Functional neuroanatomy of the human near/far response to blur cues: eye-lens accommodation/vergence to point targets varying in depth

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Abstract

The purpose of this study was to identify the networks involved in the regulation of visual accommodation/vergence by contrasting the cortical functions subservient to eye-lens accommodation with those evoked by foveal fixation. Neural activity was assessed in normal volunteers by changes in rCBF measured with PET. Thirteen right-handed subjects participated in three monocular tasks: (i) resting with eyes closed; (ii) sustained foveal fixation upon a LED at 1.2 m (0.83 D); and (iii) accommodating alternately on a near (24 cm, 4.16 D) vs. a far (3.0 m, 0.33 D) LED alternately illuminated in sequential 2 s epochs. The contrast between the conditions of near/far accommodation and of constant foveal fixation revealed activation in cerebellar hemispheres and vermis; middle and inferior temporal cortex (BA 20, 21, 37); striate cortex and associative visual areas (BA 17/18). Comparison of the condition of constant fixation with the condition of resting with closed eyes indicated activation of cerebellar hemispheres and vermis; visual cortices (BA 17/18); a right hemisphere dominant network encompassing prefrontal (BA 6, 9, 47), superior parietal (BA 7), and superior temporal (BA 40) cortices; and bilateral thalamus. The contrast between the conditions of near/far accommodation with closed-eye rest reflected an incremental summation of the activations found in the previous comparisons (i.e. activations associated with constant fixation). Neural circuits activated selectively during the near/far response to blur cues over those during constant visual fixation, occupy posterior structures that include occipital visual regions, cerebellar hemispheres and vermis, and temporal cortex.

Introduction

The subject of inquiry in this study is the functional anatomy of human eye-lens accommodation/vergence responses to blur cues. The process by which the dioptric error becomes transformed into a motor command for accommodation remains largely unknown. The near/far response (NFR) consists of a tightly coupled triad of eye movements: dioptric accommodation of the crystalline eye-lens; convergence/divergence of both eyes toward the locus of fixation; and pupillary constriction/dilatation (Mays & Gamlin, 1995; Ciuffreda, 1998). The accommodative response usually follows the presentation of an accommodative stimulus in an average reaction time of approximately 0.5-second (latency 300–400 ms, duration 200–1000 ms). Under normal viewing conditions, both disparity cues and target blur drive the NFR (Toates, 1972; McLin, Schor & Kruger, 1988; Kruger *et al.*, 1997; Lee *et al.*, 1999; Stark *et al.*, 2002; Rucker & Kruger, 2004). Higher order voluntary mechanisms may also exert noteworthy influence (Richter & Franzén, 1994; Richter *et al.*, 2000).

A dual-operating mode is often assigned to the neurological control system invoked in programming and executing most of the 'every-day' type of goal-directed eye-lens accommodation responses: initial generation of a large(r) amplitude open-loop feed-forward component is usually followed by a slower, corrective closed-loop response, after the target has been approached (Imamizu *et al.*, 1995; Ciuffreda, 1998).

To date only a few PET studies have been conducted on aspects of the NFR in healthy human participants (Hasebe *et al.*, 1999; Richter *et al.*, 1998, 2000). Data concerning the cortical and cerebellar linkages to the human NFR derives, so far, mostly from studies of the functional sequel of brain lesions in neurological patients. Damage to the cerebellum is the most common finding (Milder & Reinecke, 1983; Hain & Luebke, 1990). Kawasaki *et al.* (1993) described a patient with a cerebellar lesion as having difficulties in focusing on both near and far targets. This patient had significantly increased accommodation and relaxation times in both eyes. Ohtsuka *et al.* (1993) reported on a patient with a limited haemorrhagic lesion of the right cerebellar peduncle with the ensuing absence of accommodative vergence and fusional convergence. Monteiro *et al.* (2003) described a patient who noticed difficulties in her distant vision. The MRI showed multiple lesions: left temporal lobe; frontal and parieto-occipital regions bilaterally; high signal intensity was specifically observed in the cerebellar vermis.

The present study sought to begin the identification of neural circuits relevant to NFR through measurement of neural activity in alert and healthy human volunteers as indexed by changes in regional cerebral blood flow (rCBF) with positron emission tomography (PET) and the flow radiotracer, $H_2^{15}O$. In this study, disparity cues to NFR were removed through monocular viewing. Goal-directed monocular eye-lens responses were measured to mark changes in target position along the main axis of the dominant, fixating eye. Behavioural tasks were selected to elicit differentially relevant circuits from three states: resting (with both eyes closed), sustained foveal fixation, and near/far accommodation. A naturalistic focusing task was chosen so as to minimize problems with task compliance. The task parameters employed here to study the NFR are based on an earlier study (Han *et al.*, 1995). The rCBF changes reported in this study, during the NFR, reflect a summation of the initial (open-loop) neural response with the later closed-loop nervous events, when the brain has had time to modify its response via feedback loops (Imamizu *et al.*, 1995).

Methods

Human subjects

Thirteen young, right-handed, healthy subjects with normal or normal-corrected visual acuity and right-eye dominance participated in this study after providing written informed consent according to the guidelines of the Veterans Affairs Medical Center (Minneapolis, MN, USA) Human Studies Committee and the Radioactive Drug Research Committee. Three subjects were female, and ten were male. The subjects' mean age was 25 years (range 18–46). Prior to PET scanning, subjects underwent a complete neurological examination and were administered the Edinburgh Handedness Inventory to verify right-hand dominance (Oldfield, 1971). Eye dominance was subjectively determined. Outside the scanner, subjects were asked to indicate their habitual preference in the use of the left or right eye, when only using one eye, or alternatively, if they were indifferent to which eye to use. Inside the scanner, in pre-experimental trials, subjects were requested to choose the preferred eye to use in the NFR task when the other eye was fully occluded.

