4 **Lampropoulos CE**, Hughes GRV. The antiphospholipid (Hughes') syndrome: changing the face of neurology. *Eur J Intern Med* 2004;**15**:147–150.
5 **Dunoyer-Geindre S**, Kruithof EK, Boehlen F, *et al*. Aspirin inhibits endothelial cell activation induced by antiphospholipid antibodies. *J Thromb Haemost* 2004;**2**:1176–81.

## A third eye for the surgeon

Neurologists and engineers have developed a new camera system for surgeons, which looks where the eyes look. This innovative device uses voluntary and reflexive eye movements, which are registered in 3-D by video-oculography and then computed online, as signals to drive the camera servo motors in three planes: yaw, pitch, and roll (fig 1). Its primary objective is to allow a freely mobile user to aim the optical axis of a head mounted camera system at the target(s) at which he/she is voluntarily looking in the visual field, while the ocular reflexes stabilise any image shaking by naturally counter rolling the ''gaze in space'' of the camera during head and visual scene movements and during locomotion. The biological system of the human ocular motor control incorporates these functions, but so far, no camera system has combined free user mobility with image stabilisation and unrestricted exploration of the visual surround.

As biological and technical systems are governed by closely related physical laws, their sensorimotor control mechanisms are similar. The biological principles that have evolved over millions of years continue to serve as inspiration for new technical constructions. Here the human ocular motor system is exemplary. Visual exploration is made possible by the use of voluntary saccades when the eyes are quickly moved from one visual target to another, and voluntary smooth pursuit, when the eyes follow a moving target. The vestibulo-ocular reflex relies on inner ear sensors that signal both linear accelerations and angular head velocities to the brain. This velocity information is transformed mathematically by integration into a positional signal, which is then inverted and delivered to the eye muscles.[1 2] During head movements, the biological reflex moves the eyes in their orbits in the opposite direction to the head motion, thus ensuring a stable projection of the visual scene onto the retina. A similar mechanism becomes active when large field visual stimuli are moved in front of an observer (optokinetic reflex).

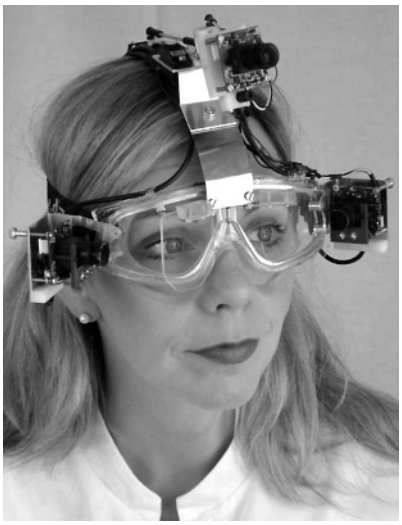

**Figure 1** The user is wearing a head mounted device equipped with video eye trackers. They consist of two laterally attached infrared video sensors and two infrared mirrors, one in front of each eye, which reflect the images of the eye to the sensors. The image information is transmitted to a video-oculography computer, which uses image processing algorithms to determine the three dimensional eye positions. The eye position is transformed into a signal for servo motors that control the optical axes of a rotatable head fixed camera system. Because the infrared mirrors of the eye movement detectors are transparent to visible light, the user's field of view is not restricted. Thus, the axis of the ''third technical eye'' is always aligned to the axes of the user's eyes. Consent was obtained for publication of this figure.

This complex ocular motor system also controls the orientation of the optical axis of the novel head mounted camera. To prevent perception of apparent motion of the visual scene (oscillopsia) during rapid eye and camera movements, an artificial saccadic suppression mechanism can be incorporated, which is triggered by saccade onset. This artificial motion suppression can be achieved by repeating (''freezing'') the last frame acquired before saccade onset for the duration of the camera saccade. Depending on the saccade amplitude, the image has to be frozen for about 100 ms.

Thus, the surgeon using this camera can move his/her head and eyes during image acquisition without having to fear image shaking artefacts, while at the same time continuously document an operation. In addition, the vergence angle of the eyes delivers valuable information for a possible autofocus functionality, as the vergence angle directly depends on the distance from the observed object.

