*Table 1 Distribution of PON1 and PON2 genotypes and allele frequencies in cases and controls**

	Controls	*Neurological controls*	*Sporadic CJD*	*Variant CJD*
PON1:				
Codon 54				
Genotype				
LL	38 (40.9)	4 (40)	7 (36.8)	8 (30.8)
LM	49 (52.7)	6 (60)	12 (63.2)	18 (69.2)
MM	6 (6.4)	—	—	—
n	93	10	19	26
Allele				
L(Leu)	0.672	0.700	0.684	0.654
M(Met)	0.328	0.300	0.316	0.346
Codon 192:				
Genotype				
AA	63 (53.8)	5 (50)	10 (52.6)	14 (53.8)
AB	44 (37.6)	4 (40)	8 (42.1)	10 (38.5)
BB	10 (8.5)	1 (10)	1 (5.3)	2 (7.7)
n	117	10	19	26
Allele				
A(Gln)	0.726	0.700	0.737	0.731
B(Arg)	0.274	0.300	0.263	0.269
PON2:				
Codon 311				
Genotype				
SS	57 (60)	5 (50)	12 (63.2)	15 (57.7)
CS	33 (34.7)	4 (40)	5 (26.3)	10 (38.5)
CC	5 (5.3)	1 (10)	2 (10.5)	1 (3.8)
n	95	10	19	26
Allele				
S(Ser)	0.774	0.700	0.763	0.769
C(Cys)	0.226	0.300	0.237	0.231

Values in parentheses are percentages. All data were analysed using Pearson's χ^2 test (significance taken as $p<0.05$). There were no significant differences between the cases and controls.

0.700 and 0.300 in neurological controls. There was no significant association between any of the PON polymorphisms studied and vCJD, sporadic CJD, or the other neurological disorders (table 1). Our data show that PON polymorphic variants are not associated with vCJD. These data, together with the data of Churchill *et al*,[6] indicate that exposure to organophosphates is unlikely to contribute to the incidence of vCJD.

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Monitoring an electroencephalogram for the safe application of therapeutic repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has come to be widely used to evaluate the CNS since the first report on the use of TMS in humans by Barker *et al*[1] in 1985. Depending on the frequency, intensity, and duration of stimulation, trains of repetitive TMS (rTMS) can transiently block or inhibit the function of a cortical region.It has been suggested that rTMS has therapeutic potential for the treatment of Parkinson's disease[2 3] and psychiatric disorders.[4] To apply rTMS as a clinical tool, an evaluation of the safety margins during the stimulation is required.

A 56 year old woman was admitted to Hokkaido University Medical Hospital on 6 October 1999 for treatment of involuntary movement of the trunk and lower limbs that had persisted for 8 years. In 1991, the patient had a spinal cord injury at thoracic and lumbar levels and a shearing fracture at the level of L1/L2. At that time, neurological examination disclosed paresis of the lower limbs, and the patient underwent a posterior fixation. Involuntary movement in her left thigh began a few months after the injury. In 1997, the involuntary movement became worse and had spread from the trunk to both limbs.

Examination using a surface EMG showed that the involuntary movement consisted of an elevation of the pelvis and a flexion and rotation of the trunk via the bilateral rectus abdominis, obliquus externus abdominis, and obliquus internus abdominis. Extension of the trunk also occurred during the involuntary movement via the bilateral quadratuus lumborum and iliocostalis lumborum. In addition, an involuntary contraction of bilateral gluteus maximus muscles was seen in the hip joints. The occurrence of the involuntary movement was irregular and was not precipitated by any obvious conditions.

The patient was able to perform voluntary movement via the bilateral rectus abdominis, obliquus externus abdominis, and obliquus internus abdominis muscles, but she was not able to perform voluntary movement using the hip flexors, which are under the contral of L2, and lower level muscles. An EEG, recorded at rest, and MRI of the brain showed no significant abnormalities. In addition, the patient had no history of seizure.

Treatment was by means of drugs (clonazepam and haloperidol), transcutaneous electrical nerve stimulation of the lower intercostal nerve, which innervates the obliquus externus abdominis, and a lumbar extradural nerve block at the level of T10–12. However, these treatments had no effect on the involuntary movement.