Eye-movements and electro-oculography recording

Under many circumstances one cannot assume a *priori* that a single fixation point (LED) can be used to precisely position the focal point onto the target (Johnson, 1976). However, the present aim was to identify brain activity with the process of accommodation (and secondary reflex vergence), not with the degree or the precision of accommodation. To ensure that the task elicited the expected eye-movements during the NFR, one representative subject underwent detailed measurements of eye-movements in the Eye Movement Laboratory of the Department of Ophthalmology, Karolinska Institute (courtesy of Dr Han Ying). The eye-movements were recorded by an infrared system (IOTA, Sundsvall, Sweden), with goggles in which light emitting and sensing elements were placed. The dynamics of the NFR in this task, such as latency time, reaction time and maximum velocity are detailed elsewhere (Han *et al.*, 1995).

Electro-oculographic (EOG) data were also recorded from all subjects during the PET scanning session. EOG recordings were made with tin electrodes arranged in an elastic Electro-Cap (ECI, Eaton, OH, USA) according to the standard 10/20 system and were orientated on the left mastoid. Eye movements were recorded with Ag-AgCl electrodes and electro-gel (Medical Associates, St. Albans, VT, USA) and were attached to both outer canthi in line with the pupil and to the

supra- and infra-orbital ridges at the midpoint between the nasion and pupil. All electrode connections had impedances below 10 KΩ.

EOG data were digitized on-line with Quantitative Neurodiagnostics Software (Neurodata Inc., Pasadena, CA, USA) at a sampling rate of 128 Hz using a 0.3 Hz low frequency filter and a 40 Hz high frequency filter. A 50 microvolt sinusoidal 10 Hz signal was used to calibrate the differential amplifiers (Neurodata Inc., Pasadena, CA, USA) prior to each recording session. In calibration files data were stored from each subject that made horizontal and vertical eye-movements to different target angles (e.g. 2°, 4°, 6°, 8° and 10°) away from a central position. A linear regression line between the raw data output associated with the eye-movements made to each and one of the different fixation points was next established. The output from the EOG system could then be converted to visual degrees. Processing of eye-movement to the fixation points at the different target angles away from a central position indicated a spatial resolution of approximately 5°.

Task paradigm

All subjects used their dominant right eye for viewing (except in the control experiment below). The non-dominant left eye was fully occluded and closed. The accommodation-fixation point stimuli consisted of light emitting diodes (LEDs) located sagittally at 24 cm (4.16 D), 1.2 m (0.83 D), and 3.0 m (0.33 D) approximately colinearly with the visual axis of the right eye. The LEDs were vertically separated by 0.3°. Three tasks adapted from Han *et al.* (1995) were presented: (i) resting with eyes closed (eyes closed rest, ECR); (ii) continuous foveal fixation/steady-state accommodation upon the active LED at 1.2 m (0.83 D), which was active only during this condition (FIX); and (iii) focusing alternately between the near (24 cm, 4.16 D) and far (3.0 m, 0.33 D) LED, each activated during sequential 2 s epochs (NEAR/FAR, Fig. 1). Task instructions for the latter two conditions were as follows: 'Keep your eye focused on the red light.' Participants performed from one to three sets of these tasks depending on available scanner time and subject comfort. All accommodative responses occurred under light-adapted dim lighting conditions. The fixation point targets had a luminous intensity of 37 cd/m^2, while the average luminance for the surrounding space measured 1.0 cd/m^2 (Quantum Instrument Inc, Photometer LX, Garden City, NJ).

As temporary flicker/visual motion constitutes a confounding variable in the present study (see Discussion), an alternative design could have involved identical LED-stimulation in both the NEAR/FAR and the FIX conditions, respectively, while the subjects either fixated on the stationary LED (FIX) or on the alternating ones (NEAR/FAR). The sensory stimuli would thus be identical in both conditions but not the subject's task (O'Craven *et al.*, 1997). This procedure would remove the visual motion/temporal flicker confound present in the NEAR/FAR vs. FIX comparison. However, it may also, in all likelihood, lead to confounding response inhibition (Lepsien &
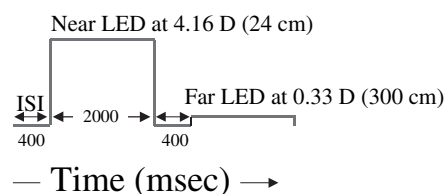
FIG. 1. A diagrammatic representation of the stimulus parameters used to study the NFR (one cycle of stimulation is shown). The two LEDs were separated by 3.83 D (2.76 m).

Pollmann, 2002) and/or unwarranted eye-movements evoked/captured by the 'extra LED(s)' (Hasebe *et al.*, 1999). The choice of naturalistic viewing parameters utilized here therefore represented a desire to mimic the task parameters employed in the Han *et al.* (1995) study and to control the oculomotor aspects of the task paradigm.

To the best extent possible, the major source of activation in the present study reflects eye-lens accommodation, and to a lesser extent, synkinetic vergence eye movements (or pupillary adjustments). However, the activity of some near-far neurons in the CNS still process both vergence and accommodation information regardless of whether or not these movements arise during normal viewing conditions, during blur-driven monocular viewing (open-loop vergence; present study), or during disparity-driven viewing (Zhang & Gamlin, 1998).

Apparent stimulus motion

Several subjects reported episodes of apparent movement (AM) of the leading LED along a straight line in depth during the NFR. While successive turning on and off of two separate stationary LEDs in the fronto-parallel plane constitute AM in its simplest (two-dimensional) form, the current three-dimensional stimulation parameters appear non-optimal at a first glance (Giaschi & Antis, 1989). Nehaus (1930), for example, reported good AM in the fronto-parallel plane between spots separated by 0.5° for inter stimulus intervals, ISIs (duration dark time or 'off-time'), of 50–250 ms. However, our LED stimulus was given an illusory movement component as cued by a change in size. The fixation point stimulus (LED) subtended 1.19° at the 24 cm viewing distance, 0.28° at 1.2 meters and 0.09° at the 3 meter distance, respectively. This circumstance may have facilitated the perception of AM because apparent looming is known to induce AM in depth (Richter *et al.*, 1994).

