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Changes in occipital cortex activity in early blind humans using a sensory substitution device

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Abstract

The purpose of this study was to investigate the neural networks involved when using an ultrasonic echolocation device, which is a substitution prosthesis for blindness through audition. Using positron emission tomography with fluorodeoxyglucose, regional brain glucose metabolism was measured in the occipital cortex of early blind subjects and blindfolded controls who were trained to use this prosthesis. All subjects were studied under two different activation conditions: (i) during an auditory control task, (ii) using the ultrasonic echolocation device in a spatial distance and direction evaluation task. Results showed that the abnormally high metabolism already observed in early blind occipital cortex at rest [C. Veraart, A.G. De Volder, M.C. Wanet-Defalque, A. Bol, C. Michel, A.M. Goffinet, Glucose utilization in human visual cortex is, respectively elevated and decreased in early versus late blindness, Brain Res. 510 (1990) 115–121.] was also present during the control task and showed a trend to further increase during the use of the ultrasonic echolocation device. This specific difference in occipital cortex activity between the two tasks was not observed in control subjects. The metabolic recruitment of the occipital cortex in early blind subjects using a substitution prosthesis could reflect a concurrent stimulation of functional cross-modal sensory connections. Given the unfamiliarity of the task, it could be interpreted as a prolonged plasticity in the occipital cortex early deprived of visual afferences.

Keywords: Positron emission tomography; Blindness; Visual cortex; Plasticity; Sensory substitution

1. Introduction

Previous studies of regional brain glucose metabolism have been performed in the same laboratory, with positron emission tomography (PET), in subjects with blindness [26,29] and deafness [5] of early onset. They demonstrated a high glucose utilization at rest in sensory deprived areas. In early blind (EB) adults affected by pregeniculate lesions from birth or in the first years of life, rates of glucose metabolism measured in primary and association visual cortex reached a level comparable to that of control subjects studied with the eyes open [26]. The metabolic increase in EB visual cortex was attributed to the persistence of synaptic contacts in an unusual high density or hyperactive state [8,26]. According to this hypothesis, transient synapses which result from the postnatal burst of synaptogenesis would not be eliminated during brain maturation because of a lack of organizing stimuli. What might be the outcome of these supranumerary and/or hyperactive connections? In a PET study, Braille reading and tactile discrimination tasks by proficient Braille readers were found to activate the occipital lobe, although some of the subjects were congenitally blind [22]. However, no definite conclusions could be drawn as to the kind of synapses involved in this metabolic increase in sensory deprived areas [3] nor to their neural usefulness in primary visual cortex [4]. Since successful results have been obtained with substitutive sensory devices [1], this question has to be raised. For instance, the representation of locomotor space, which is impaired in EB subjects, was found to improve with the help of an ultrasonic echolocation prosthesis [25]. As an attempt to gain further insight into the possible plasticity of the visual cortex in early blindness, the present study aimed at investigating, for the first time, the occipital activity changes related to the processing of new

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sensations which were provided to EB subjects by means of a sensory substitution prosthesis.

2. Materials and methods

2.1. Subjects

Five male volunteers with peripheral blindness of early onset (Table 1) were involved in the study. They were totally blind, without residual light perception and had no additional handicap. EB subjects, aged 48.0 ± 19.5 years (mean $\pm$ S.D.), were compared to four male, right-handed, blindfolded controls, aged 26.8 ± 5.0 years ($p = 0.07$, *t*-test), who present similar metabolic patterns as subjects with late-onset blindness according to previous studies [18,26]. All subjects gave their informed consent before undergoing the PET study, the protocol of which had been approved by the Medical Ethics Committee of the School of Medicine of the University of Louvain.