There are numerous commercially available head referenced scene cameras combined with an eye tracker that highlights the visual target in the scene image. However, all of these systems possess a head fixed camera that does not move with the eyes. Their field of view is restricted by the optics, and therefore the visual target is not always in the range of the scene camera. In contrast, the novel system described here covers the whole explorable field of view and therefore the camera documents every eye movement of the surgeon, for example, when he/she is looking down. The image centre captured by the scene camera coincides with the surgeon's foveal fixation, assuming there is accurate calibration of eye tracker and scene camera. The current system has an accuracy of 0.45 degrees, which is well within the 2 degrees of the foveal area.

Several medical and non-medical applications are conceivable for the camera during free locomotion:

- analysis of the ocular exploratory behaviour of freely mobile test persons or patients, for example, to assess the development of gaze control from childhood to adulthood or abnormal visual exploration in psychiatric or neurological disorders,
- animal films that correlate behaviour with visual control,
- sports newscasts showing the viewpoint of the sportsman in action,
- analysis of stimuli that control gaze for advertisement purposes,
- night vision tasks in which the user enjoys mobility while preserving his field of view and continuing watching, for example, a thermal picture projected onto the half transparent infrared mirror.

### Acknowledgements

The research project in which the camera was developed was supported by a grant of the Bavarian Research Foundation and was evaluated by an international group of experts, neurophysiologists, and engineers. We are grateful to J Benson for critically reading the manuscript.

**T Brandt**
Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Germany

**S Glasauer, E Schneider**
Center for Sensorimotor Research, Department of Neurology, L-Maximilians University, Munich, Germany

Correspondence to: T Brandt, Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Germany; thomas.brandt@med.uni-muenchen.de

doi: 10.1136/jnnp.2005.073734

Consent was obtained for publication of figure 1

Competing interests: none

### References

1 **Robinson DA**. The use of control system analysis in the neurophysiology of eye movements. *Ann Rev Neurosci* 1981;**4**:463–503.
2 **Glasauer S**, Dieterich M, Brandt T. Central positional nystagmus simulated by a mathematical ocular motor model of otolith-dependent modification of Listing's plane. *J Neurophysiol* 2001;**86**:1546–54.

## Interaction between dopamine β-hydroxylase and interleukin genes increases Alzheimer's disease risk

Healy and colleagues[1] recently reported that dopamine β-hydroxylase (DBH) activity could mediate predisposition to Parkinson's disease through its role in catalysing the conversion of dopamine to noradrenaline (norepinephrine). By studying a promoter variant (−1021 C/T) in the DBH gene which has been shown to influence plasma DBH activity, they showed that homozygosity for the low DBH expressing T allele was protective against Parkinson's disease, and proposed that lower levels of DBH protein might lead to increased ratios of dopamine to noradrenaline.[1] In Alzheimer's disease, significant reductions in noradrenergic neurones within locus coeruleus, as well as reduced brain noradrenaline levels, have often been reported.[2] In addition, there is a causative link between reduced noradrenaline content and the potentiation of β-amyloid (Aβ) induced cortical inflammation.[3] We hypothesised that relative noradrenaline deficiency associated with homozygosity for the (−1021) DBH T allele might lead to increased risk for Alzheimer's disease, either through an independent effect or through interaction with the proinflammatory interleukin (IL) 1A and IL6 genes.

The study involved 266 patients with Alzheimer's disease (68% women; mean

**Table 1** Odds ratios for Alzheimer's disease risk according to interaction of dopamine β-hydroxylase (DBH) genotypes with interleukin (IL) 1A (−889) and IL6 (−174) genotypes