PET scanning

Attenuation correction used a two-dimensional transmission scan. The camera, ECAT 953B (Siemens, Knoxville, TN, USA), was used with septae retracted and with correction for electronic dead time and randoms; no decay or scatter correction was used. A slow bolus (30 s) intravenous injection of $H_2^{15}O$ [0.25 mCi or (9.2 MBcq) per kg] was initiated upon starting the task (Silbersweig *et al.*, 1993). The activity was integrated from the time the true count rate began to rise until 90 s later. The images were reconstructed using a Hanning filter (0.5 cycles/pixel) with filtered-back projection including non-orthogonal angles (Kinahan & Rogers, 1989). The final image resolution after gaussian blurring was 12 mm full-width at half-maximum. ANALYSE (BIR, Mayo, Rochester, MN, USA) was used for image display.

Data analyses

Changes in rCBF were estimated through normalized tissue activity (mean activity within the whole brain of 1000 counts). Software provided by S. Minoshima (University of Michigan, Ann Arbor, MI, USA) enabled whole-brain normalization, AC-PC estimation, coregistration, linear stereotactic standardization, and generation of Z-images for selected contrasts between task conditions (Minoshima *et al.*, 1992, 1993, 1994). For this study, the significance threshold was set at $Z = 3.2$. This threshold was selected after performing non-parametric analyses of the data using bootstrap procedures. Briefly, individual task conditions served as both minuend and subtrahend. As a reasonable compromise between Type I and Type II errors, this

threshold yields, on average, one false positive focus per image (Zald *et al.*, 1998). As the study was designed to identify differential recruitment or increases in rCBF across the sequential tasks, only positive changes are reported. For the purpose of image display in Fig. 3A–C, the threshold was set to 2.1 ($P < 0.05$ without correcting for multiple comparisons).

Cerebral dominance and eye dependence on occipital rCBF

The subject of inquiry of the control experiment was to assess the degree of asymmetry in the functional anatomy of temporal luminance perception under conditions of monocular viewing. Unevenness in blood-flow, in striate and extrastriate visual cortex, was characterized during monocular steady state accommodation/vergence and when fixation was alternated between the left and right eye. What we are mainly concerned with here is to gain a deeper understanding of the nature and the degree of lateralization in early visual processes. The current and the previous PET study (Richter *et al.*, 2000) inconclusively supported a left hemispheric functional dominance or contralaterally evoked more rCBF. This, owing to the fact that a planned comparison between the two eyes in the same individual were never made.

Consequently, eight of the current right-handed volunteers, six males and two females (mean age 24 years, range 18–32), participated in a control experiment with the following purposes; (i) to determine whether the monocularly evoked rCBF in visual cortex shows either an eye-independent hemispheric asymmetry or a temporal visual field (i.e. nasal retinal/contralateral cortical) higher evoked activity; (ii) to quantify the range of normal asymmetry in visual cortex and (iii) to explore the degree to which the hemispheric asymmetry remains stable across two different functional states. The subjects performed three tasks counterbalanced for order effects: (i) monocular left eye (LE) viewing of a black and white checkerboard at 10 Hz, or (ii) monocular right eye (RE) viewing on a monochrome black and white checkerboard flashing at 10 Hz (FLASH), and (iii) ECR. A stimulus paradigm of great simplicity was used and required no volitional response, either cognitively or motor, in an effort to activate sensory systems only. The black and white checkerboard (approximately 1 cycle/degree) subtended 10.74° and contained a central fixation cross (1.5°) to inhibit saccadic eye-movements and to disable drifts in smooth pursuit. As stimulus rate is a significant determinant of rCBF responses in visual cortex a flashing frequency of 10 Hz was chosen so as to maximize response amplitudes (Fox & Raichle, 1984). All scans occurred under light adapted dim lighting conditions. The space average luminance intensity for the surround measured 1.0 cd/m². The average luminance of the flashing checkerboard equalled 40 cd/m².

Repeated-measures, two-tailed, *t*-tests (corrected for multiple comparison) was performed on bilateral occipital individual unsubtracted activity in spherical ROIs (≈16 mm radius) centred on the Talairach coordinates: ± 17, −87, 0 including BA 18 and 19 (see Richter *et al.*, 2000). The assymetry ratios: [(right ROI/left ROI) − 1] × −1, generally were reproducible across task conditions (*rxy*: *x*; LE, *y*; ECR, 0.84, $P = 0.009$. *rxy*: *x*; RE, *y*; ECR, 0.68, $P = 0.06$. *rxy*: *x*; RE, *y*; LE, 0.90, $P = 0.002$).

Results

Eye movements

All volunteers reported that the tasks were easily performed. Several participants noted that the active LED appeared to move in space while performing the NEAR/FAR task.

Inside the scanner, the EOG demonstrated successful performance of the NFR because the occluded (closed) eye showed synchronized convergence/divergence movements with respect to the presentation time of the near-far stimuli (cf. Fig. 2B LE, below). During constant foveal fixation/steady-state accommodation on the 0.83 D LED, no large amplitude eye movements were evident in the EOG recordings; eye position was stable and task appropriate.
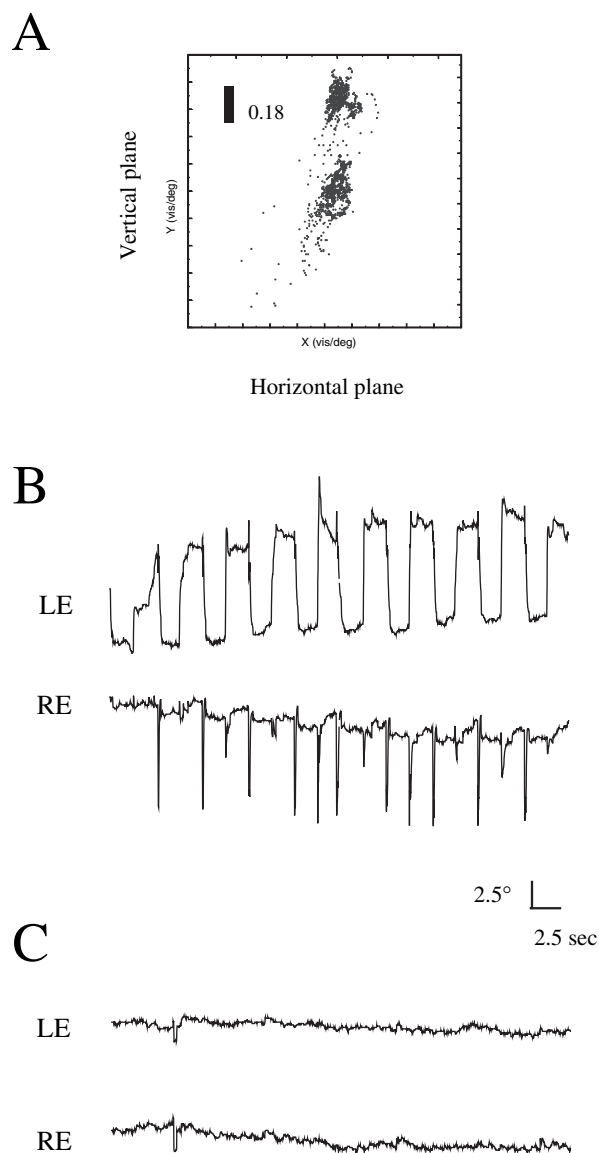

