gual fasciculations, and bulging eyes, were rare in German patients.

The clinical profile of the German patients bearing the Machado-Joseph disease mutation is indistinguishable from that of French families described as having spinocerebellar ataxia type 3 with a gene locus on chromosome 14q in the vicinity of the Machado-Joseph disease gene.[3] Spinocerebellar ataxia type 3 and Machado-Joseph disease were considered to be independent diseases, however, because of clinical differences. Identifying the Machado-Joseph disease mutation in German patients with the spinocerebellar ataxia type 3 phenotype provides good evidence for the hypothesis that Machado-Joseph disease and spinocerebellar ataxia type 3 are caused by alterations of the same gene.

With this initial study we show that the Machado-Joseph disease mutation is of major diagnostic importance as it is responsible for about 50% of dominant ataxias in German families although Machado-Joseph disease has not been described in Germany before.

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Oculographic findings in traumatic unconsciousness: prognostic implications

The analysis of saccadic eye movements can assist in the diagnosis and anatomical localisation of several neurological and psychiatric disorders. Spontaneous and reflexive eye movements may also be of value in the neurosurgical assessment of traumatic brain injury. Organised spontaneous eye movements require integrity of the brain stem, and some reflexive movements need reciprocal connections with visual and auditory cortical centres. Traumatic brain injury results in a graded centripetral disconnection of cortical and subcortical structures in a rostrocaudal direction.[1] Much of the mortality and morbidity associated with head injury is thought to be due to neural disconnection caused by diffuse axonal injury.[1] Taking advantage of the standing corneoretinal potential of the eye, it is relatively easy to record orbital movements electrographically with periorbital electrodes.[2] Ocular microtremor, which is due to the constant tonic input of brain stem oculomotor centres, has been correlated with the clinical state of comatose patients and related to prognosis.[3]

With informed consent from the next of kin, we prospectively studied the electro-oculograms of 60 comatose patients (47 male and 13 female; age range 1 to 80, mean 36·4 (SD 19·10) years) after severe, non-penetrating head injuries (range one to 23 days postinjury, mean 3·2 days). All patients were sedated with propofol (1·0 to 3·0 mg/kg/h) and morphine (0·02 to 0·15 mg/kg/h), and mechanically ventilated to maintain a $PaCO_2$ of about 35 mm Hg. Spontaneous and auditory reflexive eye movements were recorded electrographically from bipolar pairs of periorbital silver/silver chloride electrodes, attached to the infraorbital margins referenced to F7 and F8 (international 10/20 system of electrode placement), with a paper speed of 30 mm/s, gain of 50 μV/cm, and filter bandwidth of 0·3 to 35 Hz. The spontaneous and reflexive saccadic eye movements to speech (a greeting and the patient's first name) were assessed by visual inspection of the oculogram and graded according to abnormality. When present and conjugate the saccades were classified as "normal"; when present but dysconjugate they were classified as "asymmetric"; and no movement on the oculogram was classified as "absent". In 35 patients (58·3%) the saccades were judged to be normal, in 15 (25·0%) they were asymmetric, and in 10 (16·7%) they were absent (table). The patient's Glasgow coma scale scores were determined at the same time, and they correlated with the oculogram grading (Spearman's correlation coefficient, r_s = 0·37, P = 0·007). Patient outcome was assessed by personal interview at three months on the five point Glasgow outcome scale (table 1). Sixteen patients (26·7%) died, five (8·3%) were in the vegetative state, 17 (28·3%) were severely disabled, 14 (23·3%) were moderately disabled, and eight (13·3%) had made good recoveries. There was a good correlation between oculogram grade and outcome category at three months (r_s = 0·50, P = 0·0003). Of the ten patients without electrographic eye movements seven died, all of whom had histopathological evidence of diffuse axonal injury involving the upper brain stem; the absence of eye movement is therefore significantly associated with non-survival (χ^2 = 11·52, P = 0·001).