2.2. Description of the sensory substitution device

The subjects were trained to perform obstacle localization using an ultrasonic echolocation device [6,27] aimed at vision rehabilitation through audition. This sensory substitution system includes a pair of spectacles worn on the head and equipped with three ultrasonic transducers and two earphones. The first transducer emits ultrasounds in the ambient air in a cone of about 70° whereas the two others, acting as microphones, receive, respectively, the right and left echoes reflected by the obstacles. A light, battery powered, electronic case is connected to the spectacles; it emits the signals and processes the echoes by decoding them into audible sounds which are sent to the user's earphones. The pitch of the sound (slope = 1880 Hz/m) is proportional to the distance to obstacles and the direction is coded by the binaural intensity balance. Head movements help the user to scan the environment. Using this device, a 9 cm diameter and 2 m height pole could be detected at up to 6 m, with the related auditory frequency being 10.8 kHz [6].

Table 1
Summary of clinical features in the five subjects affected by early blindness

Subjects	Age	Handedness	Onset	Etiology of blindness
EB 1	52	Right-handed	< 1 year	Unknown (enucleated)
EB 2	62	Right-handed	Birth	Unknown
EB 3	67	Right-handed	< 3 years	Lens calcification
EB 4	18	Ambidextrous	Birth	Retronal fibroplasia
EB 5	41	Right-handed	18 months	Retinoblastoma (enucleated)

The subject handedness was assessed using the laterality test of Raczkowski and Kalat [19].

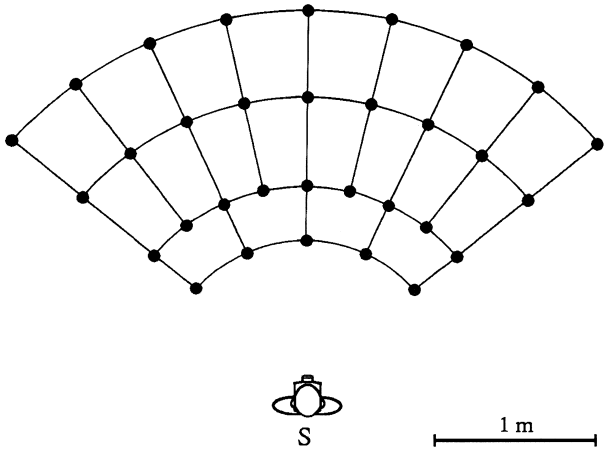


Fig. 1. Layout of the area with the 32 possible pole positions (indicated by the large dots) for the spatial localization task using the ultrasonic echolocation device. Subjects, EB or blindfolded controls, were seated in front of this area in such a way that the three ultrasonic transducers lay at the center (S) of the coordinate system. Total angular aperture was 100° and radii of the four arcs of circle were 0.9, 1.25, 1.85 and 2.4 m. Pole diameter and height were 0.09 and 2 m, respectively.

2.3. Training

The learning program included six 1-h training sessions, distributed over 3 to 4 weeks before the PET examination. Sighted controls were trained blindfolded. All subjects progressively learned to recognize a wall and a pole as well as to walk and detect the location of doors and stairs. The progressive ability to use the device was assessed by asking the subject to estimate the relative position of two poles (cardboard tubes of 9 cm diameter and 2 m height) located in an experimental area (Fig. 1) at a distance ranging from 0.9 to 2.4 m of the sitting subject. Subject's performance in each of 40 trials was scored on a 3 point scale: 0 if no pole was detected, 1 or 2 if one or two poles were correctly located (by pointing the head in the respective direction), plus 1 point for correct distance evaluation (i.e., identifying which of the two poles was the nearest). At end of training, performance level (as scored on a maximum of 120 points for all 40 trials) was consistently above 90% for both groups of subjects.

2.4. Experimental conditions during PET scan

Two tasks were designed for physiological activation during the period of tracer incorporation. They were assessed in two separate PET sessions in counterbalanced order.