FIG. 2. Eye movements during monocular accommodation to the square-wave LED target (NEAR/FAR task) or during sustained foveal fixation to the stationary LED (FIX task) sampled at 50 Hz. (A) Eye position for right fixating eye (left eye occluded) during monocular accommodative responses to the near (4.16 D) and the far (0.33 D) LEDs (separated vertically by <0.3°). The vertical microsaccades indicate fixation-point shifts. (B) Typical accommodative/vergence step responses in left (occluded) eye (mean amplitude 9.6°; SD ± 0.71). Although most vergence in the fixating right eye is inhibited, small order conjunctional vergence movements can be observed (mean amplitude 0.71°, SD ± 0.22). The large amplitude diversions refer to eye-blinks (restricted to the right eye). Systematic eye-blinks were generally not present in any of the subjects. (C) Typical amplitudes of eye movement during the control condition that included sustained foveal fixation/steady-state accommodation upon an intermediate LED (0.83 D). RE, right eye position;. LE, left eye position. Downward movement deflection denotes eye-movement to the left. The calibration bar is the same in both B and C.

Outside the scanner, highly sensitive measurements in a typical subject using an infrared eye-tracker demonstrated, during NFR, that most eye movements in the fixating eye were inhibited during accommodation to the LED targets except for vertical microsaccades (< 0.75°) (Fig. 2A) occurring simultaneously with low-amplitude (0.25–1°) conjunctional vergence movements (Fig. 2B; RE). The occurrence of these minute eye-movements is in full agreement with earlier studies. Even if targets are correctly aligned to elicit pure accommodation, in depth microsaccades (Enright, 1986) and/or conjunctional vergence movements (Richter *et al.*, 2000) are still elicited. When the NFR is studied under naturalistic conditions it is virtually impossible to eliminate this potential confound. Momentary engagement of the saccadic eye-movement system, with largely separate anatomical and physiological substrates, during the NFR constitutes testimony to the strong linkage between these two systems under natural viewing conditions. The expected synkinetic accommodative vergence movements of the occluded eye were also demonstrated (Fig. 2B; LE). No large amplitude eye movements occurred in the control condition (Fig. 2C).

Activation in NEAR/FAR vs. FIX conditions

The principal comparison of interest involved the contrast between the conditions of near/far accommodation and of sustained foveal fixation/steady-state accommodation (i.e. NEAR/FAR minus FIX, see Table 1 (A) and Fig. 3A). This contrast shows that the NFR task recruits circuits beyond those mediating foveal fixation; a network comprised of cerebellar, occipital, and temporal regions. The cerebellum was the structure in which most of the activation arose; bilateral cerebellar hemispheres (foci 3, 4, 7, 8, 9) and vermis (focus 2). The left visual cortex (BA 17/18, focus 1) and the area at the right fusiform/inferior temporal (BA 20/37; focus 11) gyrus were activated. In addition, foci of activation occurred in the right and left middle temporal gyri (BA 21; foci 5, 10). Of note, no significant activation was observed in the prefrontal cortex.

Activation in FIX vs. ECR conditions

The contrast, FIX minus ECR (see Table 1 (B) and Fig. 3B), highlighted bilateral striate/peristriate visual cortices (foci 2, 4, 23), and a right-hemisphere dominant network encompassing the prefrontal cortex (BA 44, focus 1; BA 47, foci 5, 8, 14; BA 6, foci 20, 21; BA 11, foci 3, 15; anterior insula, foci 11, 12) and parietal cortex (BA 40, foci 6, 16). Also, the cerebellar vermis (foci 7, 9) and lateral cerebellar hemispheres (foci 10, 13, 17, 18) were activated. Subcortically, the thalamus was activated bilaterally (foci 19, 22).

Activation in NEAR/FAR vs. ECR conditions

The locations and magnitudes of the responses associated with the contrast between the conditions of NEAR/FAR and of ECR are listed in Table 1 (C) and Fig. 3C. The general pattern of results observed here reflects the respective contributions identified in the previous two contrasts (i.e. summation of NEAR/FAR minus FIX and FIX minus ECR; see above). Some regions that failed to reach the significance threshold in the above comparisons passed the threshold in this global comparison, e.g. Table 1 (C), focus 21 is subthreshold in Table 1 (A and B).

Activation in flashing checkerboard vs. ECR conditions

Stimulation with the flashing checkerboard relative to ECR resulted in ≈10% change in calcarine rCBF. The anatomical localization of the

