occurred only in early blind individuals. Sadato and colleagues also reported blood flow increases in both striate and extrastriate visual cortex induced by performance of similar tactile tasks in early but not late blind individuals (Sadato et al. 1996, 1998). Such differences are possibly predictable given the known developmental dependence of the visual system on experience during the early critical period. Another PET study, however, found activation of extrastriate cortex in early blind, but striate cortex in late blind subjects during a language task incorporating Braille reading (Büchel et al. 1998a). The present work used functional magnetic resonance imaging (fMRI) to study the effect of age at onset of blindness on visual cortex responses during performance of a language task involving Braille reading. We especially examined possible differences in activation of primary (e.g., striate cortex) and higher tier (e.g., extrastriate) visual areas in subjects with early versus late onset blindness.

Another important question is whether blood flow changes in visual cortex of blind individuals reflect specific functionality. An alternative interpretation is that these responses are nonspecific excessive modulations consequent to early sensory deprivation. This view garners some support from finding of above normal metabolic rates for glucose in visual cortices of early blind subjects (De Volder et al. 1997; Wanet-Defalque et al. 1988). In addition, absent specificity or diversity of functions has been proposed to explain recordings of slow negative potentials over visual cortex of blind subjects during an attention or arousing task that was unrelated to reading (Roder et al. 1997). Early blindness might leave visual cortex immature and prone to abnormal responses (Snyder and Shapley 1979) because of absent pruning of normally expressed exuberant synapses, and an excess of retained excitatory connections (Roder et al. 1997). We attempted to address this question by carefully correlating the distribution of active cortex with detailed analyses of the underlying anatomy. Specificity may be inferred by showing a close correspondence between active regions and anatomy. To achieve this goal, the protocol was designed to provide statistically reliable results within individual subjects, thereby allowing optimal inspection of the anatomy of active foci.

A second goal was to study the correspondence between active foci in occipital cortex of blind individuals and the multiple visual areas of sighted subjects (Felleman and Van Essen 1991). FMRI studies in humans have reinforced a model of the visual cortex consisting of a distributed network of specialized regions each with its own functions (DeYoe et al. 1996; Dumoulin et al. 2000; Engel et al. 1997; Hadjikhani et al. 1998; Sereno et al. 1995; Tootell et al. 1996, 1997). Finding evidence of activity circumscribed to anatomically distinct portions of visual cortex in blind individuals might suggest functional specialization like that attributed to corresponding regions in sighted individuals. The presence of separable foci provides evidence that activity in visual cortex of blind people is specific as opposed to a

pathological consequence of visual deprivation. Detailed comparisons were imperfect in previous neuroimaging studies because the PET-based data relied on averages across subjects, which limit the correlation of cortical anatomy with activation patterns.

To view all potentially affected cortical areas, we employed whole brain scanning without a priori selection of particular regions of interest. We also used a repeated measures design with enough trials to obtain sufficient statistical power to delineate significant activity patterns in individual subjects. An emphasis on within subject analyses is especially important due to differences in Braille reading fluency, education, chronological age, and age of blindness. For example, potential differences in Braille reading strategies between early versus late blind individuals might affect the distribution of activity in visual cortex. The obtained, high resolution correspondence between anatomy and activated regions from within subject analyses also aided comparisons between these data and previously identified, and functionally interpreted, foci from many studies in sighted subjects.

Another addressed question concerns the cortical representation of language in blind individuals and the possible dependence of this representation on age at onset of blindness. We hypothesized that the same functional anatomy should be seen in blind and sighted individuals because the lexical and semantic aspects of language should be comparable irrespective of the sensory channel used to convey orthographic information. In sighted individuals, where language tasks involve similar orthographic-lexical operations, different laboratories concur in identifying activity increases in discrete areas in left inferior and dorsolateral frontal cortex (Binder et al. 1997; Demonet et al. 1994; Fiez et al. 1995; Kelly et al. 1998; Klein et al. 1995; McCarthy et al. 1993; Paulesu et al. 1997; Petersen and Fiez 1993; Phelps et al. 1997; Poldrack et al. 1999; Rumsey et al. 1997; Zatorre et al. 1996). Tasks dominated by phonological features activate posterior language areas, especially left parieto-temporal and superior temporal regions (Büchel et al. 1998; Rumsey et al. 1997).

Several factors, however, might lead to variations in activated language areas in blind people. First, reading by touch dramatically differs from reading of print (Millar 1997). For example, most Braille readers use two hands, which might influence the left dominance of language areas in blind individuals. Countervailing this possibility is that only one hand reads while the other acts as a place marker (Millar 1997). Second, phonological associations are the only way to learn Braille without sight, which might be reflected by adaptive changes in the language areas dominated by phonics. This change, however, possibly manifests only in individuals with early onset blindness because they never have remembered visual associations with letter shapes when learning Braille through phonics. Countering the notion of possible differences in the activation of the phonologically dominant language areas is that fluent Braille reading does not involve phonological coding (Millar 1984, 1987; Nolan and Kederis 1969; Pring 1985, 1994).

We selected verb generation for Braille nouns as the language paradigm because this task has been extensively studied in sighted subjects reading print (see reviews in Gabrieli et al. 1998; Seger et al. 1999) and provides a potent language task in the broadest sense. Generating verbs for presented nouns in comparison to a nonlexical or minimal language control stimulus reliably produces robust functional responses. We chose not to use a multiple level language task design with a factorial paradigm of paired contrasts (i.e., reading words with and without verb generation, reading pseudo-words, *etc*). The objective of this study was to assess functional reorganization due to long term blindness. It was not an experiment to study the organization of language processing.

We also considered whether changes occurred in the activated extent or components of the somatosensory system because of the intense dependence on tactile perceptions when

reading by touch. We hypothesized expansion of the representation for the Braille reading finger in the somatosensory cortex given prior evidence of remarkable plasticity in this cortex (Merzenich and Jenkins 1993; Pons et al. 1991; Ramachandran 1996, 1998). Countering this idea was a study which showed that blind individuals had greater difficulty detecting near threshold tactile stimulation of adjacent digit tips normally used in reading Braille. They interpreted this as evidence of a disorganized representation for these digits in somatosensory cortex (Sterr et al. 1998).

For corollary reasons that Braille reading involves substantial use of fine finger movements, we hypothesized expansion of the finger-hand area in the cortical motor areas. A prior study with TMS found a use dependent expansion of a lower threshold region over the motor representation of the reading fingers in early blind, fluent Braille readers (Pascual-Leone et al. 1995). In addition, due to differences in reading skills between most early and late blind individuals, we hypothesized distinctions in the extent and nature of activated cortical motor areas in these two groups. Less proficient Braille readers presumably attend to global-holistic letter or word shapes, information obtained through more frequent and sequential trapezoidal shaped up/down movements across Braille cells (Millar 1984, 1987; Nolan and Kederis 1969; Pring 1985, 1994). The lowest level operation during fluent Braille reading involves processing lateral dot-gap shearing density within individual Braille cells (Millar 1987; Pring 1994). This information arises through distinctively smooth, continuous movements across the Braille field. Thus differences in motor cortex activations might reflect these distinguishing motor behaviors in early and late blind Braille readers.

METHODS

Subjects

Sixteen blind, proficient Braille readers from the greater St. Louis community volunteered and were paid for their participation. Subjects provided informed consent in accordance with guidelines approved by the Human Studies Committee of Washington University. We obtained a detailed neurologic history in each subject using a standardized questionnaire. Only neurologically normal (excepting visual function) subjects were scanned. We report here functional data only from subjects with normal anatomical MR images. Nine (4 female, 5 male; aged 34–67, Avg 44.78) were early-blind having no sight at birth or by 5 yr of age. Seven (4 female, 3 male; aged 36–66, Avg 49.14) were late blind having lost sight after an average age of 12.7 yr (range 10–25); one subject retained sufficient vision to read large print.

We assessed handedness with a modified Edinburgh handedness inventory (previously validated questions 1,2,5,7,11,15 and 23 in Raczkowski et al. 1974). When required to read Braille with one hand, all but one early and one late blind subject used their right hand. Only the early blind left-hand reader was left-handed.