2.4.1. Auditory control task

During this task, a portable loudspeaker emitting bursts of 800 Hz tones at 97 dBa was randomly located at 25 different positions, defined within a 90° area, at distances

ranging from 1 to 3 m in front of the seated subject. An experimenter changed silently the target position and controlled the auditory stimulation which was administered at a rate of 5 s duration with intervals of 3 s between stimuli. Subject was asked to move the head to assist in sonorous target localization and to orient the head towards the sound position.

2.4.2. Use of the ultrasonic echolocation device

During this task, each subject was sitting in front of an experimental area as illustrated in Fig. 1. A pole (height: 2 m, diameter: 9 cm) was randomly positioned within this area. For each pole location assessment, the subject was requested to explore the space, while doing head movements, to detect the pole (detection was assessed by stabilization of head movements) and to evaluate its distance, imagining his own displacement up to the detected pole. Between two successive pole location assessments, a sound absorbing foam screen was placed in front of the echolocation device and the pole was then silently displaced by an experimenter. It was subsequently located randomly at another position (see Fig. 1). Mean period between two successive stimuli was found to be about 18 s.

Before each PET study, subjects were specifically familiarized with the related stimulation task. Subjects remained mute and still, except for head movements, and sighted volunteers were studied blindfolded.

2.5. Positron emission tomography

Positron emission data were collected with an ECAT III tomograph (CTI/Siemens) and [F-18]fluoro-2-D-deoxyglucose (FDG) as previously described [26]. A 22-gauge catheter was placed in the antecubital vein of one arm for radiotracer injection and a 24-gauge catheter (Abbocath™) was inserted at random in a radial artery under local

Table 2
Glucose metabolic rates measured in the principal brain structures in early blind and control subjects