TABLE 1. Brain regions implicated in the near/far response

Region	Talairach coordinates			Magnitude of peak activation (Z-score)
	x	*y*	*z*	
(A) Regions activated by the near/far response (NEAR/FAR minus FIX)				
1, Left visual cortex (BA 17/18)(V1/V2)	−8	−80	14	4.17
2, Cerebellar vermis*	−3	−67	−2	3.92
3, Left cerebellar cortex	−28	−69	−2	3.86
4, Right cerebellar cortex	33	−55	−20	3.86
5, Right middle temporal gyrus (BA 21)	51	−46	9	3.81
6, Cerebellar vermis (R)	8	−67	−9	3.65
7, Left cerebellar cortex	−39	−64	−18	3.56
8, Right cerebellar cortex	10	−85	−22	3.37
9, Left cerebellar cortex	−17	−64	−16	3.30
10, Left middle temporal gyrus (BA 21)	−53	8	−16	3.30
11, Right fusiform/inf. gyrus (BA 20/37)	44	−35	−14	3.22
(B) Regions activated by visual fixation (FIX minus ECR)				
1, Right inferior frontal gyrus (BA 44)	39	44	0	5.70
2, Right inferior occipital gyrus (BA 18)	28	−89	−4	5.47
3, Right middle frontal gyrus (BA 11)	30	44	−14	5.01
4, Left visual cortex (BA 17/18) (V1/V2)	−24	−91	−4	4.97
5, Right inferior frontal gyrus (BA 47)	19	30	−18	4.92
6, Right supramarginal gyrus (BA 40)	46	−51	38	4.77
7, Cerebellar vermis (R)	1	−71	−25	4.75
8, Right inferior frontal gyrus (BA 47)	21	17	−20	4.60
9, Cerebellar vermis (R)	1	−49	−27	4.23
10, Right lateral cerebellum	37	−73	−16	4.18
11, Right anterior insula	39	19	2	4.10
12, Right anterior insula	42	14	4	4.10
13, Left lateral cerebellum	−30	−71	−22	4.08
14, Right inferior frontal gyrus (BA 47)	48	35	−11	3.86
15, Left middle frontal gyrus (BA 11)	−19	30	−16	3.80
16, Left inferior parietal lobe (BA 40)	−44	−51	45	3.80
17, Left lateral cerebellum	−35	−60	−25	3.76
18, Right lateral cerebellum	44	−64	−25	3.75
19, Left thalamus	−8	−15	2	3.68
20, Left superior frontal gyrus (BA 6)	−6	19	58	3.59
21, Right precentral sulcus (BA 6)	46	1	36	3.36
22, Right thalamus	12	−8	69	3.32
23, Right extrastriate visual cortex (BA 19)	19	−69	36	3.28
(C) Regions activated by the near/far response (NEAR/FAR minus ECR)				
1, Left cerebellum	−28	−71	−22	7.29
2, Cerebellar vermis	−1	−71	−22	6.11
3, Right precentral sulcus (BA 6)	44	−1	40	5.40
4, Right lateral cerebellum	42	−62	−20	5.36
5, Right middle frontal gyrus (BA 10)	42	44	−2	4.94
6, Right insula	37	14	4	4.88
7, Right inferior frontal gyrus (BA 47)	21	17	−20	4.44
8, Left primary visual cortex (BA 17)	−21	−91	−9	4.36
9, Right supramarginal gyrus (BA 40)	55	−40	29	4.24
10, Right inferior occipital gyrus (BA 18)	26	−87	−7	4.17
11, Right thalamus	6	−13	9	4.03
12, Right middle temporal gyrus (BA 21)	57	−46	7	3.89
13, Primary visual cortex (BA 17)(V1) (L)	−3	−82	7	3.71
14, Right superior frontal gyrus (BA 11)	30	55	−14	3.63
15, Left thalamus	−6	−15	2	3.52
16, Right inferior frontal gyrus (BA 47)	17	28	−18	3.46
17, Right middle frontal gyrus (BA 11)	26	44	−16	3.40
18, Right inferior frontal gyrus (BA 47)	42	26	−16	3.40
19, Right orbitofrontal cortex (BA 11)	26	23	−18	3.39
20, Visual cortex (BA 17/18) (V1/V2) (R)	6	−89	−4	3.32
21, Inferior temporal sulcus (BA 37)	44	−60	7	3.27
22, Right middle temporal gyrus (BA 21)	51	−35	−11	3.22
23, Right medial frontal gyrus (B A6)	10	−1	56	3.21
(D) Regions activated in response to right eye monocular viewing on a flashing checkerboard (right eye stimulation minus ECR)				
1, Left striate visual cortex (BA 17/V1)	−8	−87	−2	10.52
2, Right striate visual cortex (BA 17/V1)	6	−89	−2	9.94
3, Cerebellar vermis	1	−46	−29	3.42
4, Superior colliculus	1	−5	15	3.41
5, Left lateral cerebellum	−30	−46	−29	3.13*

TABLE 1. Continued

Region	Talairach coordinates			Magnitude of peak activation (Z-score)
	x	y	z	
(E) Regions activated in response to left eye monocular viewing on a flashing checkerboard (left eye stimulation minus ECR)				
1, Left striate visual cortex (BA 17/V1)	−6	−87	−2	10.20
2, Left lateral cerebellum	−30	−69	−27	3.42
3, Cerebellar vermis	1	−46	−29	3.42

Response magnitudes and locations in coordinates of the atlas of Talairach & Tournoux (1988). Coordinates *x*, *y* and *z* (in mm) correspond, respectively, to right-left, anterior-posterior, and superior-inferior dimensions of the brain with respect to the intercommissural plane. Right, anterior, and superior sides have positive coordinates. BA refers to approximate Brodmann areas as listed in the atlas. *Focus just outside the brain.

region of peak rCBF was determined to be the left occipital lobe along the calcarine fissures regardless of which eye was used to view the flashing stimuli (Table 1, D and E). Also, the left cerebellar cortex and vermis were activated (Table 1, D and E). Inspection of surface activation images (not shown) indicated that the extent and intensity to rCBF increases were very similar across the cerebellum in both tasks. The mean unsubtracted activity condition within the bilateral spherical 16 mm ROI, centred on the occipital lobules, showed a left hemispheric dominant rCBF in all three task conditions (two-tailed *t*-test, left hemisphere vs. right hemisphere: ECR; $P < 0.05$ RE FLASH; $P = 0.03$ LE FLASH; $P < 0.01$). All participants showed consistent left hemispheric dominance in rCBF although the magnitude difference was sometimes negligible. The mean occipital asymmetry increased during processing of the retinal output from the non-dominant LE as compared to ECR (two-tailed *t*-test, asymmetry ratios LE vs. asymmetry ratios ECR; $P < 0.01$ mean: 8% increase in unsubtracted rCBF; SD 0.037; range 4–16%). The occipital asymmetry ratios resulting from viewing with the RE did, however, not differ relative to those evoked during ECR (RE vs. ECR; $P > 0.1$). There was no difference between the RE asymmetry ratios relative to those evoked by the LE ($P = 0.22$). We conclude that hemisphere and eye-dominance constitute important determinants of asymmetric rCBF in visual cortex.