Oculogram grade against three month Glasgow outcome scale (GOS)

	Oculogram		
	Normal n (%)	*Asymmetric n (%)*	*Absent n (%)*
GOS:			
Dead	4 (6·7)	5 (8·3)	7 (11·7)
Vegetative state	3 (5·0)	1 (1·7)	1 (1·7)
Severely disabled	11 (18·3)	5 (8·3)	1 (1·7)
Moderately disabled	11 (18·3)	2 (3·3)	1 (1·7)
Good recovery	6 (10·0)	2 (3·3)	0 (0)

It is well known that eye movements have prognostic significance in brain injury, in particular when spontaneous and reflexive movements are absent, suggesting midbrain and brain stem dysfunction respectively.[4] Indeed the clinincal categorisation of eye movement has been used in the Innsbruck coma scale for predicting non-survival after head injury.[5] This simple electrodiagnostic test and classification allows quantification of eye movements, and may assist clinicians in the objective prediction of outcome after severe, coma producing traumatic brain injury. It is relatively easy to include the technique as part of the routine prognostic electrophysiological assessment of cerebral function, and it does not have some of the limitations or risks associated with eliciting oculocephalic and oculovestibular reflexes in patients with trauma affecting the cervical spine or tympanic membrane. The test cannot supplant clinical diagnosis, however, as in our experience its sensitivity is only 43·7% and its specificity is 93·2%, and we do not know exactly how eye movements are affected by the level of consciousness. Because spontaneous and reflexive eye movements require an intact neural circuitry, we suggest that their asymmetry or loss reflect increasingly extensive neural dysfunction or disconnection. It is possible that widespread diffuse axonal injury may provide the pathological substrate for this loss of functional integrity.

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Limbic system dysfunction in Alzheimer's disease

Positron emission tomography studies of cerebral glucose metabolism in Alzheimer's disease have shown a pattern of hypofunction in temporal, parietal, and frontal lobes

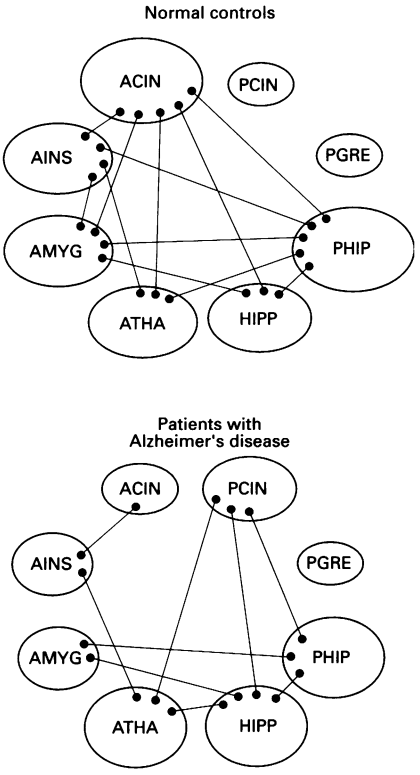
to a degree consistent with the severity of cognitive decline. By contrast, the primary sensory, motor, and visual cortices, brain stem, basal ganglia, and cerebellum seem largely spared.[1] Limbic system structures are known to be affected neuropathologically in Alzheimer's disease[2]; however, their functional state remains relatively unexplored. We therefore used PET technology (Neuro-PET camera; 6 mm resolution; fluorodeoxyglucose tracer) to evaluate 37 patients who met NINCDS-ADRDA criteria for probable Alzheimer's disease and 21 age, sex, and education matched normal controls. Metabolic values in the amygdala, hippocampus, posterior gyrus rectus, anterior insula, parahippocampal gyrus, posterior and anterior cingulum, and anterior thalamus were determined with circular regions of interest (7·8 mm diameter) and then normalised to the brain stem metabolic value, which showed no statistically significant differences between patients (mean (SD) 5·5 (0·8) mg/100 ml/min), and controls (5·5 (0·9) mg/100 ml/min). As there were no significant laterality or interaction effects, homologous structures from the two hemispheres were averaged.

Patients with Alzheimer's disease showed statistically significant hypometabolism in the amygdala (mean ratio (SD): patients 0·90 (0·12); controls 1·01 (0·10)), hippocampus (patients 0·91 (0·10); controls 1·06 (0·13)), posterior gyrus rectus (patients 1·10 (0·17); controls 1·30 (0·19)), anterior insula (patients 1·23 (0·20); controls 1·43 (0·17)), and parahippocampus (patients 0·95 (0·09); controls 1·05 (0·14)) ($P < 0·05$; analysis of variance (ANOVA) with Bonferroni correction). Decreases ranged from 10–16% below values of control subjects. Metabolism in the posterior and anterior cingulum and the anterior thalamus did not differ significantly from normal controls. Thus it seems that relative reductions in glucose metabolism in Alzheimer's disease, although widespread, are not uniform throughout the limbic system, but rather mainly affect specific regions. These regions generally correspond with those having the highest density of neuropathological abnormalities.[2]