| Genotype | DBH (T/T) | Alzheimer | Controls | OR (95% CI) | p Value | OR (95% CI)† | p Value |
|---|---|---|---|---|---|---|---|
| IL1A (1/2+2/2) | | | | | | | |
| − | − | 134 (50.3%) | 158 (57.9%) | 1 (reference) | | 1 (reference) | |
| − | + | 10 (3.8%) | 15 (5.5%) | 0.79 (0.34 to 1.81) | 0.571 | 0.73 (0.29 to 1.83) | 0.498 |
| + | − | 112 (42.1%) | 98 (35.9%) | 1.35 (0.94 to 1.93) | 0.100 | 1.34 (0.90 to 1.99) | 0.153 |
| + | + | 10 (3.8%) | 2 (0.7%) | 5.90 (1.25 to 27.90) | 0.011 | 2.93 (0.56 to 15.25) | 0.203 |
| Total | | 266 | 273 | | | | |
| IL6 (G/G) | | | | | | | |
| − | − | 116 (47.9%) | 121 (54.3%) | 1 (reference) | | 1 (reference) | |
| − | + | 8 (3.3%) | 10 (4.5%) | 0.83 (0.32 to 2.19) | 0.713 | 0.54 (0.19 to 1.54) | 0.249 |
| + | − | 106 (43.8%) | 89 (39.9%) | 1.24 (0.85 to 1.82) | 0.263 | 1.36 (0.89 to 2.08) | 0.154 |
| + | + | 12 (5.0%) | 3 (1.3%) | 4.17 (1.13 to 15.42) | 0.020 | 5.66 (1.37 to 23.35) | 0.017 |
| Total | | 242 | 223 | | | | |

*Crude odds ratio.
†Odds ratio adjusting by age, sex, and APOE genotype (using multiple logistic regression).
CI, confidence interval; DBT (T/T) (−), dopamine β-hydroxylase C/C+C/T; IL1A (1/2+2/2) (−), interleukin 1A 1/1; IL6 (G/G) (−): interleukin 6 G/C+C/C; OR, odds ratio.

(SD) age at the time of study, 75.4 (9.1) years, range 50 to 98; mean age at onset, 71.6 (9.0) years, range 48 to 95) who met NINCDS/ADRDA criteria for probable Alzheimer's disease, and 273 controls (71% women; mean age 80.3 (7.8) years, range 63 to 100). The controls underwent a complete neurological and medical examination which showed that they were free from significant illness and had mini-mental state examination scores of 28 or more. Cases and controls were not related. The Alzheimer's disease and control samples were white and originated from a homogeneous population in a limited geographical area in northern Spain. Blood samples were taken after written informed consent had been obtained from the subjects or their representatives. The study was approved by the ethics committee of the University Hospital ''Marqués de Valdecilla''.

(−1021) DBH,[1] (−889) IL1A,[4] and (−174) IL6[5] polymorphisms were determined as described previously (we used the Taqman assay to genotype DBH, as stated in the paper by Healy *et al*[1]), and all genotypes were in Hardy–Weinberg equilibrium. Association between dichotomous variables was analysed with the odds ratio, and 95% confidence intervals were estimated by the Cornfield method or the exact method. Probability (p) values were estimated by $\chi^2$ or Fisher exact tests. Interrelations were analysed by stratification. Odds ratios for interaction of DBH with interleukins were adjusted for variables including age, sex, and APOE genotype; APOE was included as the APOE ϵ4 allele is the main recognised genetic risk factor for sporadic Alzheimer's disease, and not because it might fit a ''proinflammatory'' hypothesis.

When the risk was considered for a single polymorphism, the presence of the DBH T/T genotype was not associated with Alzheimer's disease. However, on evaluation of the interactive effects of DBH and either (−889) IL1A or (−174) IL6 polymorphisms by stratification (table 1), the subjects carrying both the DBH T/T genotype and the (−889) IL1A allele 2 (1/2 and 2/2 genotypes) or the (−174) IL6 G/G genotype had a higher risk of developing Alzheimer's disease than subjects without these risk genotypes. We chose to look only at minor allele homozygous patients for DBH and interleukin genes, because the heterozygous alleles showed no association. An additional synergistic effect of the these three loci (IL1A and IL6 in conjunction with DBH) on the risk of Alzheimer's disease could not be analysed, as stratification of the sample resulted in rather small groups.