A trial study of rTMS was designed to investigate whether it could improve the involuntary movement of the trunk and lower limbs. The study was performed using a commercially available stimulator (MagStim 200) and a round coil (13 cm in diameter) according to the following protocol: 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the right prefrontal cortex in the counterclockwise direction of the electrical current in the coil. In succession, 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the left prefrontal cortex in the clockwise direction of the electrical current in the same coil. One session consisting of these 100 stimuli was delivered once a day and was repeated for 5 consecutive days.

The motor threshold was assessed by application of a single stimulation with interstimulus interval of more than 10 seconds to the presumed motor area[5] for activation of the contralateral abductor pollicis brevis muscle.[3 4] The directions of the electrical current of motor threshold measurement and rTMS of the ipsilateral prefrontal cortex were the same. This assessment was carried out an hour earlier than the first rTMS session. Motor threshold intensity was defined as the lowest stimulation intensity that induced five motor evoked potentials (MEPs) of 0.05 mV in peak to peak amplitude in 10 trials. Motor threshold intensities of the right and left abductor pollicis brevis muscles were 55% and 52% of the maximum stimulator output, respectively.

Left and right prefrontal cortex stimulations were defined as stimulations with the same coil centred over a point 5 cm anterior to the frontal scalp position for activation of the contralateral abductor pollicis brevis muscle.[4] The patient agreed to participate in this trial before application of rTMS and gave informed consent to the study, which was approved by the local ethics committee.

During the application of rTMS, an EEG was recorded through F3, F4, C3, and C4, according to the International 10–20 system, in addition to monitoring MEPs on the bilateral obliquus externus abdominis muscles. Conventional EEGs recorded at rest before and after the rTMS trial did not show any abnormalities. Seizure was not seen during the measurement of motor threshold, although an EEG was not recorded. For the purpose of avoiding skin burn, radial notched electrodes were used while recording the EEG.

A focal slow wave (3–4 Hz) was recorded on C4 after the 4th stimulation of rTMS to the right prefrontal cortex on the first day of the trial. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave (fig 1). When rTMS to the right

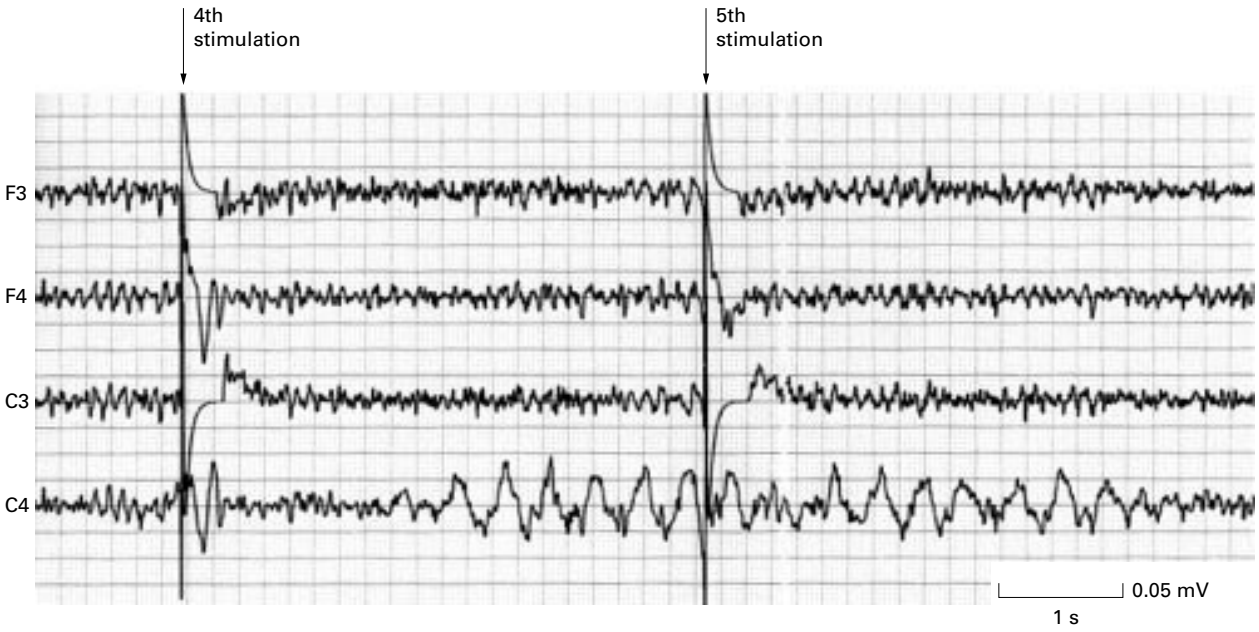

Figure 1 Change in the EEG during rTMS. After rTMS to the right prefrontal cortex had been initiated, the EEG recorded on C4 showed a slow wave. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave. This change was reproducible in rTMS performed on another day.

prefrontal cortex was restarted, a slowing wave of the EEG recurred and lasted longer after the 4th stimulation. This change did not occur during rTMS to the left prefrontal cortex. The recurring slow wave began and disappeared in the same manner.