All subjects had read Braille for more than a decade (Table 1) and many currently did so one or more hours daily. Reading proficiency was measured using a standard 266 word Braille text. Early-blind subjects read more rapidly on average than late-blind (Table 1). Allowances for these different reading speeds were made during the MR scans (see following text).

Task and test apparatus

Single words and control fields in Braille II spelling were presented to subjects using a MR compatible device. Braille-embossed paper was threaded through an extended, two-chamber Plexiglas box (approximately 8 feet × 1 ft × 4 inches) supported over the subjects as they lay in the scanner. The stimuli were organized as a single column of words and control fields

segmented into three practice and eight test runs. Each fMRI run contained 128 stimuli: 8 control Braille fields followed by 20 groups of three words followed by three controls (see following text). The paper was manually advanced in synchrony with scanner frames (Fig. 1) to present each Braille field in a 3 by 1 inch reading window suspended over the subject's waist.

During practice trials the subjects learned to complete the following sequence taking 3–5 s per Braille field. The reading finger(s) of the preferred hand rested on smooth paper at the left edge of the reading window. Reading was initiated on sensing the end of paper movement by moving the finger rightward. Braille embossing started 4 cm from the left edge of the reading window. After reading and appropriate responding, the hand returned to the left edge of the reading window to wait for the next stimulus. We instructed the subjects always to touch the entire Braille field even if they identified the contents prior to the end. There were no restrictions on Braille reading strategies except to use only one hand and minimize arm movements. Most subjects made one pass across most words with their right index finger while abducting the wrist. Re-reading occurred occasionally.

The word stimuli were concrete and abstract nouns (mean word length = 5.8 letters). The control stimulus was the Braille pattern for six number signs (“#####”). The task was generation of a compatible verb for each noun (e.g., “bake” for “cake”). Explicit instructions to read the noun and generate a verb were given to the subjects before each run. The 480 nouns were selected to maximize variety of compatible verbs without regard to word frequency. The list was similar to one used previously (Snyder et al. 1995). Each noun occurred once to minimize practice effects. The explicit instruction for the control stimulus was “to empty your mind and think of nothing.” [Subjects understood this instruction to mean that they were not to perform a lexical task in response to the control field.] As the same control field was repeated throughout the study, and as all fluent Braille readers understand that the Braille symbol for “#” normally precedes numbers, identifying the control task was trivial for these readers. They instantly recognized the control field and proceeded to touch it as they would a regular word but without doing a lexical language task. In practice sessions subjects read and responded overtly. During fMRI the responses were covert.

The control field (“#####”) was designed to balance the word stimuli in somatosensory content and gross motor demands. Reading both types of stimuli required the same orienting of the reading finger in the display window, initiation of hand movements in response to paper advancement, and attention to the spatial extent of the Braille field. The processing engendered by the control field was likely automatic as this stimulus was presented throughout the experiment. During the practice runs it was observed that the late-blind subjects made more micro-movements over words than the control fields (Millar 1997). The early blind subjects usually read all fields using the same smooth motion.

Confining the paradigm to a single contrast ensured that the quantity of fMRI data obtained in each subject had statistical power sufficient for image analyses within individuals. This objective was important because variability in Braille reading skills, education, and age of the two groups of blind individuals might have compromised analyses based solely on averaged images. The least quantity of data collected from a given subject was 80 trials (1 trial = three generate frames + three control frames). Most subjects provided twice this amount.

MRI acquisition

Functional MR scans (fMRI) were collected on a Siemens 1.5 Tesla Vision scanner, using a custom, single-shot asymmetric spin-echo, echo-planar (EPI) sequence sensitive to blood

oxygenation level-dependent (BOLD) contrast. We used a 64×64 image matrix, oversampled to reduce noise, blipped readout (Howseman et al. 1988) and direct 2D-FT reconstruction. The field of view was 240 mm (3.75×3.75 mm in-plane pixels). This maximized signal to noise sensitivity at a T_2^* evolution time of 50 ms from a flip angle = 90° (Conturo et al. 1996; Ogawa et al. 1990). Whole brain coverage was obtained with 16 contiguous 8 mm slices. Reconstruction, transfer, and storage following a 128-frame fMRI acquisition run took 2 min. Up to 8 fMRI runs were acquired in a 2.5 h session including anatomical imaging. We held EPI to 2.178 s to minimize the effects of inflowing blood, head movement (Friston et al. 1996), and to allow a sufficiently long quiet interval (see Fig. 1) for Braille reading.

EPI occupied only the first 2.178 s of each frame (Fig. 1) leaving the remaining time quiet during which the subjects read the Braille field and covertly responded. The induced BOLD responses were detected in subsequent frames. In most subjects the frame TR was 5 s. We extended the frame TR to not more than 7 s according to the capacity of the slower readers to keep up with the task.¹ This ensured that each subject completed word reading before the start of the next frame. The inequality of TR over subjects precluded estimation of averaged event related response time courses. Nevertheless, the response profiles (intensity as a function of frame) were similar in all subjects (see Fig. 7) although the trials were of unequal duration (i.e., 30 to 42 s).

PrefMRI structural imaging included a coarse (2 mm cubic voxel, 79 s scan) magnetization prepared rapid gradient echo (MP-RAGE) scan which was used to automatically compute standard fMRI slice prescriptions parallel to the anterior commissure-posterior commissure plane. A fast T2-weighted spin echo (SE) image ($1 \times 1 \times 8$ mm, TR = 3800 ms, TE = 22 ms) also was acquired using the same prescriptions. A fine ($1 \times 1 \times 1.25$ mm) T1 weighted sagittal MP-RAGE (TR = 9.7 ms, TE = 4 msec, flip angle = 12° , TI = 300 ms) was used for definitive atlas transformation and ROI analysis. A sequence of affine transforms (first frame EPI to SE to fine MP-RAGE to atlas representative target MP-RAGE) was computed and combined by matrix multiplication. Reslicing the functional data in conformity with the atlas then involved only one interpolation. For cross-modal (e.g., steady state EPI to T2) image registration, we locally developed an algorithm (related to the method of Andersson et al. 1995), which has comparable or better precision than AIR (Woods et al. 1993). We enabled in-plane stretch partially to compensate for EPI distortions (particularly in the phase encoding direction). The above described EPI-anatomical registration scheme is demonstrated in a previous publication (Ojemann et al. 1997).

Image analysis

The data were subjected to a two-stage analysis. The first stage included preliminary processing of the images and estimation of response magnitudes for each subject. The second stage used these magnitudes in a random effects model. Preliminary processing involved 1) compensation for systematic slice-dependent time shifts (136 ms/slice), 2) elimination of systematic odd/even slice intensity differences due to interpolated acquisition, and 3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion (Ojemann et al. 1997). The data then were transformed to atlas space, interpolated to isotropic 2 mm voxels, and smoothed using a 2-voxel Gaussian kernel. For each subject, per voxel response time-courses were computed using the general linear model (Friston et al. 1995; Worsley and Friston 1995). The variance of the data at each voxel was estimated from the residuals. Each six-frame trial (3 verb generate frames followed by 3

¹These different TR times also varied the sensitivity across subjects because of more complete T1 relaxation at longer TRs. However, sensitivity declined only 0.9% between 5 and 7 s TRs.

control frames) was treated as a single event. Overall activation magnitudes were computed by cross-correlating estimated time-courses with a delayed gamma function for the hemodynamic response (Boynton et al. 1996; Dale and Buckner 1997), which was convolved with a boxcar function posited to model the duration of neuronal firing that follows stimulus duration (Ollinger et al. 2001). The ratio of these magnitudes to their SD was used to compute *t* statistics. These *t*-statistics were then “Gaussianized,” i.e., transformed to normally distributed statistics with the same significance probabilities. These Z-score statistical maps were corrected for multiple comparisons using a Monte Carlo simulated distribution, and inspected using a Z-score threshold of 4.5 over a minimum of 3 contiguous voxels ($P = 0.05$) (Forman et al. 1995).