		Auditory control task						Use of ultrasonic echolocation device					
Subjects		EB1	EB2	EB3	EB4	EB5	Mean ± SD	EB1	EB2	EB3	EB4	EB5	Mean ± SD
Area 7	R	38.9	48.2	30.8	51.7	32.3	40.4 ± 9.3	39.7	45.4	38.5	41.1	55.8	44.1 ± 7.1
	L	40.7	47.3	32.9	46.5	33.3	40.2 ± 6.9	40.2	44.4	38.4	39.7	56.4	43.8 ± 7.4
Area 8	R	38.4	41.5	26.6	42.8	28.4	35.5 ± 7.6	36.1	38.1	27.1	35.9	42.1	35.9 ± 5.5
	L	38.5	41.5	28.4	39.5	28.1	35.2 ± 6.5	35.1	40.9	29.3	34.7	43.8	36.8 ± 5.7
Area 17–18	R	56.2	64.2	46.5	46.9	39.2	50.6 ± 9.7	50.5	63.7	52.0	42.5	67.9	55.3 ± 10.4
	L	55.1	63.2	41.7	43.4	39.6	48.6 ± 10.1	49.7	60.4	46.7	43.9	70.8	54.3 ± 11.1
Area 19	R	47.3	59.4	40.3	38.7	34.4	44.0 ± 9.8	44.0	58.4	45.2	35.4	64.0	49.4 ± 11.6
	L	47.3	57.0	36.1	38.5	34.6	42.7 ± 9.4	44.1	57.5	40.8	37.6	63.5	48.7 ± 11.2
Area 20	R	35.7	47.5	33.3	34.4	32.5	36.7 ± 6.2	32.1	44.6	33.8	30.7	48.9	38.0 ± 8.2
	L	37.7	49.8	29.3	32.9	30.1	36.0 ± 8.4	33.2	41.1	32.4	30.6	49.6	37.4 ± 7.9
Area 22	R	37.7	50.7	35.2	37.5	33.5	38.9 ± 6.8	36.3	49.8	36.3	34.2	56.2	42.6 ± 9.9
	L	41.9	50.6	31.8	39.0	31.0	38.9 ± 8.0	36.2	45.8	32.8	34.1	51.0	40.0 ± 8.0
Area 41–42	R	42.8	47.5	30.5	41.0	32.8	38.9 ± 7.1	38.6	46.1	31.1	37.1	53.7	41.3 ± 8.7
	L	44.4	48.2	29.7	43.8	32.2	39.6 ± 8.2	37.1	48.5	31.3	38.6	54.5	42.0 ± 9.3
Area 44–45	R	45.5	50.4	36.6	45.2	33.4	42.2 ± 7.0	39.4	49.9	39.1	40.6	54.8	44.8 ± 7.1
	L	43.2	50.9	29.2	47.0	33.0	40.7 ± 9.2	37.3	48.6	32.3	40.7	54.4	42.7 ± 8.9
Mean gray		39.2	47.2	30.6	38.9	30.0	37.2 ± 7.1	34.8	44.4	32.7	33.8	49.6	39.0 ± 7.5
Subjects		C1	C2	C3	C4		Mean ± SD	C1	C2	C3	C4		Mean ± SD
Area 7	R	57.3	44.0	40.1	43.6		46.2 ± 7.6	54.1	35.0	47.7	40.4		44.3 ± 8.3
	L	56.9	43.2	40.0	42.8		45.7 ± 7.6	52.6	35.0	45.2	37.2		42.5 ± 8.0
Area 8	R	49.2	34.4	34.0	41.3		39.7 ± 7.1	43.5	28.9	40.7	38.0		37.8 ± 6.4
	L	48.2	34.2	34.6	41.4		39.6 ± 6.6	49.7	29.7	39.8	38.8		39.5 ± 8.2
Area 17–18	R	54.1	43.7	37.7	35.3		42.7 ± 8.4	47.1	37.3	41.6	40.4		41.6 ± 4.1
	L	52.3	44.2	37.9	36.0		42.6 ± 7.4	48.0	38.1	38.8	42.4		41.8 ± 4.5
Area 19	R	48.5	37.8	32.6	34.1		38.2 ± 7.2	43.2	35.3	38.2	34.6		37.8 ± 3.9
	L	47.3	37.8	33.2	33.1		37.9 ± 6.7	42.8	35.8	36.7	32.1		36.9 ± 4.5
Area 20	R	43.0	32.6	33.9	37.8		36.9 ± 4.7	42.5	32.0	36.1	37.9		37.1 ± 4.3
	L	47.4	37.7	34.5	38.4		39.5 ± 5.5	41.3	28.5	35.1	38.5		35.8 ± 5.5
Area 22	R	51.2	35.1	36.4	41.4		41.0 ± 7.3	47.9	36.2	39.7	38.1		40.5 ± 5.1
	L	49.0	36.9	37.1	37.6		40.1 ± 5.9	44.6	34.7	38.8	39.1		39.3 ± 4.1
Area 41–42	R	47.9	37.6	36.2	39.5		40.3 ± 5.3	46.1	36.9	42.9	34.7		40.1 ± 5.3
	L	50.5	39.9	37.4	40.9		42.2 ± 5.7	45.6	34.8	43.8	39.4		40.9 ± 4.8
Area 44–45	R	51.5	43.7	39.0	46.0		45.1 ± 5.2	51.5	39.3	44.0	44.4		44.8 ± 5.0
	L	51.9	44.0	39.0	46.0		45.2 ± 5.3	49.1	35.6	42.8	47.7		43.8 ± 6.1
Mean gray		46.1	35.2	32.8	36.5		37.6 ± 5.8	42.7	32.0	37.2	36.2		37.0 ± 4.4

Absolute values in μmoles/(100 g min).

anesthesia with bipuvacaïne. For a given examination, 5 mCi of FDG was administered i.v. as a slow bolus of 30 s duration. Two minutes before injection, the specific task (auditory control task or pole localization using the ultrasonic echolocation device) was started and carried out continuously until the end of a 35 min period allowed for tracer incorporation. Throughout the stimulation period, the input function was determined by silent manual arterial blood sampling. After tracer incorporation, the subject was driven to the scanner room. Positioning of the subject in the gantry was accomplished by aligning two sets of low power laser beams with the suborbitomeatal and the sagittal line and head-restraining adhesive bands were used. Plasma radioactivity was counted in a gamma well counter cross-calibrated against the PET tomograph and the plasma glucose levels were monitored with a Beckman™ glucose analyzer (Beckman Instruments, Fullerton, California).