Interregional metabolic correlations

Regions	*Normal controls*	*Patients with Alzheimer's disease*
Amygdala:		
Hippocampus	0·607*	0·598**
Anterior insula	0·610*	NS
Parahippocampus	0·549*	0·518**
Anterior cingulum	0·705**	NS
Hippocampus:		
Parahippocampus	0·836**	0·577**
Posterior cingulum	NS	0·531**
Anterior cingulum	0·744**	NS
Anterior thalamus	NS	0·430*
Anterior insula:		
Parahippocampus	0·599*	NS
Anterior cingulum	0·551*	0·798**
Anterior thalamus	0·632*	0·639**
Parahippocampus:		
Posterior cingulum	NS	0·424*
Anterior cingulum	0·740**	NS
Anterior thalamus	0·592*	NS
Posterior cingulum:		
Anterior thalamus	NS	0·476*
Anterior cingulum:		
Anterior thalamus	0·568*	NS

*$p < 0·01$; **$p < 0·001$; Pearson correlation coefficient: right and left mean; no correction for multiple comparisons.
Regions with no significant correlations are not shown.



Interregional connection patterns; ACIN = anterior cingulum; AINS = anterior insula; AMYG = amygdala; ATHA = anterior thalamus; HIPP = hippocampus; PHIP = parahippocampus; PGRE = posterior gyrus rectus; PCIN = posterior cingulate.

Functional interactions between limbic structures also seemed substantially abnormal in Alzheimer's disease. Differences between patients and controls in interregional metabolic correlations[3] (table) suggest that the anterior cingulum, which showed the greatest decrease in significant correlations to other regions in the Alzheimer's disease brain, may be decoupled from the amygdala, anterior thalamus, hippocampus, and parahippocampus (figure). In addition, the anterior insula may be disconnected from the amygdala and the parahippocampus, and the parahippocampus from the anterior thalamus. The posterior cingulum on the other hand, which did not correlate with any other region in normal controls, may have increased interactions with the anterior thalamus and hippocampal and parahippocampal formations in Alzheimer's disease, as may the hippocampus with the anterior thalamus. This altered pattern of functional interaction likely contributes to the memory impairment associated with Alzheimer's disease. Regions relatively unaffected by the degenerative processes of the disease may become dysfunctional due to selective disconnection, raising the possibility of experimental intercession with the aim of restoring function to these areas.

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Delayed ischaemia after subarachnoid haemorrhage: a role for small vessel changes

Vasospasm complicating subarachnoid haemorrhage is common and associated with morbidity and mortality. Vasospasm has, however, a variable relation with ischaemia, raising the possibility of other factors being important in disturbing blood flow.[1] We describe a patient with phosphorus magnetic resonance spectroscopy (MRS) changes of ischaemia, and decreased cerebral perfusion demonstrated by single photon emission computed tomography (SPECT), but without evidence of vasospasm with angiography or transcranial Doppler.

The patient, a 62 year old right handed woman, presented with a sudden severe headache and loss of consciousness. At admission, she was alert (Glasgow coma scale (GCS) 15/15), with meningism but no focal neurology. Computed tomography confirmed subarachnoid blood concentrated in the right sylvian fissure. On day 3, the first MRS study was performed with our normal protocol.[2] Spectra from the left hemisphere were normal. On the right side, (the side of the haemorrhage), the inorganic phosphate (Pi) peak split at a depth of 4–6 cm (figure), suggesting an area of normal pH and an acidotic region with pH 6·35.

On day 6 she deteriorated, becoming confused, (GCS 13/15). Repeat spectroscopy (figure) showed decreased phosphocreatine and adenosine triphosphate peaks in the region which had been acidotic, whereas the acidosis was resolving (pH 6·8). These are the spectroscopic changes of ischaemia progressing to infarction. Decreasing blood flow inhibits aerobic metabolism and anaerobic glycolysis with lactic acid production occurs,[3] explaining the acidosis on day 3. With further metabolic compromise, high energy phosphate compounds may no longer be maintained. With their loss, membrane ion pumps fail and cell death occurs.[3] With cell death, lactic acid production ceases, the acidosis resolving.

Also on day 6, SPECT (using 500 MBq of technetium-99m hexamethylpropylene amine oxime and an IGE-400XCT camera) was performed. The right frontal lobe was greatly underperfused (mean counts (SD)