In the second stage of the analysis, we first defined regions from average maps across all right-hand readers from each group. These average images were calculated by summing across the Z-score results from individual subjects within early and late blind groups and dividing the sums per voxel by the square root of the sample size. This yielded composite images for each group. Next, using interactive image display software (ANALYZE, Biodynamics Research Unit, Mayo Clinic, Rochester, MN), we established 3-D regions of interest (ROI) centered on these local average Z-score maxima. Again using the ROI option in ANALYZE, the regions defined from the average Z-score maps were used for initial identification of comparable loci in the Z-score images from each subject. We adjusted the boundaries of these regions to conform to the cortical anatomy and observed distribution of activity in each subject. An automatic search routine determined the centers of mass, Z-score peaks and stereotaxic coordinates of these maxima in each of the defined 3-D regions for every subject. The dependent measures of spatial extent in 2 mm voxels, average % MR signal change per voxel, and time-course of %MR signal change were separately calculated for each defined region in each subject. These individual subject values then were analyzed using a random effects model and standard GLM ANOVA methods and post hoc *t*-tests (Tukey) in relation to subject, frame, and group variables for each region.

RESULTS

The results detailed below were obtained in 7 early and 7 late blind individuals. Essentially the same distribution of focal responses was found in two additional early blind subjects studied using a different task protocol (6 frames generate verb followed by 6 frames control) and analysis strategy. Nearly two dozen distinct regions with significantly increased BOLD signals are present in our data (Table 2). The distribution of active regions generally is similar in the early and late blind subjects. Figures 4–6 show averaged results from the six right hand, early-blind and all late blind readers. Figures 2 and 3 include separate images from each of the left-hand readers. Table 2 identifies the regions as cross-referenced in the figures, lists peak coordinates in the average Z-score images, and provides Brodmann area (BA) designations according to the atlases of Talairach and Damasio (Damasio 1995; Talairach and Tournoux 1988). As our data are exclusively imaging rather than histological, we regard these designations as provisional. We categorize the activated regions using broad functional labels following a variety of previous imaging studies in sighted individuals. The DISCUSSION relates our interpretation of these functional designations to the relevant literature.

Significant task related BOLD decreases also were found and were similar in the two subject groups. Additional details concerning the negative BOLD responses will be presented in a subsequent paper.

We first describe active regions in, especially, primary visual cortex of individual early and late blind subjects. The following presents average images that compare the wider

distribution of active regions for each group. Last are the analyses of spatial extent and time course of BOLD responses measured within individually determined regions.

Active regions in primary and secondary visual cortex

Both groups have bilateral BOLD responses in posterior and medial occipital cortex, i.e., peri-calcarine regions BA 17 and 18. The latter includes lower and upper banks of the calcarine sulcus and the immediately adjoining lingual and cuneus gyri. Labels for these regions are, respectively, LBCS and UBCS in Table 2. As illustrated by subjects Early 1–5, all right-hand reading subjects have significantly greater activity over much of the left peri-calcarine cortex (Fig. 2, *A–E*; Fig. 6, *A* and *B*). All but subjects Early 3 and 4 also have similarly located significant, but smaller, BOLD responses on the right, i.e., ipsilateral to the reading hand (Fig. 2, *A*, *B*, and *E*). The left-hand reader (Early 6) shows a more nearly symmetrical activation pattern in the peri-calcarine region (Fig. 2*F*). In contrast, all late blind readers show greater BOLD responses in the peri-calcarine cortex ipsilateral to the reading hand (Fig. 3). All right-hand readers have higher Z-scores in the right hemisphere (Fig. 3 Late 1–3 and 5,6); the left-hand reader (Late 4) has predominant activation in the homologous region on the ipsilateral, left side (Fig. 3*D*). Smaller but significant BOLD responses occur in the hemisphere contralateral to the reading hand in all late blind individuals (Fig. 3 and Fig. 6, *C* and *D*). Despite magnitude lateralization, the coordinates of the peaks in the average Z-score maps for each group are similar (Table 2).

Different individuals show distinctions in activity across both upper and lower banks of the calcarine sulcus (Figs. 2 and 3). Some early blind individuals (Fig. 2, *A*, *B*, *E*, and *F*) have peaks on both sides, but with the largest magnitude responses on the lower bank; in others peaks are confined to the upper (Fig. 2*C*) or lower banks (Fig. 2*D*). All but Early 4 have BOLD responses over the posterior half of the occipital cortex (Fig. 2, *A–C*, *E*, *F* versus *D*). The average Talairach AP coordinate for foci in both banks and both hemispheres is -87 . All late blind subjects also show peaks principally occupying the posterior pole of the lower bank of the calcarine sulcus (Fig. 3, *A–C*, *E*, and *F*). The peak in Late 4, the left-hand reader, also is over the lower bank, but at a more anterior location (Fig. 3*D*). The average AP coordinate for both sides of the calcarine and both hemispheres is posterior in the late blind at -91.5 . The above detailed individual response differences are not apparent in the composite analyses e.g., Fig. 4.

Active regions in higher tier visual areas

Both groups have extensive, bilateral BOLD responses lateral to the collateral sulcus and throughout posterior parts of the fusiform gyrus (Fig. 4, *A* and *B*), which include portions of BA 18 and 19. Response peaks have similar coordinates in both groups (Table 2). BOLD responses are always more prominent in the left fusiform gyrus of early blind individuals irrespective of the hand used for reading. The activity along the fusiform gyrus on the left mostly matches that on the right in late blind individuals except at more anterior levels, where BOLD responses are completely left lateralized in all subjects. The average anterior-posterior domain of activity in the fusiform gyrus region is approximately 2 cm across, extending from Y values of approximately -75 to approximately -55 .

A separate activation occurs in the cuneus gyrus, but only in early blind individuals. This site is at the same AP level as responses on the upper bank of the calcarine sulcus, especially on the left (Table 2). This isolated cuneus gyral region always is in cortex medial to the parietal occipital sulcus, which separates it from the more lateral BOLD responses within the intraparietal sulcus. A good example of this functional anatomy is seen in subject Early 2 (Fig. 2*B*, $X = -11$).

Close to the occipital pole in both groups are separable peaks in the lateral occipital gyrus (LOG) (BA 18 in Table 2). These BOLD responses are lateral to foci along the calcarine sulcus and cuneus gyrus, and lateral and posterior to those in the posterior portion of the fusiform gyrus (Fig. 4D). Responses occur bilaterally in both subject groups with peaks at similar coordinates (Table 2).

Summary of activity in occipital cortex

Activated foci occupy upper and lower banks of the calcarine sulcus and adjoining cortex on the lingual and cuneus gyri. In most subjects the lower bank (upper visual field representation in sighted humans) response is greater than the upper bank response. BOLD responses are prominent along the inferior surface of the occipital lobe within the collateral sulcus, fusiform gyrus and temporo-occipital sulcus. Activation within the fusiform gyrus extends anterior toward the temporal lobe. In posterior occipital cortex, active regions include inferior parts of the lateral occipital gyrus. Both groups show bilateral foci. However, the early blind show more extensive activation of peri-calcarine cortex in the hemisphere contralateral to the reading hand. Right- and left-hand, late blind readers have larger responses in the hemisphere ipsilateral to the reading hand. Both the number of foci and the spatial extent (see following text) of peri-calcarine foci are greater in early blind in comparison to late blind subjects.

Active visual areas in temporal cortex

Early blind individuals show BOLD responses in the left inferior temporal gyrus and sulcus (BA 19, 37; Fig. 4C; 5C: Early, $X = -43$). These mostly are laterally contiguous but separable from the activations in the fusiform gyrus. As illustrated by the Z-score peaks in Table 2, responses of nearly half the magnitude are found on the right in early blind or in both hemispheres in the late blind. A medial-lateral separation between the fusiform and inferior temporal gyrus foci is best seen when the BOLD responses are smaller (e.g., the right hemisphere of early blind and both sides in the late blind, Table 2). The medial-lateral coordinates of the peaks in the left FG and left ITG from the average Z-score maps are similar and within the margins of error in the results from early blind individuals. In these cases BOLD responses are greater and fill much of the ventral occipital and inferior temporal cortex. Sulcal anatomy is more distinguishable in individual subjects, and in these the peak site of activation in the fusiform gyrus always lay between the collateral and, at different anterior-posterior positions, the temporal-occipital or inferior temporal sulci. The peaks in the inferior temporal gyrus always occur lateral to the inferior temporal sulcus.