For each PET investigation, 9 brain levels were sequentially acquired at 1 cm intervals, with a slice thickness of 15 mm FWHM, and reconstructed with a Hanning filter at an in-plane resolution of 9 mm FWHM. Attenuation correction was carried out with a contour-finding algorithm and an effective attenuation coefficient of 0.088 [16]. Emission density data were converted into maps of glucose utilization, expressed in μmoles/(100 g min), according to the autoradiographic method of Phelps et al. [17] with the following rate constants: $k1 = 0.092\ \text{min}^{-1}$; $k2 = 0.14\ \text{min}^{-1}$; $k3 = 0.075\ \text{min}^{-1}$; $k4 = 0.0056\ \text{min}^{-1}$; and the lumped constant: LC = 0.42. No significant differences were found between the groups of EB and control subjects for the glycemia (85.0 ± 10.2 and 91.4 ± 6.0 mg/dl, respectively, $p = 0.14$, *t*-test). Within each group, the glycemia was also similar in the two tasks ($p > 0.12$, paired *t*-test).

2.6. Data analysis

Irregular regions of interest (ROI's) were drawn, under visual control, on the color-coded metabolic images with reference to common neuroanatomical hallmarks, to atlases [15,24] and to individual MRI plates, as previously described [29]. Due to the limited precision in ROI definition, only well-defined areas were considered for analysis. Volumes of interest (VOI's) were subsequently outlined by summing the planar regions related to anatomical structures which were present on adjacent planes. Regional cerebral metabolic rates for glucose (rCMRGlc) were estimated in 16 VOI's (eight in each hemisphere), encompassing the primary (Brodmann's areas (BA) 17–18) and associative visual cortex (BA 19), auditory cortical regions (BA 41–42 and BA 22), the Broca's area (BA 44–45), the frontal eye field (BA 8) and additional regions in the parietal and temporal association cortices (BA 7 and BA 20). The metabolic value averaged from the overall cortex, basal ganglia and cerebellum was defined as the mean gray matter (MGM) value. We did not attempt to define confidently the exact border between Brodmann's area 17 and adjacent area 18 since the two structures are physiologically interconnected and hardly distinguishable on medical images [30]. Glucose metabolic rates were compared for their regional differences between EB and control subjects by using analysis of variance–covariance