Discussion

Compared with a resting state, we found that rCBF increases in the striate and extrastriate cortices, cerebellum as well as temporal cortex, during ongoing monocular accommodation between two opposing near and far visual targets. These activations, reflect sensorimotor processing along the reflex arc of the accommodative system, and therefore add to the current understanding of the brain processes underlying accommodation of the human crystalline eye-lens.

Occipital cortex involvement in NFR

The anatomical localization of the region of peak rCBF in the NEAR/FAR–FIX comparison was determined to be the occipital lobes along the calcarine fissures with a left (contralateral) hemispheric dominance. Focusing alternately between the near and far LED relative to continuous foveal fixation upon the stationary LED resulted in ≈4% change in calcarine rCBF. The increased visual activation during NEAR/FAR as compared to FIX (Table 1, A; Fig. 3A) cannot be explained so readily. Even if the subjects were completely accurate in their accommodation (an unrealistic view), no activation during NEAR/FAR over that in FIX would be expected based upon considerations of retinal contrast (Franzén *et al.*, 1994). In FIX, the visual target was always in focus. Contrast adaptation in FIX

is also an unlikely cause for this activity (see Richter *et al.*, 2000). The activation of left BA 17/18 in the contrast between the conditions of NEAR/FAR vs. FIX instead suggests that these regions may participate in computations relevant to the estimation of blur (in an even-error sense) for use in modulating NFR. A supplementary source of the striate activation may arise from feed forward gain control by eye position signals on activity of striate neurons (Trotter & Celibrini, 1999). Modulation related to cognitive 'top-down' processing during ongoing accommodation/vergence may also occur (Rockland & Van Hoesen, 1994; Somers *et al.*, 1999; Richter *et al.*, 2000). Although the present experiment did not entail switching the viewing eye (but see below) the hemisphere laterality effect seen in the current study is consistent with our previous report (Richter *et al.*, 2000).

Cerebral dominance and eye dependence on occipital blood flow during temporal luminance stimulation

The left hemisphere constituted an important determinant of asymmetric rCBF in visual cortex during ECR and across all monocular (left or right eye) stimulation conditions. This result is in full agreement with our previous findings (Richter *et al.*, 2000) where the degree of left hemisphere dominance in occipital ROIs for nine subjects during right eye monocular viewing on a checkerboard averaged 8% (range 4–11%), whereas the right dominance for the remaining four subjects averaged 4% (range 3–6%). The left hemispheric dominance observed in the current study was interestingly extraretinally modulated, as seen during ECR, and importantly also accentuated during viewing with the non-dominant (left) eye as compared to the neutral resting state (ECR). Although the accumulated findings from the present and our previous PET study lend strong support to a left occipital functional dominance in rCBF during monocular tasks the exact relationship between this asymmetry and sensory and/or motor ocular dominance still needs to be addressed in more refined studies in the future. Results obtained via alternative brain imaging technologies must also be considered (Miki *et al.*, 2001; Erdogan *et al.*, 2002; Liu *et al.*, 2002).

Cerebellar involvement in NFR

The activation of the cerebellum during NEAR/FAR, as contrasted with constant fixation, converges with previously cited human lesion data, with neurophysiologic studies in paralysed anaesthetized cat preparations (Buchtel *et al.*, 1972; Buchtel *et al.*, 1973; Hultborn *et al.*, 1973; Ijichi *et al.*, 1977; Hosoba *et al.*, 1978; Bando *et al.*, 1979; Bando *et al.*, 1984a,b; Kato *et al.*, 1987; Kato *et al.*, 1988; Bando & Toda, 1991), with studies in non-human primates (Ron & Robinson, 1973; Westheimer & Blair, 1973; Westheimer & Blair, 1974; Miles *et al.*, 1980; Judge, 1987; Gamlin & Clarke, 1995) and with human brain imaging data.
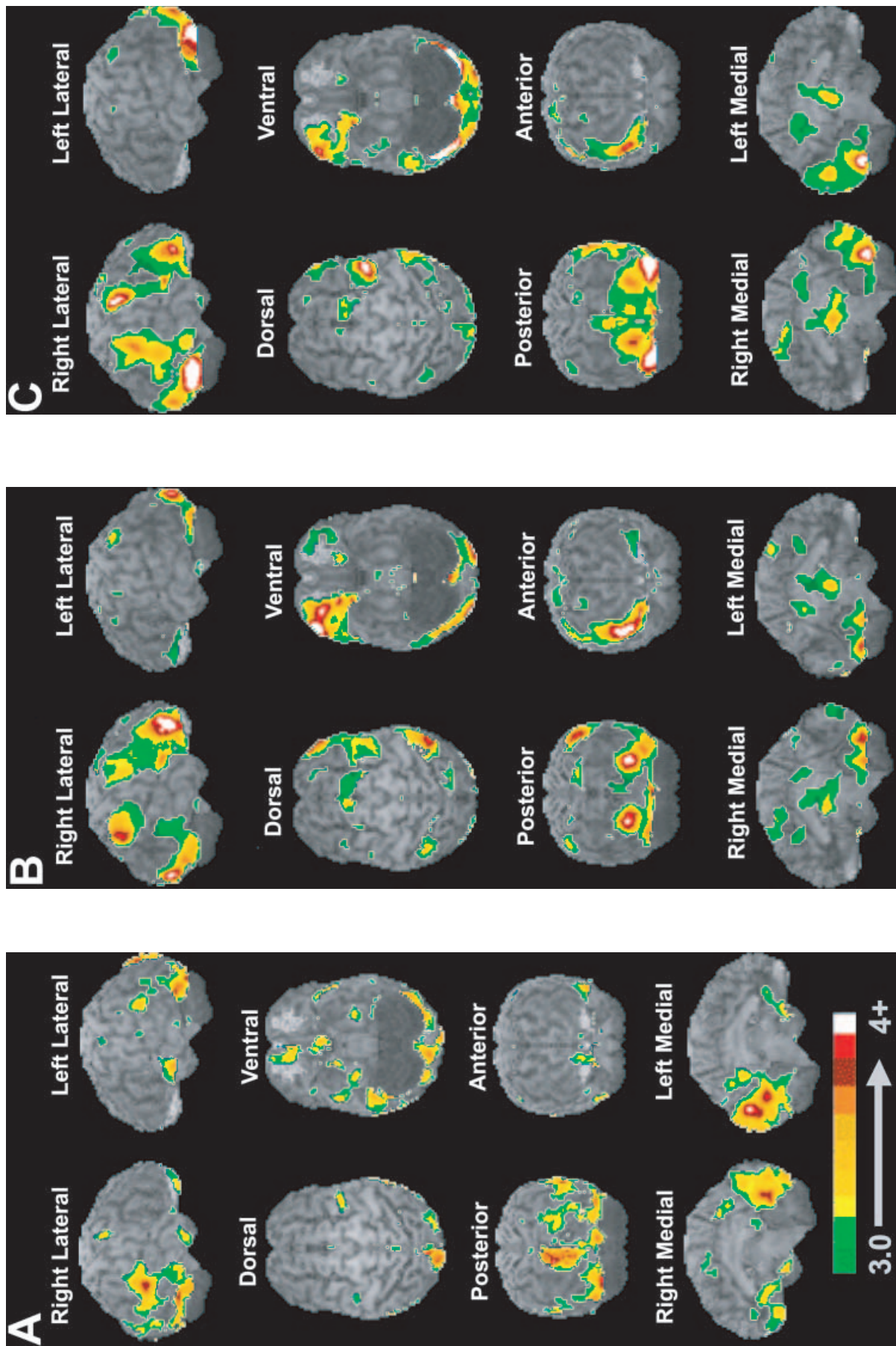
FIG. 3. *In vivo* PET visualization of cerebral activations during accommodation of the human crystalline eye-lens (projections of increased rCBF passing a threshold of $P < 0.05$, uncorrected for multiple comparisons). Regions activated by the NEAR/FAR response shown as surface rendering of activations along lateral, dorsal, ventral, posterior, frontal and medial aspects of each hemisphere. (A) NEAR/FAR minus FIX. (B) FIX minus ECR. (C) NEAR/FAR minus ECR. Response magnitudes and stereotactic coordinates for the major foci are listed in Table 1A–C.