An exclusively early blind response appears in the medial temporal gyrus (MTG). It is anterior, lateral and superior to the focus in the inferior temporal gyrus (ITG) and mostly occupies BA 21. Sagittal sections of the early blind average image (Fig. 5A, C: $X = -43$ and -51) show this focus over posterior portions of MTG. There is a variable superior extension into the superior temporal gyrus in some subjects. As in the coronal section in Fig. 4C, this MTG region may be a superior extension of the ITG focus. However, the MTG peak is >1 cm superior and anterior to that in the ITG (Table 2).

Active visual attention areas in parietal-occipital cortex

The BOLD responses in the lateral occipital gyri are contiguous with inferior and posterior extensions of bilateral foci within the intraparietal sulci (IPS) in both groups (Fig. 4, E and F). The average spatial extent of the IPS region is large. It mainly involves BA 19, and is similar across groups (Fig. 7B1). The IPS region contains one dominant peak at nearly the same coordinates in both groups, which is ventrally situated close to the junction with the occipital cortex (Table 2 and Fig. 4, E and F). The BOLD response magnitudes near this ventrally located peak are also similar across the groups (Fig. 4, E and F and Fig. 7B2).

These responses extend within the posterior portion of the IPS toward the superior surface of the brain. A hint of a second focus exists at this more dorsal site, but it is not sufficiently separated to be distinguished from the ventral peak.

Active regions in somatosensory cortex

A third parietal region is seen on the left in both groups. It is a separable anterior extension of the larger posterior region. It mainly occupies the postcentral sulcus (Fig. 4*F*; $Z = 32$). Portions of this anterior parietal region extend onto the postcentral gyrus (BA 2; Fig. 5*A*, $Z = 42$; and all sagittal sections). Spatial coordinates of peak Z -scores (Table 2) are similar in the two groups. BOLD responses occur between the postcentral sulcal focus (label #16 in the figures and Table 2) and the larger responses within the intraparietal sulcus (label #11 in Table 2 and Fig. 4*F*, $Z = 32$; Fig. 5*A*, $Z = 42$). This activity appears only on the left, near the anterior extension of the intraparietal sulcus. A small local maximum exists on the average Z -score images (Figs. 4*F* and 5*A*) but it is not separable from the surrounding larger responses. This region occupies part of the superior parietal lobule normally labeled BA 7.

A small region with a barely significant Z -score appears within the depths of the central sulcus in some late blind individuals. No subject shows a significant response within the parietal operculum along the upper bank of the lateral sulcus.

Language areas in frontal cortex

Both groups show multiple foci over the lateral frontal convexity. The most inferior location of these activations extends to the left frontal operculum and adjoining inferior frontal gyrus (Fig. 5*C*; IFG) including parts of Brodmann areas 45 and 47. A second region lies in the dorsolateral frontal cortex. The latter activations occupy both the superior-posterior part of the inferior frontal gyrus and inferior part of the middle frontal gyrus (Fig. 5*B*; I/MFG) through Brodmann areas 9 and 46. The distribution of these two regions and the coordinates of their peaks (Table 2) are similar across the groups irrespective of the hand used for Braille reading. Several late blind individuals also show additional, symmetrically located low Z -score responses on the right, which is reflected in the average images across all subjects (Fig. 5: *A*, $Z = 42$; *B*, $Z = 28$; *C*, $Z = 14$).

Active regions in premotor cortex

A third, more posterior site of activation in frontal cortex of both groups occupies the left precentral sulcus and neighboring precentral gyrus where it mostly is within Brodmann area 6 (Fig. 5*A*; PrCS; Table 2). This activated region extends forwards to the middle frontal gyrus where it probably includes part of Brodmann area 8.

Medial frontal cortex, especially on the left, contains multiple BOLD responses (Fig. 6; Fig. 5: *A*, $Y = -3$; *B*, $Y = 3$). Both groups have one focus that is posterior and superior (BA 6; Table 2) to a second, more anterior and inferior site on the rostral cingulate gyrus (BA 24,32; Table 2). Two foci are found in every early blind (Fig. 2, *A*, *B*, *D–F*) and nearly all late blind subjects (Fig. 3, *A*, *B*, and *D*). The larger, posterior one extends over the medial superior frontal gyrus (mSFG); the smaller anterior focus occupies the cingulate gyrus and sulcus bilaterally (Table 2, Fig. 6, *B–D*). In addition, late blind subjects show a third focus between the two more prominent medial frontal sites (Fig. 6*C*).

Spatial extent of BOLD responses

The spatial extent of BOLD responses is significantly greater in the early blind only in part of visual cortex. This difference is seen in active regions in upper and lower banks of the calcarine sulcus. The distinctions between groups persist even when comparing dominant contralateral responses in peri-calcarine cortex for the early blind to the ipsilateral responses

in the late blind (Fig. 7A2, UBCS and LBCS). The spatial extent of the active region over FG and LOG also are significantly greater in the early blind (Fig. 7, A2 and B2). In each of these regions, the spatial extent for individuals who lost sight after the age of three declines precipitously (Fig. 7A1 and B1). The results from UBCS, LBCS and FG are best fit with a negative exponential, nonlinear regression function. A negative linear regression is the best fit for the data from LOG. The spatial extent in all other active regions are not significantly different between the groups. However, several regions (IPS, I/MFG, and PrCS), whose data are best fit by a negative exponential function (Fig. 7, B1 and C1), show a trend of larger spatial extent in early blind individuals.

Time course of BOLD responses

The time course of BOLD signal modulation in all subjects and all regions exhibited a common pattern characterized by signal increase during the three verb generation trials and decrease during the three control trials. The BOLD modulation peak generally appears 1 to 2 frames after the task switch, i.e., during frames 2–3 and 5–6. There is no evidence of a time course dependence on locus. The pattern of BOLD modulation as a function of frame is the same in both groups despite a modest increase in TR for the slowest late blind readers (Fig. 8). The small standard error bars in these plots further attests to response profile consistency over all subjects.

DISCUSSION

Our task paradigm (covertly generate verb for Braille embossed noun versus read Braille “#####”) induced an extensive array of BOLD responses in both early and late blind individuals. Activated regions include visual, visual/attention, somatomotor, and language areas in frontal cortex. What follows is an attempt to explain these results in terms of functionality identifiable in sighted individuals. We suggest that, in response to blindness, specialized areas retain their intrinsic mechanisms, which become adapted to the challenge of reading by touch. We argue that visual cortex recodes sensory information into a format used by the language areas of the brain.

Regions usually activated by visual stimuli in sighted subjects

Occipital Cortex—We find extensive activation of visual cortex in early and late blind individuals, generally in agreement with prior PET studies (Büchel et al. 1998; Sadato et al. 1996, 1998). Involved cortex in both groups includes regions previously labeled V1, V2, VP, possibly V4v, and LO in sighted subjects (DeYoe et al. 1996; Dumoulin et al. 2000; Engel et al. 1997; Hadjikhani et al. 1998; Malach et al. 1995; Sereno et al. 1995; Tootell et al. 1995–1998; Watson et al. 1993). Our early blind subjects also show activity in V5/MT, V8 and possibly V3A.