The patient remained alert and seizure was not seen. These changes were reproducible in an rTMS trial performed on another day. We considered that these changes were induced by the application of rTMS and immediately discontinued the trial. During measurements of motor threshold and rTMS, the involuntary movement of the trunk and lower limbs continued and was unchanged. We could not assess the efficacy of rTMS for involuntary movement, because the trial study was discontinued in the middle of the protocol.

The slow wave activity was not present on the adjacent recording site. A possible explanation for our findings is that the spatial variation of the magnetic field intensity acting on the cortex may have resulted in an all or none response by the neurons. Another possibility is that neurons located in a responsive cortical region may have been more sensitive to the electric current induced by rTMS.

In the guidelines for rTMS,[6] monitoring an EEG is only a recommendation. In some case studies, the relation between seizures and EEG changes was investigated.[6 7] In most of those cases, the EEGs obtained immediately after the seizures showed slowing waves, but, they normalised within 1 or 2 days. In our case, a slow wave was seen without any accompanying clinical symptoms. However, we could not rule out the possibility of a consequent seizure if the rTMS trial had been continued in this patient. These findings suggest that further investigations of EEG changes during rTMS are required to apply rTMS safely.

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Early onset epileptic auditory and visual agnosia with spontaneous recovery associated with Tourette's syndrome

Potentially recoverable impairments of cognition, behaviour, and movement are integral to early onset epilepsies.[1] The classic epilepsy syndrome presenting as developmental regression is Landau-Kleffner syndrome, in which receptive aphasia and behavioural, cognitive, and motor impairments occur with centrotemporal discharges enhanced in sleep.[2] We report a novel biography of domain specific impairments and recovery in infantile spasms.

At 12 years of age the patient presented with Tourette's syndrome, with an extraordinary developmental history of epilepsy, regression, and recovery. He was normal until 6 months, being socially responsive, visually alert, reaching and transferring objects. Development slowed from 7 months. There was no relevant family history.

At 8 months runs of typical symmetric flexion spasms at intervals of 5–10 seconds, 3–4 times/day began. The EEG was disorganised, with bilateral very high amplitude (450 μV) activity and more left temporal area multifocal spikes and polyspikes, approaching classic hypsarrhythmia. ACTH (10 units daily and 40 units daily from 10–12 months) stopped the spasms after 2 weeks. Electroencephalography, CT, metabolic investigations, electroretinography, and visually evoked potentials were normal. CMV antibodies were present in blood, and virus in the urine.

Physical examination was normal. At 1 year an EEG showed excess of irregular slow activity without spikes. A sleep record was not performed.

One to two brief generalised seizures a week, consisting of slumping, losing consciousness and bilateral limb shaking, continued to 5 years of age. Occasional brief absences continued, were not treated, and stopped at 10.6 years. An EEG at 12 years was normal.

He lost smiling, visual following, and responsiveness at 7 months, 2 weeks before spasms were recognised. At 10.5 months development was assessed at a 7 month level. Development remained very slow to 3–3.5 years. At 3 years he could not understand speech or visually recognise his mother and performance skills were poor—for example, he could not thread beads. Cognition was assessed at less than half his chronological age, indicating educational needs as a child with severe learning difficulties. At 3.5 years speech understanding appeared, and by 4.5 years he was using a lot of speech. His family felt that "their child had returned".

On the Portage scale at 2.5 years of age, the raw scores and age level were socialisation 38: 1–2 years; language 7: 0–1 years: self help 24: 1–2 years; cognitive 18: 1–2 years; motor 68: 2–3 years. Non-motor skills were below 2 years with severe language retardation.

A Griffiths assessment at 3.10 years showed significant recovery: hearing and speech 3.8 years; performance 3.6 years;