In the present study vermis showed systematic rCBF increases in both the NEAR/FAR vs. FIX comparison and the FIX. vs. ECR comparison with two important differences. During the former contrast (invoking lens accommodation) vermis activated at more superior Talairach coordinates. In the NEAR/FAR vs. ECR comparison, inferior ('fixational') coordinates again activated (Fig. 3C). Thus, the placement of the cerebellar peak activations along the vertical dimension depended on whether the oculomotor activity was caused by fixation or lens accommodation. A corollary is that the NFR task also involved contributions from the 'fixational vermis'. The cerebellar activation observed in the NEAR/FAR vs. FIX comparison might in principle also arise from small amplitude goal-directed vertical microsaccades (Fig. 2A); particularly the hemispheric foci. Hayakawa et al. (2002) reported individual fMRI activations (leaving out the Talairach coordinates) within the bilateral cerebellar hemispheres and the vermis caused by saccadic eye-movement processing to a central target jumping horizontally 10° left/right at a frequency of 0.5 Hz. Individual activation patterns were noted specifically in the cerebellar hemispheres. However, the vermal activity observed here during NEAR/FAR replicate closely an activation foci obtained by PET imaging of voluntary activation of accommodation (Talairach coordinates x, 8; y, −67; z, −2; see Richter et al., 2000). The only other comparable PET study on the NFR did not include cerebellum due to a limited field of view (Hasebe et al., 1999). In the Richter et al. (2000) study this specific area of vermis showed activation even though the cortical systems specialized for visual search (FEF, BA 6 and left parietal lobule, BA 39/40) (Fox et al., 1985; Petit et al., 1993; Paus et al., 1995; Paus, 1996; Sweeney et al., 1996; Petit et al., 1997) disengaged and despite the fact that the cerebellar hemispheres lacked any visible activation. To summarize, it seems unlikely that the superior vermal rCBF increases observed here in the NEAR/FAR vs. FIX comparison are spurious (e.g. due to small amplitude eye-movements only). A more credible working hypothesis is that this region of the vermis is a structure uniquely involved in processing human lens accommodation/vergence (cf. Monteiro et al., 2003).

Sensorimotor processing along the reflex arc of the pupillary system is also an expected outcome of temporal luminance stimulation with the flashing checkerboard stimulus (Hultborn et al., 1973; Ijichi et al., 1977; Bando & Toda, 1991; Pong & Fuchs, 2000). Two foci that localized to the vermis in the flashing checkerboard vs. ECR comparison are of principal interest here. The exact Talairach coordinates for the magnitude of the peak activation replicated across eye (Table 1, D, foci 3 and Table 1, E, foci 3). This activity was confined to more inferior/anterior coordinates relative to the foci seen in the NEAR/FAR vs. FIX comparison.

The proposed net effect of the Purkinje, climbing-fibre, mossy-fibre, and deep-nuclei streams of diverse information reaching into and being sent back from the cerebellum is an integration of multiple internal representations with self-generated accommodative-oculomotor responses, the end result being inhibition-disinhibition of visuomotor subroutines formulated elsewhere (Cordo et al., 1997; Schmahmann, 1997; Le et al., 1998). Vermis may in this respect constitute a microzone that includes both the forward and the inverse models of motor control (Wolpert et al., 1998) reciprocally connected to the cortical areas activated in parallel during the NFR (Middleton & Strick, 1998).

Temporal lobe involvement in NFR

The activation of the right human temporal cortex during NEAR/FAR, as contrasted with constant fixation, is consistent with neurophysiologic studies in the phylogenetically translated feline (Westheimer & Blair, 1974; Bando et al., 1984a,b; Toyama et al., 1986; Bando & Toda, 1991; Sawa et al., 1992) and the non-human primate (Jampel, 1960; Watson et al., 1993; Gnadt & Mays, 1995; Bundo et al., 2000; Takemura et al., 2001; Hagen et al., 2002) as well as with PET studies in healthy human subjects.