We cannot assign a particular function to each occipital locus of activation. However, four findings suggest that these areas play a role during Braille reading. First, a prior study reports that TMS over occipital cortex disrupts Braille reading although only in early blind subjects (Cohen et al. 1997, 1999). We find bilateral responses in visual cortex of many blind subjects. However, most late blind subjects show responses only ipsilateral to the reading hand and mostly in inferior occipital cortex. These results suggest that TMS focused over the inferior surface of the occipital cortex ipsilateral to the reading hand might disrupt reading by touch in late blind individuals. Second, clinical evidence supports the idea of a contribution from visual cortex in Braille reading. Specifically, an early blind individual with bilateral occipital strokes developed alexia for Braille without tactile agnosia (Hamilton et al. 2000). Third, the present results, especially as detailed in individual subjects, show highly localized activations of visual cortex. In studies of visual cortex in sighted

individuals, such patterns of localized activity are taken as evidence for a distributed network of functional areas (DeYoe et al. 1996; Dumoulin et al. 2000; Engel et al. 1997; Hadjikhani et al. 1998; Malach et al. 1995; Sereno et al. 1995; Tootell et al. 1995–1998; Watson et al. 1993). Accordingly, the finding of focal activations in blind individuals counters the notion that responses in these regions are nonspecific or a pathological consequence of visual deprivation (Roder et al. 1997). To the extent that these regions selectively respond to visual features, it is parsimonious to speculate that comparable specificity exists for processing tactile features needed to translate Braille into a neural code used by the language areas of the brain. Fourth, the predominant hemisphere with pericalcarine activity differs in left- and right-hand Braille readers, which implies specific early processing of tactile information from the reading hand.

The within subject analyses show that, despite individual variability, blind subjects in both groups exhibit active regions in pericalcarine cortex. Most subjects show responses over the lower bank of the calcarine and much of the inferior occipital cortex. The superior foci are more restricted except for extensions onto surface cortex (i.e., cuneus gyrus) at the occipital pole. The across subject variance does not necessarily indicate functional inconstancy. A recent quantitative histological analysis of Brodmann areas 17 and 18 (i.e., V1 and V2) reported that substantial variability normally occurs in sighted individuals (Amunts et al. 2000). Comparable variability is likely in blind individuals.

The pericalcarine BOLD responses occupy predominantly what is, in sighted subjects, the representation of the upper visual field. The extent of activation superior to the calcarine sulcus is less clear. All late blind and most early blind individuals show little or no activation of V3, which normally represents lower visual space. However, the within subject analyses in early blind individuals show some activity within that part of the cuneus gyrus previously identified as V3A (Tootell et al. 1997). The active region corresponds best to that portion of V3A dedicated to upper visual space, i.e., more inferior, lateral domain of V3A. Thus the same visual representation appears to be engaged in different subdivisions of visual cortex. This correspondence further argues against the notion that the responses in these regions are nonspecific. The explanation for the predominant activation of “upper visual space” representations is uncertain. Possibly, it is due to the supine position assumed during the scans.

The greater spatial extent of activity in primary and secondary visual cortex in early blind subjects (Fig. 7) appears to be related to age of blindness onset and not Braille reading fluency. Nonparametric tests (Spearman rank correlation coefficient and Kendall's τ) show no concordance between Braille reading rates and the spatial extent or magnitude of MR responses in visual cortex. However, the best late-blind Braille reader (Late 6) shows primary visual cortex activity that is comparable to that observed in nearly all but the least fluent early blind readers. Extensive training was responsible for this subject's fluency. However, before suggesting that intensive rehabilitation in late blind might yield more responses in visual cortex, additional testing is needed with early and late blind people who are paired for Braille reading fluency.

Occipital-Temporal Cortex—Early and late blind individuals show activity within the lateral edge of the fusiform gyrus, and still further lateral in the inferior temporal sulcus and gyrus. There was a significantly greater spatial extent of this focus in early blind individuals. The responses in lateral FG overlap with a region at 42.8 ± 2.7 , -72.7 ± 8 , -18.2 ± 9.8 , which is a lateral occipital center (LO) for object identifications in sighted subjects (Malach et al. 1995; Tootell et al. 1996). In addition, an object processing region, previously localized within the left posterior basal temporal/fusiform region of sighted subjects, and

which encompasses posterior Brodmann area 37 (Moore and Price 1999), also corresponds with activated regions in the present study.

It is possible that the basis for this overlap with object recognition centers in sighted subjects is in relation to processing Braille fields as objects. First, prior studies show that fluent Braille readers recognize whole words (Krueger 1982), which reflects a conceptualization of the word as a single object. Braille reading also entails projecting personal contact with the dot patterns, which, unlike print reading, involves obtaining a three dimensional percept of the Braille field. Therefore we surmise that activity in LO and posterior parts of area 37 in both subject groups might arise from a complex series of steps: touching, recognizing and identifying the word Braille fields as particular noun objects. These operations must precede generating an appropriate verb.

We observed no responses in an anterior-medial extension of the fusiform gyrus (Brodmann area 20/37). Previous reports based on PET list this site as a recognition center for integrating tactile information in word reading in early blind subjects ($-40, -38, -16$ in Büchel et al. 1998b). PET studies in sighted subjects report blood flow increases in the same region during tasks requiring semantic relative to perceptual information such as viewing meaningful words or objects ($-32, -40, -20$ in Moore and Price 1999). The absence of such responses in the present data may be attributable to “blind spots” inherent in EPI (Ojemann et al. 1997).

One additional extension of activated occipital-temporal cortex occurs along the lateral surface of the inferior temporal gyrus in every early blind and no late blind individual. This activity reaches the ascending limb of the inferior temporal sulcus. This sulcal landmark provides a unique identifier for the motion selective MT/V5 (Dumoulin et al. 2000; Tootell et al. 1995; Watson et al. 1993).

We speculate that characteristics of fluent Braille reading, especially in early blind individuals, might be responsible for these responses in MT/V5. Thus because V5 is known to respond especially to coherent motion (Tootell et al. 1996), V5 might be particularly suited to process tactile contrast arising from hand motion across different words and parts of words in Braille reading. Tactile contrasts are likely important when reading Braille, because, contrary to earlier ideas (Loomis 1981), hand movements across Braille cells create a textural image of the word that is based on lateral dot-gap shearing density within individual Braille cells (Millar 1984, 1986, 1987, 1997; Nolan and Kederis 1969; Pring 1985, 1994). The sensory information about the orthographic characteristics of individual Braille cell letters is processed serially and at a low spatial frequency. Fluent Braille reading involves selection of hand motion and direction that scans across the spatial form of individual letters.

Another extension of activation within the inferior temporal gyrus occurs anterior and inferior to the major foci in the fusiform gyrus. This region includes the coordinates of what Hadjikhani and colleagues describe as a major color processing center in sighted subjects, V8 at $\pm 33, -65, -14$ (Hadjikhani et al. 1998). Unlike the responses to color existing in lower tier visual areas, individuals with lesions affecting V8 lack the ability to process the spectral complexity of a scene (Hadjikhani et al. 1998). In reading Braille the spectral dimensions of roughness affect judgements about textural tactile differences for different letters in a word (Millar 1986, 1987, 1997). We hypothesize that mechanisms related to analyzing spectra of a varying tactile surface, when applied to the tactile domain of Braille, might explain the activity detected in V8 in early blind subjects.

Our late blind subjects, with one exception, read less fluently. Reading in these cases possibly involves determining the structure of individual Braille cells rather than a holistic,

texture perception of letters, combinations of letters or whole words. Thus less fluent Braille reading is affected more by orthographic elements (Millar 1997). A consequence might then be greater reliance on activity in lower tier visual areas as opposed to V5/MT in late-blind individuals. Why these responses occur predominantly in the hemisphere ipsilateral to the reading hand remains a puzzle.

Parietal regions activated by attention in sighted subjects

Ips Regions—The present study finds the largest magnitude BOLD responses in the same part of the ventral intraparietal sulcus (vIPS) identified in sighted subjects performing eye-movements (Petit and Haxby 1999), detecting and attending to visual motion (Shulman et al. 1999; Tootell et al. 1995), and voluntary orienting of attention to visual space (Corbetta et al. 1998a,b, 2000). A separate focus in pIPS is not apparent, although extension of the BOLD responses (Z -scores >15), with a peak in vIPS, includes the atlas coordinates of the sites previously described as pIPS in sighted subjects. We observe no activations in anterior IPS (Corbetta 1998, 2000; Shulman et al. 1999). In the light of the above-cited literature, we suggest that Braille reading induces left-lateralized prefrontal modulation of spatial attention and voluntary orientating toward the reading hand (fingers) as it moves across successive Braille cells. Additional experiments will be required to dissociate spatial attention, tactile perception and language processes in IPS.