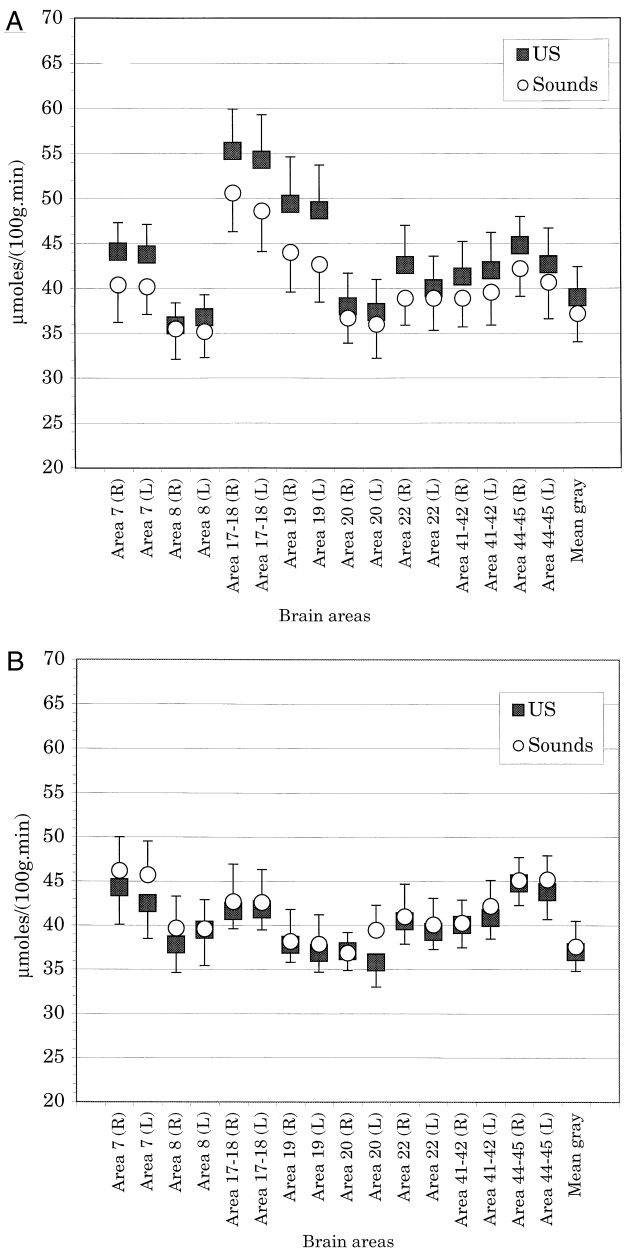
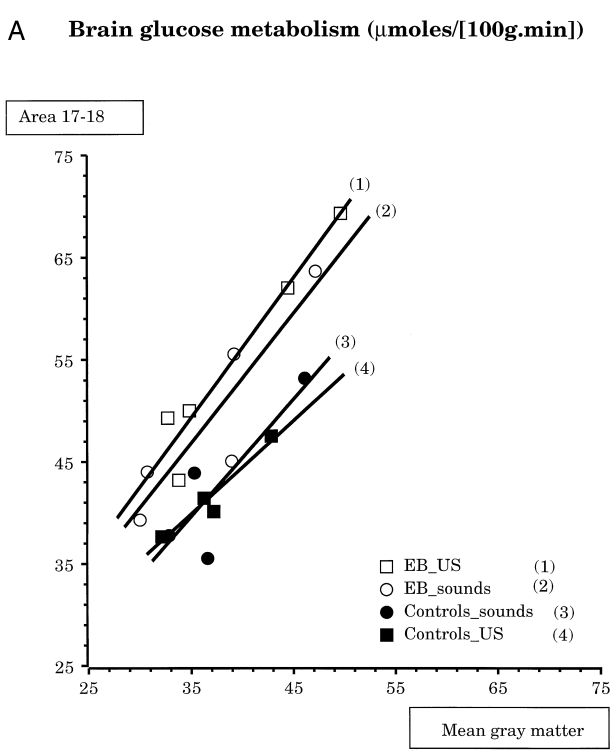
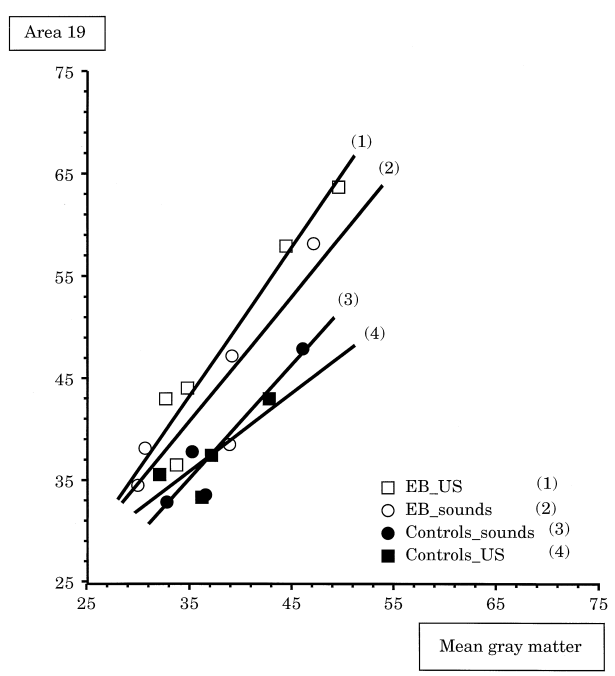


