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1. *In-vitro* predictors of severe hypersensitivity to aromatic anti-epileptic drugs—Amjad BaniHani¹, Manuela Neuman², Alexandra Stefanel³, Paul A. Hwang⁴ (¹Department of Neurology, RMS, Amman, Jordan, ²In Vitro Drug Safety and Biotechnology and Department of Pharmacology & Toxicology, University of Toronto, ³Faculty of Pharmacy, University of Toulouse, ⁴NYGH&UTERP, University of Toronto, ON, Canada)

Objective: To study lymphocyte toxicity assay (LTA) and HLA-B*1502 haplotype as predictors to severe hypersensitivity reactions (HSRs) to aromatic anti-epileptic drugs (AEDs).

Materials and methods: An ongoing prospective cohort study of patients that had severe HSRs to aAEDs is performed. A total of 20 patients were enrolled in this study. Sixteen (80%) suffered from hypersensitivity to AEDs. Four (20%) patients who tolerated the drugs were selected as controls. HLA-B*1502 genotyping and *in-vitro* LTA were performed against different aAEDs including carbamazepine, phenytoin, phenobarbital and lamotrigine.

Results: LTA was positive to the incriminated drug in 75% ($n = 12$) of the HSR ($n = 16$) patients, while all the controls had negative *in-vitro* results. Only in Chinese subjects of Han origin ($n = 6$) was the HLA-B*1502 haplotype predictive of enhanced risk of severe HSRs to these AEDs, including severe cutaneous reactions such as Steven-Johnson syndrome and toxic epidermal. The non-Chinese were HLA-B*1502 negative ($n = 6$).

Conclusion: This study showed that the LTA provides a strong prospective *in-vitro* predictor for HSRs toward aAEDs. It is possible using this test to avoid exposing patients to the high risk of hypersensitivity against these drugs. Moreover the patients can be safely changed to a tolerated alternative AED. The HLA-B*1502 is unlikely to be associated with AED-related HSRs except in Han Chinese population. Further investigations are required using a larger sample size of subjects at risk as well as controls.

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2. Immunologic testing of anti-epileptic-induced hypersensitivity syndrome—Marco Trepanier¹, Neil H. Shear², Izabella Mal-kiewicz¹, Manuela G. Neuman¹ (¹In Vitro Drug Safety and Bio-

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Background: Hypersensitivity syndrome reaction (HSR) is a severe idiosyncratic reaction that is a major concern in clinical practice. We previously validated a Lymphocyte Toxicity Assay (LTA) to reflect the severity of lesions in anti-convulsant-HSR.

Objectives: Objectives were to evaluate the utility of cytokine analysis as an ancillary diagnostic tool and compare it with the LTA in anti-epileptic-HSR.

Method: Sixteen patients with a documented anti-epileptic-HSR and with a positive LTA to each of carbamazepine (C), phenytoin (P), and lamotrigine (L) and 16 controls, tolerating the drug and having LTA-negative underwent cytokine testing. Serum cytokines (ELISA) are given (TNF- α , IL-6 pg/mL and Fas ng/mL) as mean \pm SE. Differences among samples in time in the same group were determined using analysis of variance.

Results: Among the 16 patient tested, 4 patients (25%) show an interaction between C and P. One patient with a C-HSR had a positive test to C as well as with PH. LTA test showed a 99% sensitivity and 98% specificity with a positive predictive value of 89%. LTA performed at the initial presentation was correlated with the LTA performed in the same individual 2–3 years later when the patch test was performed. TNF α (133 ± 3) were significantly higher in LTA positive than LTA-negative (40 ± 6) ($p < 0.001$). Baseline Fas levels were lower in LTAs negative (2.3 ± 0.2) than LTAs positive (5.4 ± 0.4) ($p < 0.05$). IL 6 was not significantly different.

Conclusion: LTA is a sensitive diagnostic marker in patients with anti-epileptic-HSR. Cytokine environment may play a role in anti-epileptic-HSR.

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3. The importance of febrile seizure length in the development of spontaneous seizures and hippocampal atrophy in the abnormal rodent brain—Steve A. Gibbs, Rose-Marie Rébillard, Sébastien Desgent, Maxime Lévesque, Lionel Carmant)

Rationale: Retrospective studies strongly identify prolonged febrile seizures as a risk factor for mesial temporal lobe epilepsy, a syndrome in which some patients also exhibit subtle malformations of cortical development (dual pathology). In the rat model of hyperthermic seizure (HS), an underlying cortical malformation induces a longer HS that hinders brain development and generates spontaneous recurrent seizures (SRS). This study aimed to clarify the role of HS length in the abnormal rodent brain in the development of SRS and chronic hippocampal atrophy.

Methods: Following a right fronto-parietal freeze lesion at post-natal day (P) 1 and an HS at P10, video-EEGs were intermittently recorded in the right amygdala of 16 rats over a period of 120 days (P50–P170). In a subset of rats, we halted the HS by administering diazepam. To localize the seizure onset, local field potentials were recorded in the right amygdala, hippocampus and frontal cortex in a separate group of rats. Lastly, hippocampal volume estimations were carried out at P80.