Our data includes the intriguing observation of opposite IPS lateralization in early versus late blind individuals. We find greater bilateral symmetry in the size of the vIPS foci in right hand, late blind readers compared with predominantly contralateral, left sided sites in right hand, early blind readers. In the left-hand, early blind reader, the activated site is also only on the contralateral, right side; while the late blind, left-hand reader has bilateral foci, but the larger site is on the right. These group differences might reflect an under developed sense of projected external space in early blind individuals (Millar 1994). Thus the regional asymmetry in vIPS activations in the early blind might indicate a relatively greater awareness of immediate personal space. Late blind individuals, through prior visual experience, possibly project more readily into a wider spatial environment, which could explain the more symmetrical, bilateral activation of vIPS in late blind individuals. Thus in late blind a combination of voluntary attention to personal and extra-personal space might contribute to contralateral responses for personal space with respect to the reading hand, and a right hemisphere dominance for wider extra-personal space that contains the Braille field.

Postcentral Sulcus—Responses centered around the left postcentral sulcus coincide with a region modulated by attention to tactile stimuli on the right hand, and which lies anterior and lateral to visual attention regions within the IPS (Burton et al. 1999). It is certain that our subjects attended, as reading Braille is difficult even under optimal conditions. Accordingly, we interpret the left postcentral sulcus activations as due to tactile attention to the Braille fields during word reading.

Regions activated by touch

We find little or no BOLD modulation in most somatosensory cortical regions including the parietal operculum, i.e., second somatosensory cortical area (S2). Only scant responses occur within the central sulcus, i.e., in primary somatosensory cortex (S1). In view of the remarkable plasticity of somatosensory cortex (Buonomano and Merzenich 1998; Pons et al. 1991; Ramachandran 1996, 1998), it would be reasonable to suppose that some component of the adaptations underlying Braille skill should be manifest in this part of the brain. Normally sighted subjects who receive tactile stimulation show robust activations in portions of anterior and lateral parietal cortex (Burton 2001) and suppression of visual cortex activity (Drevets et al. 1995). Touching Braille cells clearly provides potent

somatosensory stimulation of the skin and, therefore we might expect comparable cortical responses in these subjects. The minimal responses observed do not exclude the possibility that Braille reading finger(s) have an expanded cortical representation.

There are two possible explanations for the unexpectedly small responses in somatosensory cortex. A procedural explanation suggests that when the subjects touched the control fields they successfully balanced tactile stimulation and gross motor behavior with the demands of word reading. We instructed our subjects to duplicate their Braille word reading strategies as they touched the control fields. Greater imbalance in tactile stimulation between activation and control trials could account for previous reports of increased blood flow in somatosensory and motor cortex of early blind individuals (Sadato et al. 1998).

Alternatively, it may be that, in adapting to read Braille, blind individuals redirect tactile discrimination processing away from primary and secondary somatosensory areas to the visual cortex, possibly through dorsal parietal association areas. This question could theoretically be illuminated by studying sighted subjects reading Braille, in which a more balanced activation of somatosensory cortex with minimal or no responses in visual cortex might be expected. Unfortunately, no one with these skills was available in our local community. Many of our late blind subjects had normal visual experiences for a decade or longer. These subjects showed slightly greater activation of somatosensory cortex, which could be viewed as evidence of reduced adaptations to Braille reading. However, again, a procedural explanation is more likely because in reading Braille less fluently, these subjects touched the Braille cells for words with more exaggerated movements compared with the control fields. Early blind subjects showed similar smooth sweeping movements for words and control fields.

An observation potentially related to the question of adaptive changes associated with Braille reading is that, in sighted subjects, visual cortex normally is suppressed during tactile discrimination tasks (Drevets et al. 1995). Even where a tactile task engages a portion of parietal-occipital cortex in sighted subjects (Sathian et al. 1997), primary visual cortex shows no activity while somatosensory cortex exhibits expected responses. The normal suppression of visual cortex by tactile stimulation clearly does not occur during fluent Braille reading in blind individuals.

Regions activated by motor behavior

Premotor Cortical Regions—We find no BOLD modulation in the anterior bank of the central sulcus, i.e., primary motor cortex as traditionally defined (Cramer et al. 1999; Crespo-Facorro et al. 1999; Fink et al. 1997). However, extensive responses occur throughout several previously identified non-primary motor areas (Fink et al. 1997). In all subjects, the largest BOLD responses in the frontal cortex occur on the lateral convexity on the left side. This activation is in the left lateral premotor cortex regardless of the hand used for Braille reading.

We find bilateral activation around the precentral sulcus very near the area identified as the frontal eye fields (Corbetta et al. 1998; Petit and Haxby 1999). The major portion of the present activation, however, mostly borders the lateral and anterior portion of the previously described eye movement related response. The main peak of the PrCS region is within a component of premotor cortex, which suggests these responses reflect motor planning. Especially in our early blind subjects, this response overlaps part of the left PrCS region described in a study of complex object manipulations (Binkofski et al. 1999) or simple flexion-extension movements of the right hand and fingers (Fink et al. 1997). The center of activity in our data are superior and posterior to the object manipulation area of Binkofski et al. (1999). These differences may reflect minor differences in the target images used to

compute atlas transformations. This response most likely is attributable to activation of the premotor representation for the fingertips.

Braille reading ordinarily is accompanied by a slight increase in the downward pressure exerted by the reading finger as it moves across each Braille cell (Millar 1997). This likely serves to increase stimulation of the slowly adapting pressure receptors, thereby increasing the transmission of salient information. It is possible that our readers omitted this action as they touched the control field because the content was entirely predictable. In any case, consistent motor differences between the word and control fields, whatever they were, manifested as premotor but not primary motor activation.

Activity exclusively in the left PrCS, even in left-hand readers, suggests that the PrCS region may not just encode motor behavior. In a study of complex object manipulations, maximum responses were observed in cortex contralateral to the used hand (Binkofski et al. 1999). In contrast, a similar left hemisphere specialization exists in deaf subjects using sign language (Neville et al. 1998). The left dominance with Braille reading might therefore reflect some abstraction of the learned special motor behavior for language functions, which are normally dominant in the left hemisphere.

Activity along the medial wall of premotor areas could arise from particular motor programs needed for Braille reading. The more posterior and superior region in this study has coordinates that place it posterior to the vertical anterior commissure line (Vca), which centers it within the domain of the arm representation of the supplementary motor area (SMA) (Fink et al. 1997; Kwan et al. 2000; Picard and Strick 1996; Thickbroom et al. 2000). SMA is especially active in sequential movements such as typing that are also integrated with received sensory information (Gordon et al. 1998). This is exactly what occurs during Braille reading.

Prior human imaging studies distinguish between SMA proper, which is engaged by simple, automatic movements, and a more anterior, inferior pre-SMA region, which serves more complex movements, possibly associated with skill acquisition (Picard and Strick 1996). More intense activation of these medial motor areas also occurs for motor tasks timed unpredictably to external events (Thickbroom et al. 2000). Only late blind subjects show a focus just anterior to Vca, within the pre-SMA area. Most of our late blind subjects are less fluent Braille readers and probably use slightly different reading strategies. Fluent readers exhibit rapid, smooth, relatively stereotyped horizontal scans across Braille fields. During Braille learning, reading with less fluency, or reading physically degraded Braille cells, readers make minute trapezoidal, up-down motions over each Braille cell during horizontal scanning (Millar 1987, 1997). Such selective motor behavior has less predictable timing, and might require more complex motor programs, which are known to activate a pre-SMA area (Fink et al. 1997; Thickbroom et al. 2000). This might explain the greater activation of this region in late blind subjects.

Both subject groups show activation of the cingulate sulcus and gyrus nearly 1 cm anterior to Vca and > 1 cm inferior to the SMA site. The coordinates of this focus place it within a posterior part of the anterior cingulate cortex previously associated with motor behaviors (Fink et al. 1997; Kwan et al. 2000; Picard and Strick 1996) similar to those used in Braille reading. Other processes which may be invoked to account for activation in this region include cognition (Whalen et al. 1998), verb generation (Petersen and Fiez 1993; Raichle et al. 1994) and attention (Burton et al. 1999; Corbetta et al. 1991). The present paradigm does not provide a means of distinguishing between these possibilities. The activated zone is more than 3 cm posterior to anterior cingulate regions associated with effort (Whalen et al.