Fig. 2. Regional metabolic rates for glucose during use of the ultrasonic echolocation device (US) and during auditory control task (sounds) in EB (a) and control subjects (b). (a) In EB subjects, higher metabolic rates are observed in areas 17–18 and area 19 as compared to other regions, in both tasks. However, the metabolic rates in visual areas are also slightly more elevated during the use of the ultrasonic echolocation device than during the control auditory task. (b) By contrast, results from control subjects do not disclose any similar task-related change in their regional pattern of metabolism. Error bars represent 1 S.E.M.

(ANCOVA with F tests) [9] with VOI and task as the within subject factors and subject state (EB or control) as the grouping factor and with the mean metabolic value for the whole cortical gray matter as covariate. Post-hoc multiple pairwise comparisons of selected means were performed without correction of p-values because of small sample sizes. All tests were two-tailed and the significance level was set to 5%.





3. Results

Mean values of glucose metabolism in the whole gray matter averaged 37.2 ± 7.1 μmoles/(100 g min) during the control auditory task vs. 39.0 ± 7.5 μmoles/(100 g min) during the use of the ultrasonic echolocation device in blind subjects. They averaged, respectively, 37.6 ± 5.8 vs. 37.0 ± 4.4 μmoles/(100 g min) in controls (Table 2). Despite similar values for the mean gray matter metabolism whatever the task in both groups of subjects, the regional distribution of metabolic rates appeared significantly different between the two tasks in EB subjects ($p = 0.03$, F test for interaction between VOI and task, see Fig. 2a). By contrast this distribution was found to be unchanged in control subjects ($p = 0.90$, F test for interaction between VOI and task, see Fig. 2b). When the two groups of subjects were compared, the highest metabolic rates were found in the primary and association visual cortex of EB subjects in both conditions. However, this regional hypermetabolism in EB visual cortex (BA 17–18 and BA 19) tended to be more pronounced when EB subjects used the ultrasonic echolocation device (Fig. 2). Despite non-significant third-level interaction ($p = 0.25$, F test), a trend towards increase in metabolic activity in visual areas was observed in blind subjects during the sensory substitution condition as compared with the control auditory task (Fig. 3). By contrast, the results obtained in control subjects did not show any consistent change in the visual areas when comparing the two tasks (Fig. 3). No additional task-related difference in regional metabolism could be found in any of the other regions studied, whatever the group of subjects. No asymmetry was found in the regional metabolic values.

4. Discussion

This study shows a high rate of glucose utilization in the occipital cortex of subjects affected by early blindness

Fig. 3. Regional brain glucose metabolism in visual areas is plotted against the mean gray matter metabolic value (used as covariate in ANCOVA analysis). (a) In areas 17–18 (averaged from the two hemispheres), higher metabolism is observed in EB subjects as compared to controls in both tasks. Although unsignificant task-related differences were found between EB and controls for this structure ($p = 0.68$, interaction between group, task and global mean in ANCOVA), individual data show a trend towards higher metabolic activity in EB visual cortex during the ultrasonic task (US) as compared with control task (sounds). This trend is not observed in control subjects. (b) In area 19 (averaged from the two hemispheres), a similar trend towards higher metabolic activity during the use of the ultrasonic device is observed in EB subjects whereas this trend is not present in controls.

when compared to blindfolded controls, as already described [8,26,29]. This high metabolism in EB occipital cortex is observed whatever the task assessed (auditory control task or spatial localization of a pole by using the ultrasonic prosthesis). Moreover, a tendency towards larger metabolism in visual areas is observed in EB subjects (and not in controls) when they are using the ultrasonic echolocation device as compared to the control task.