Our findings suggest, for the first time, that DBH allelic variations interact synergistically with the IL1A and IL6 polymorphisms on the development of Alzheimer's disease. The (−889) IL1A allele 2 and (−174) IL6 G allele have a functional effect; they are associated with increased production of IL1A and IL6, respectively, and could confer increased risk for Alzheimer's disease,[4. 5] probably by inducing an increase in cytokine mediated inflammation in the Alzheimer brain. Recent data implicate a role for noradrenaline in attenuating the cortical inflammatory response to Aβ protein: in control animals, Aβ induced IL1 and IL6 expression in microglial cells, and following noradrenaline depletion by systemic treatment of animals with the selective noradrenergic neurotoxin DSP4, there was a robust increase and prolonged expression of both IL1 and IL6.[3] In the light of recent findings that inflammatory processes contribute to Alzheimer's disease pathogenesis, it is tempting to speculate that loss of noradrenaline mediated anti-inflammatory protection associated with the (−1021) DBH T/T genotype might increase the risk of Alzheimer's disease by exacerbating inflammatory events linked to IL1 and IL6 polymorphisms. Our sample size had 70% power to detect an odds ratio of 5 or greater for a risk effect of IL1A interacting with DBH, and 63% power to detect an odds ratio of 4 or greater for a risk effect of IL6 interacting with DBH. This synergistic interaction needs to be confirmed by additional studies using different sets of patients and control subjects.

## Acknowledgements

This work was supported by ''Centro de Enfermedades Neurológicas (CIEN) (C03/C06)''.

**I Mateo, J Infante, E Rodríguez, J Berciano, O Combarros**
Neurology Service, ''Marqués de Valdecilla'' University Hospital (University of Cantabria), Santander, Spain

**J Llorca**
Division of Preventive Medicine, University of Cantabria School of Medicine, Santander

Correspondence to: Dr Onofre Combarros, Neurology Service, ''Marqués de Valdecilla'' University Hospital, 39008-Santander, Spain; combarro@unican.es

doi: 10.1136/jnnp.2005.075358

Competing interests: none declared

## References

1 **Healy DG**, Abou-Sleiman PM, Ozawa T, *et al*. A functional polymorphism regulating dopamine β-hydroxylase influences against Parkinson's disease. *Ann Neurol* 2004;**55**:443–6.
2 **Lyness SA**, Zarow C, Chui HC. Neuron loss in key cholinergic and aminergic nuclei in Alzheimer disease: a meta-analysis. *Neurobiol Aging* 2003;**24**:1–23.
3 **Heneka MT**, Galea E, Gavriluyk V, *et al*. Noradrenergic depletion potentiates β-amyloid-induced cortical inflammation: implications for Alzheimer's disease. *J Neurosci* 2002;**22**:2434–42.
4 **Nicoll JAR**, Mrak RE, Graham DI, *et al*. Association of interleukin-1 gene polymorphisms in Alzheimer's disease. *Ann Neurol* 2000;**47**:365–8.
5 **Pola R**, Flex A, Gaetani E, *et al*. The −174 G/C polymorphism of the interleukin-6 gene promoter is associated with Alzheimer's disease in an Italian population. *Neuroreport* 2002;**13**:1645–7.

## Interleukin 1β –511 C/T polymorphism and risk of aneurysmal subarachnoid haemorrhage

Production of the proinflammatory cytokine interleukin 1β (IL1β) increases in several acute or chronic diseases.[1] The IL1β gene is a member of the IL1 gene family clustered on chromosome 2.[1] A C/T polymorphism in the promoter region of the IL1β gene at position −511 influences the protein production, with the highest levels in T allele carriers.[2]

Data suggest that inflammation plays a role in the pathogenesis of subarachnoid haemorrhage (SAH) from ruptured aneurysm.[3] We hypothesise that individuals genetically predisposed to an exaggerated cytokine production may be at risk of aneurysmal SAH. We studied the significance of IL1β –511 C/T polymorphism in patients with aneurysmal SAH and in healthy controls.

We included 231 unrelated patients with aneurysmal SAH, of a total of 401 patients with SAH admitted to the Institute of