1998) and pain (Kwan et al. 2000). It is therefore reasonable to suggest that our task paradigm did not invoke modulation of emotional processes.

Language areas in frontal and temporal cortex

The subject of word reading overall and verb generation in particular have been under continuous inquiry in the neuroimaging (for reviews see Fiez and Petersen 1998; Gabrieli et al. 1998) and neuropsychology literature (Illes et al. 1999; Thompson-Schill et al. 1998) since the verb generation task was first employed in functional imaging (Petersen 1988, 1989). The task of verb generation, while admittedly linguistically complex, consistently produces left lateralized responses in right-handed individuals and, when performed naively (Raichle et al. 1994), activates traditional language related areas of the cerebral cortex. We employed this robust language task as a means of obtaining an overall assessment of the distribution of language processing in blind subjects. We did not propose to isolate linguistic, memory, motor and attention processes, as has been done by others and ourselves. Rather, we merely sought to determine if the functional anatomy of language is different in blind individuals.

Prefrontal Cortex—We believe the results clearly demonstrate that blind subjects use the same general neural processing architecture employed by sighted individuals when performing the verb generation task. The presently observed functional anatomy replicates prior descriptions of left prefrontal activations observed in a variety of language tasks (Fiez 1997; Gabrieli et al. 1998; Illes et al. 1999; Petersen and Fiez 1993; Poldrack et al. 1999). All subjects show two distinct activations in prefrontal cortex. One focus resides entirely within the inferior frontal gyrus in Brodmann areas 45 and 47. The other focus spreads across the inferior frontal and middle frontal gyri on the dorsolateral convexity with its peak centered in the middle frontal gyrus. This region includes portions of Brodmann areas 9 and 46 according to the Damasio atlas (Damasio 1995).

In studies with sighted subjects, inferior prefrontal activity is most prominent when contrasting semantic to nonsemantic processing even when the latter is a more difficult task (reviewed in Gabrieli et al. 1998; Poldrack et al. 1999). This view supports earlier PET studies (Fiez 1997). The prefrontal foci in the present study are essentially coextensive with these two regions. This raises the question as to whether the current task similarly is divisible into semantic and phonological processes.

Verb generation is a language task with substantial semantic processing (Fiez 1997; Gabrieli et al. 1998; Illes et al. 1999; Petersen and Fiez 1993; Seger et al. 1999). In the present study we contrast verb generation with reading and interpreting the Braille embossed field for the number sign. Normally, when the Braille symbol for a number sign appears first in a word, readers know the following Braille cells represent numbers. Thus detecting the number symbol involves some semantic processing. However, by presenting these strings of number signs during the initial eight baseline scans, priming effects (Raichle et al. 1994; Seger et al. 1999) produce instant recognition, and minimal semantic demands when similar Braille fields alternate with words within the runs. Therefore the semantic demands of verb generation were predominant.

Word reading involves phonological processes (Fiez et al. 1997, 1998; Gabrieli 1998). The dorsolateral prefrontal region also is activated by word/object encoding tasks (Kelly et al. 1998) and object naming (Moore and Price 1999). Such encoding must precede the semantic aspects of verb generation. Although the present experiment does not attempt to differentiate various language operations, our results do suggest that, in blindness, early or late, there is no reorganization of semantic or phonological representations.

In the absence of sight, phonology and phonemics provide the only basis for associating the tactile feel of a Braille word and its meaning (Millar 1975a,b, 1984, 1997; Nolan and Kederis 1969; Pring 1982, 1985). However, in skilled readers, attention to phonology interferes with fluent Braille reading (Millar 1975a,b, 1997; Pring 1982). In the light of this observation, it is possible that early blind Braille readers, being less dependent on phonology, should show relatively reduced dorsolateral prefrontal responses. This result is not evident. The absence of distinctions between early and late blind individuals in dorsolateral prefrontal activity possibly relates to prior findings that this same region is also particularly concerned with word/object encoding (Kelly et al. 1998) or specific word or object naming (Moore and Price 1999). Our subjects must encode the words into some object or concept for, respectively, concrete or abstract nouns before doing the semantic task of generating a verb. Thus activation of this dorsolateral region (and, for similar reasons noted above, posterior basal occipital temporal cortex) possibly occurs because of word encoding rather than phonological processing.

Posterior Temporal Cortex—Only early blind individuals show activation of the middle temporal gyrus (BA 21). There is no consensus regarding which linguistic operations are most specific to this area (Binder et al. 1997; Fiez et al. 1996; Petersen and Fiez 1993; Pugh et al. 1996; Vandenberghe et al. 1996; Warburton et al. 1996; Zatorre et al. 1996). Rumsey and colleagues suggest that the posterior temporal region is especially engaged in letter identification, i.e., processing of visual orthography. The detailed structure of a Braille cell (i.e., the location of dots in the left or right column and in upper or lower rows) arguably is comparable to the arrangement of intersecting line segments which make up letters. The BA 21 activation, however, is absent in late blind subjects who are more likely to attend to the shapes of individual Braille cells (see above). This response is present in the early blind who perceive Braille more holistically. Early blind individuals attend to shifting textural patterns formed by the different Braille letters, and possibly process an overall orthography similar to the holistic interpretations of letters in reading print. Such holistic analyses would require the integrative mechanisms more likely in higher visual/language areas in posterior temporal cortex.

Conclusions

We confirm earlier reports of visual cortex activation by Braille reading. Two entrenched ideas make this finding surprising. First, based on its neuroanatomical connections, particularly those involving the thalamus, this cortex is visual. Second, loss of vision presumably renders the affected region inoperable. Yet, blind subjects show clear, well localized activation of both lower and higher tier visual areas. The lower tier responses in large measure correspond to retinotopically organized visual cortex subregions in sighted individuals. These findings indicate a need to reexamine the contribution of occipital cortex to reading. One possibility is that blind Braille readers use occipital cortex in a novel way, unlike the use of this cortex for early vision in sighted people. Another possibility is to suggest that mechanisms and connections within occipital cortex are necessary for encoding orthography (visual or tactile) into information used by language areas in frontal, and possibly temporoparietal, cortex. Accordingly, the activity in occipital cortex of blind individuals is not a totally novel adaptation. Rather, it represents a function already present in sighted individuals, namely recoding information for language areas. Loss of vision does not remove this role from occipital cortex, which accounts for the fact that this region is active in blind individuals.

Each of the many additional foci of significant activity in parietal, frontal and temporal cortex possibly relates to characteristic features of Braille reading. Thus the necessity of focusing attention on the fingertips when touching Braille might be expected to engage

parietal attention regions. We also suggest that minute movement strategies used when touching Braille cells selectively might increase activity in medial, frontal premotor areas. Braille reading obviously is at least in part a somatomotor task. However, the contribution of primary somatomotor cortex evidently can be balanced by a suitably implemented low-level control task. Potential differences in the reading strategies of early and late blind individuals possibly explains the distinctions in activated temporo-occipital foci including MT/V5, V8 and BA 21.

The verb generation task used in this study matches semantic and phonological features extensively studied in sighted individuals. There is a corresponding match of the observed left-lateralized prefrontal functional anatomy. We also suggest that word recognition precedes the semantic processing in the verb generation task, and possibly that touching Braille cells involves object recognition. Thus word and object encoding foci previously described in sighted subjects in dorsolateral prefrontal cortex and ventral occipital temporal cortex are correspondingly engaged in blind individuals during Braille reading.

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Fig. 1.

Task and EPI timing within an example 5 s TR (frame) interval. Each horizontal line corresponds to one slice. EPI occupied only the first 2.178 s of each TR, leaving a "quiet" time without scanner pulses. During the latter interval, subjects read the Braille cells, and then covertly generated an appropriate verb if the field contained a noun. As BOLD responses are delayed by two or more seconds, the hemodynamic consequences of task performance were first detected by EPI at the beginning of the next frame.

Fig. 2.