The right hemisphere activations associated with the NFR in the present study localized to the middle temporal gyrus (BA 21) and to the fusiform/inferior gyrus (BA 20/37) (NEAR/FAR vs. FIX comparison). In the NEAR/FAR vs. ECR comparison both cortical areas continued to show activation with the following two differences. First, the activation in the inferior temporal sulcus became more confined to the Human MT (hMT/V5) area; the activation focus was displaced towards posterior and superior coordinates. Second, blood-flow within the right middle temporal gyrus (BA 21) showed increased intensity. A second foci also became discernable. Because none of these later foci surfaced in the FIX vs. ECR comparison they appear to be directly implicated in processing the NFR. A left middle temporal gyrus (BA 21) foci visible only in the NEAR/FAR vs. FIX comparison did however, not replicate in the NEAR/FAR vs. ECR comparison.

The fusiform/inferior gyrus (BA 20/37) activation reported here appear strikingly similar to the bilateral temporooccipital activity reported by Hasebe et al. (1999) in their conjunctive analysis of 'vergence movements made in response to a bar (moving virtually at a rate of 500 mm/ s) vs. fixation' comparison with 'vergence vs. ignore moving bar' comparison. The left BA 37 rCBF increase observed here was in all likelihood spurious as temporary flicker/visual motion constituted a confounding variable, as was the case in the study of Hasebe et al. (1999). The right fusiform/inferior gyrus (BA 20/37) activity seen in our study in all likelihood reflect the functional anatomy of the mental representation of AM and illusory motion processing (Giaschi & Anstis, 1989; Goebel et al., 1998; Sunaert et al., 1999; Kourtzi & Kanwisher, 2000). Such a signal may in some subjects have provided an odd-error signal of defocus and thereby helped in encoding the third dimension, in driving and/or in facilitating in the programming and posturing of the eye-lens movements (Zeki, 1974a; Nakayama, 1985; McLin et al., 1988; Takemura et al., 2001). The BA 37 activation appears adjacent and overlapping, but not identical to, the reported location of human V5 complex (Watson et al., 1993; Zeki, 1974b; Maunsell & Van Essen, 1983a,b; Zihl et al., 1983; Zeki, 1991; Watson et al., 1993; Tootell et al., 1995; Bundo et al., 2000; Hagen et al., 2002; Ffytche et al., 1995).

The activation in the vicinity of the right middle temporal gyrus (BA 21), in the present study may, in analogy to the caudal area in the lateral suprasylvian area (LS) area in the feline, be more related to motor processes (although the latter did not show the right hemisphere lateralization as in humans). The neurons here could provide efferent motor signals to control eye-lens accommodation. The right middle temporal gyrus activation (BA 21) may specifically allow translation of a disambiguated afferent (odd-error) blur signal into an appropriately scaled focusing command signal.

Frontal and parietal lobule involvement in NFR

No rCBF increases occurred in the frontal or the parietal lobule from the NEAR/FAR vs. FIX comparison (or flashing checkerboard vs. ECR). Hasebe et al. (1999) also did not report any activity in the vergence related frontal eye-field detailed recently in the non-human primate by Gamlin & Yoon (2000). Some of the frontal activation seen in the contrast fixation (FIX) minus ECR converges with previous findings of a right-hemisphere dominant system encompassing parietal and prefrontal cortices during sustained visual attention to a central

fixation mark (Pardo *et al.*, 1991). Petit *et al.* (1995; 1999) identified similar regions during foveal fixation. Their inclusion of the control state, resting with stationary eyes in the dark, revealed the additional recruitment of FEF and inferior parietal lobules, visualized here also with the control state, ECR. Studies have shown that at least part of the prefrontal and parietal circuitry in the right hemisphere mediates on-line, visuospatial (working) memory (Jonides *et al.*, 1993; Smith *et al.*, 1995). These circuits show striking homology to those identified using anatomical and electrophysiological techniques in non-human primates (Goldman-Rakic, 1987); however, the non-human primates lack the hemispheric asymmetry seen in humans.

Conclusion

Posterior brain systems mediate the NFR as driven by blur cues. When networks involved in foveal fixation and visuospatial working memory are dissected from neural circuits mediating NFR, three principal structures surface: (i) cerebellar vermis; (ii) cortices surrounding the right superior temporal sulcus and inferior temporal gyrus and (iii) extrastriate cortex.

The subcortical contribution to lens accommodation converges with an extensive body of lesion and neurophysiological literature supporting a key role for the cerebellum in the modulation of accommodation and vergence. Vermis may constitute a microzone that includes both the forward and the inverse models of motor control reciprocally connected to the cortical areas activated in parallel during the NFR. The right middle temporal gyrus activation (BA 21) could allow translation of a disambiguated blur signal into an appropriately scaled focusing command signal. The activation in the right temporal regions may reflect human homologs of the feline lateral sylvian area (LSA), which has been shown to contain accommodation units and to interact with the cerebellum. The increased blood flow to the right inferior temporal cortex (BA 37/V5 complex) probably represents the functional anatomy of the mental representation of AM of a looming stimuli or illusory motion processing. Such a signal may have provided an odd-error signal of defocus and thereby helped in encoding the third dimension, in driving and/or in facilitating the programming and posturing of the eye-lens movements. The extrastriate cortex might contribute to motion processing as well as provide computation of blur (even-error) to cue the NFR. The left hemisphere appears in this regard to be an important determinant of rCBF response in the visual cortex.

Further systematic detailed brain imaging investigations involving simultaneous *in vivo* measurements of ocular accommodation and more elaborate stimulus paradigms are crucial to understand more precisely were and how the estimate of the dioptric error is made and were the site of the sensorimotor transform for computation of a motor signal for lens accommodation is made.

Acknowledgements

Abbreviations

ECR, eyes closed rest; FIX, sustained foveal fixation upon LED; NFR, near/far response; NEAR/FAR, focusing alternately between the near and the far LED; RCBF, regional cerebral blow flow; ROI, region of interest.

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