The limitations of the autoradiographic PET/FDG method and its application to activation studies have been discussed elsewhere [13]. The use of FDG (half-life: 110 min) for activation studies could be considered suboptimal since short-lived blood flow tracers now allow to repeat scans and to reassess several physiological conditions during a unique session with lesser radiation exposure. However, in the present study, the head movements which are needed for efficient use of the echolocation device imposed that the stimulation (which took place outside the gantry) did not interfere with data acquisition. Moreover, blood flow and glucose metabolism have been found to increase proportionally in activated brain areas [12]. The signal to noise ratio is even superior in the FDG method although replication of FDG scans can hardly handle more than two times, which results in restricted statistical power. This restriction (one scan per condition), the limited number of subjects and the scanner characteristics (single slice tomograph) did not allow to obtain suitable tri-dimensional PET images for a voxel by voxel analysis using SPM [10], leading us to adopt a classical VOI analysis of variance–covariance with post-hoc tests to compare selected structures from the whole brain. Since only men were included for ethical reasons, our observations could also obviously not be extended to women. Notwithstanding these limitations, our study provides the first data concerning the metabolic activity in early deprived visual cortex during a sensory substitution procedure.

Auditory signals delivered by the ultrasonic echolocation device provide the user with a distance information related to the distal space. The processing of distance information is normally achieved using the visual system. Indeed, the natural audition does not allow any absolute, measurable, distance assessment. Auditory processing does only provide an evaluation of relative distances for a sound source of known fixed intensity [28]. The processing of absolute distance information extending the prehension space is, therefore, totally new for the EB subject because no neural tissue in the brain has had any chance to develop for this purpose. Accordingly, the tendency towards cortical activation reported here when EB subjects were using the ultrasonic echolocation device would result from the processing of a new kind of information in the early visually-deprived brain.

From a morphologic point of view, experiments performed in various animal species have shown that early deprivation may result in a different functional organization of the brain as compared with sighted animals. In kittens, transient extrinsic projections from auditory, somatosensory, and motor cortices to cortical layers of BA 17, 18 and 19 persist until about the fifth week of life and are subsequently eliminated during brain maturation [7,14]. However, in early visually-deprived animals, extrinsic projections to occipital cortex are still present until at least 6 to 7 months of age [2]. A reorganization of sensory representations with crossmodal expansion of non-visual modalities into normally visual brain areas has also been demonstrated, using electrode recordings, in early visually-deprived animals [20]. A similar persistence of extrinsic projections to the occipital cortex of early blind humans has been suggested to explain the occipital activation observed during Braille reading [4,22] and would also support the present observations. According to this hypothesis, the use of such projections to convey the new coded distance information provided by the ultrasonic prosthesis towards the occipital cortex would be a form of prolonged cross-modal plasticity. Rewiring experiments indicated that this kind of plasticity might take place in animal brain by the demonstration that visual functions were performed by neural structures normally involved in auditory processing [11,21,23].

Provided these observations are confirmed, they indicate that the high metabolism demonstrated, at adult age, in early blind's occipital areas would not pertain to a 'frozen' state. The occipital cortex might thus be susceptible to be recruited in new physiological activities. The observed tendency to occipital metabolic enhancement in EB subjects using the echolocation device suggests that learning would induce the adult occipital cortex of early blind subjects to carry out highly novel functions, i.e., the processing of new spatial information provided through the auditory pathways. More stringent demonstration of auditory inputs to occipital cortex is needed to sustain this claim. Nevertheless, this study suggests that such cross-modal plasticity processes might be recruited in novel abilities with the help of sensory substitution prostheses. Additional activation studies should further assess this point which opens a hopeful perspective in the field of blindness rehabilitation.

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