Location of significant Z-scores for BOLD responses in medial occipital cortex from single early blind individuals. The age of blindness was at birth for results shown in *A–D* and *F* and at 3 yr of age in *E*. Subject identifiers (Early #) cross reference Table 1, which lists characteristics, including cause of blindness. Each panel (*A–F*) shows two closely spaced sagittal sections (Talairach atlas X values) from the left and right hemispheres. Images in *A–E* from subjects who read with their right hand (RH) and in *F* from a subject who used the left hand (LH). Numbered pink lines point to correspondingly numbered regions of interest identified in Table 2. Color scale has different maximum Z-score value for each subject (MAX =).

Fig. 3. Location of significant Z-scores for BOLD responses in medial occipital cortex from single late blind individuals. Subject identifiers (Late #) cross reference to Table 1, which lists characteristics, including cause of blindness. The age of blindness onset ranged from 6 (A) to 25 (F) years of age. Each panel (A–F) shows two closely spaced sagittal sections as in Fig. 2. Images in A–C, E and F from subjects who read with their right hand (RH) and in D from a subject who used the left hand (LH). Numbered pink lines point to correspondingly numbered regions of interest identified in Table 2. Color scale has different maximum Z-score value for each subject (MAX =).

Fig. 4.

Location of significant average Z-scores for BOLD responses mainly in extra-striate and occipital-parietal cortex. *A*, *C*, and *E*: data taken from 6 early, right-hand Braille readers. *B*, *D*, and *F*: data taken from 7 late blind subjects (6 right- and 1 left-hand Braille readers). Activation data overlaid on average structural images from the same subjects. All images aligned and interpolated to atlas coordinates using 2 mm voxels. Paired images in each panel show coronal (on left) and transverse (on right) slices through or near peak Z-scores for the numbered regions of interest identified in Table 2. Pink lines show the registration of the alternate slice orientation. Color scale has different maximum Z-score value for each group of subjects (MAX =).

Fig. 5.

Location of significant average Z-scores for BOLD responses mainly in frontal cortex. Left three images for each panel, A–C, show slices at three orientations for averages (Z-scores and corresponding structural images) from the same 6 early and 7 late blind subjects shown in Fig. 4. Data shown are at or near peak activations overlying the precentral sulcus (PrCS) (A), the inferior/middle frontal gyri (I/MFG) (B), and the inferior frontal gyrus (IFG) (C). Sagittal slices shown on the far right taken from averages for the same early or late blind individuals. The data from these two were added and averaged to create the images shown on the left. Numbered regions of interest identified in Table 2. Perpendicular pink lines

show the registration of the alternate two slice orientations. Color scale has different maximum Z-score value for averages across all or within each group of subjects (MAX =).

Fig. 6. Location of significant average Z-scores for BOLD responses mainly in medial frontal cortex in 6 early (A and B) and 7 late (C and D) blind subjects (same subjects as in Fig. 4). Activation data overlaid on average structural images from the same subjects. Paired images in each panel show sagittal (on left) and coronal (on right) slices through or near peak Z-scores for the numbered regions of interest identified in Table 2. Pink lines show the registration of the alternate slice orientation. Color scale has different maximum Z-score value for each group of subjects (MAX =).

Fig. 7. Activation focus volume as a function of age of blindness onset. Each ROI was individually defined for each subject (data points shown on the left, A1–D1). Average and standard errors of the mean for early and late blind individuals for the same ROI shown on the right (A2–D2). In A1–D1 linear or nonlinear (negative exponential) regression curves that had the highest correlations were fit to the data for each ROI. Abbreviations for ROI are identified in Table 2. Significant differences ($P < 0.05$) between early and late blind groups are marked with asterisks (*).

Fig. 8. Time course of BOLD responses per voxel in selected ROI for 7 early and 7 late blind individuals. For each group, data includes responses from 6 right- and 1 left-hand readers. Data for each frame shows mean and standard error of the mean. Average percentage change in MR signal was obtained in the selected ROI defined in individual subjects and these values were then averaged as shown.

Table 1

Subject characteristics

Subject	Age	Sex	Preferred	Braille	Words/Minute	Years Blind	Light	Yrs Reading	Cause of Blindness
<i>A. Early blind</i>									
Early 1	49	F	Right	Right	145.4	49	None	45	Retrolental fibroplasia
Early 2	48	M	Right	Right	152	48	None	42	Retrolental fibroplasia
Early 3	49	F	Right	Right	143.8	49	None	45	Optic nerve hypoplasia
Early 4	34	F	Left	Right	76	34	Some	26	Optic nerve hypoplasia
Early 5	39	F	Right	Right	99.6	36	None	34	Glaucoma
Early 6	23	M	Right	Left	76	23	Some	18	Retrolental fibroplasia
Early 7	67	M	Right	Right	63.8	62	None	60	Cataracts
Early 8	51	M	Right	Right	n/a	51	None	25	Optic nerve hypoplasia
Early 9	43	M	Right	Right	n/a	43	None	39	Retrolental fibroplasia
<i>B. Late blind</i>									
Late 1	36	F	Ambi	Right	81.8	36	Yes	30	Rubella
Late 2	50	M	Right	Right	66.5	40	None	45	Glaucoma
Late 3	40	M	Right	Right	72.5	29	None	29	Coats disease
Late 4	62	M	Right	Left	83.9	51	None	55	Glaucoma
Late 5	66	F	Right	Right	n/a	46	None	48	Retinitis pigmentosa
Late 6	46	F	Right	Right	125	21	None	18	Retinitis pigmentosa
Late 7	44	F	Right	Right	n/a	32	Some	14	Optic nerve atrophy

Table 2

List of cortical regions and the atlas coordinates of peaks from averaged Z-score images from early and late blind individuals who read with their right hand

Regions	BA *	Early Blind				Late Blind			
		x	y	z	Z Score	x	y	z	Z Score
1 Lower calcarine (LBGS)	17	-5	-83	-4	23.94	-1	-93	-6	8.1
2 Lower calcarine (LBGS)	17	11	-87	-6	14.26	11	-89	-8	14.3
3 Upper calcarine (UBGS)	17	-15	-91	6	23.14	-1	-93	-2	9.7
4 Upper calcarine (UBGS)	17	11	-87	-2	13.8	9	-91	-4	14.8
5 Cuneus (Cun)	18	-7	-95	12	25.62				
6 Cuneus	18	11	-89	14	11.47				
7 Lat occipital G (LOG)	18	-17	-93	4	25.3	-29	-91	2	12.12
8 Lat occipital G	18	31	-87	6	17.48	27	-89	4	15.3
9 Fusiform gyrus (FG)	19	-41	-69	-10	31.74	-31	-73	-18	14.61
10 Fusiform gyrus	19	31	-59	-22	16.1	29	-67	-18	15
11 Ventral intraparietal S (vIPS)	19	-23	-75	22	32.10	-25	-67	22	16.01
12 Ventral intraparietal S	19	27	-71	30	17.61	23	-67	34	19.15
13 Inferior temporal G (ITG)	19,37	-39	-71	-8	30.82	-43	-57	-16	14.1
14 Inferior temporal G	37	43	-61	-12	15.62	45	-67	-20	9.9
15 Mid temporal G (MTG)	21	-45	-51	2	17.58				
16 Postcentral S (PoCS)	40	-49	-39	48	13.91	-35	-39	36	15.36
17 Inferior frontal G (IFG)	45,47	-41	29	8	22.05	-41	29	8	11.4
18 Inferior/mid frontal G (l/MPFG)	9,46	-49	13	28	23.04	-43	7	28	19.5
19 Pre-central S (PreCS)	6,8	-51	1	38	28.06	-43	3	28	22.98
20 Pre-central S	6	33	3	30	13.16				
21 Cingulate G (CG)	24,32	-5	9	44	22.97	-7	11	42	12.77
22 Cingulate S	24,32	5	7	42	16.41				
23 Medial sup frontal G (mSFG)	6	-5	-1	54	26.85	-1	1	54	17.73

* BA designates Brodmann Area labeled in Talairach atlas (Talairach and Tournoux 1988 #107) for nearest section with corresponding coordinates.