Results: Only lesioned pups with hyperthermic seizure (LHS) developed SRS (4/4 rats). The earliest recorded seizures were at P135 and recorded seizures had a mean duration of 21.73 ± 8.72 s. The seizure onset was characterized by high-amplitude low-frequency epileptiform spikes (2–3 Hz) preceded by a short period of highly rhythmic activity (7 Hz) in the hippocampus, confirming the suspected focal limbic origin. None (0/6 rats) of the lesioned pups whose HS was stopped with diazepam (LHSD) developed SRS. Hippocampal volumes of LHS pups were significantly asymmetric when compared to LHSD rats and non-lesioned control rats. Regional volume analysis showed that hippocampal volume loss was maximal in the CA1 and CA3 regions.

Conclusion: Our findings highlight the importance of HS length, at least in the abnormal brain, for chronic hippocampal injury and limbic epilepsy. Furthermore, they stress the importance of better understanding the process of epileptogenesis following a prolonged febrile seizure.

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4. Does epilepsy due to TBI increase the risk for substance abuse?—M.G. Sumner¹, R.N. Janet Shaw², Paul Hwang³ (¹ Consultant Neuropsychiatrist, UK, ² EEG Lab, HSC and North York, Canada, ³ UTERP, U of Toronto ON, Canada)

Objective: To determine substance abuse in people who have epilepsy with and without traumatic brain injury (TBI).

Material and methods: Epilepsy is a generalized brain disease often producing dysfunction in multiple arenas. This dysfunction is evident in people with epilepsy who often have comorbidities, ADD, learning disabilities and other neuropsychiatric disorders which are risk factors for substance abuse. TBI is a risk factor both for epilepsy and for substance abuse. People with damaged brains may have a higher burden of medical problems including substance abuse. Medications that are used to treat symptoms of ADD and chronic pain, which are often present in this patient population, are often both necessary, but maybe subject to abuse. The literature of behavioral problems and substance abuse in this patient population is reviewed.

Results: This issue was discussed using two patients who have had traumatic brain injuries, both with chronic pain, who are likely to have cryptogenic seizures, and one was labeled as having a problem with substance abuse.

Conclusion: The anatomical substrate underlying substance abuse is not fully understood but may involve dopamine and/or 5-HT systems. It is likely that many persons with epilepsy have problems with substance abuse or are at higher risk, but this is not

proven. Additionally many medications used to treat these patients can be lead to dependency and possibly to abuse.

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5. Cognitive impairment caused by cortical dysplasia in rats with early life seizures—Marcella M. Lucas¹, Pierre-Pascal J. Lenck-Santini¹, Qian Zhao¹, Forest Miller¹, Gregory L. Holmes¹, Rod C. Scott^{1,2} (¹ Department of Neurology, Dartmouth Medical School, Lebanon, New Hampshire, USA, ² UCL, Institute of Child Health, London, United Kingdom)

Rationale: Malformations of cortical development (MCD) are a common cause of epilepsy and cognitive impairment in children. Methylazoxymethanol acetate (MAM) causes MCDs of differing severity in rats when injected into the pregnant Dam at gestation days 15 (E15) and 17 (E17). Environmental enrichment (EE) has been shown to improve cognition and learning in normal rats. We have shown that EE for long periods post-weaning improves spatial cognition in rats with MCDs that have not been exposed to seizures. It is unclear whether short-term, pre-weaning EE improves cognition. Here we investigated the potential effect of EE and early life flurothyl seizures on the cognitive impairment associated with MCDs in developing rats.

Methods: Pregnant female rats were injected with saline or 20 mg/kg MAM, a DNA methylating agent, at E15 or E17 to vary the severity of the cortical malformations. From P0 to P9, half the pups received a total of 50 flurothyl induced seizures. From P10 to P21 half of the pups in each group were placed in an environmental enrichment set-up, containing a running wheel and various tubes and toys, for 4 h/day. All rats underwent testing in the Morris water maze to test spatial memory during development at P25 or during early adulthood at P45 ($n = 4-8$ per subgroup). At the completion of the experiment, the rat brains were harvested and histologically assessed for number of heterotopias and brain weights.

Results: Rats treated with MAM during gestation show significantly higher latency to platform in the Morris water maze (40.85 ± 2.68 and 44.96 ± 2.80 s for E15 and E17, respectively) compared to controls (22.53 ± 1.68 s, $p < 0.001$). Brain weights showed significant differences ($p < 0.001$) with E15 brains weighing 1.00 ± 0.030 g, E17 weighing 1.27 ± 0.028 g, and controls weighing 1.47 ± 0.030 g. Long term, post-weaning EE showed an improvement in spatial cognition in rats with MCDs, suggesting EE may be a powerful adjunct to therapy for children with MCDs and epilepsy. However, short-term, pre-weaning EE showed little effect on spatial cognition. There does appear to be an additional detrimental effect of seizures in immature but not in mature animals.

Conclusions: From this study, it can be concluded that cortical malformations impair spatial cognition. The adverse effect of seizures is primarily in the developing brain, and cognition appears to normalize with aging. Thus, seizures may slow normal developmental processes rather than cause permanent disruptions. Therefore, mature individuals with epilepsy and cortical dysplasias may have impaired cognition mainly due to the brain malformation, rather than the seizures per se.

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6. Value of overnight EEG monitoring in the ICU—Omar I. Khan, Justin Montanye, Christina J. Azevedo, Juan C. Gonzalez, Syed T. Arshad, Mark A. Natola, Stephen D. Surgenor, Richard P. Morse, Richard E. Nordgren, Gregory L. Holmes, Barbara C. Jobst, Vijay M. Thadani)

Rationale: During critical illness, the threshold for clinical and subclinical seizures is lowered. Several studies have shown that subclinical seizures and status epilepticus are common in the ICU (10–20% of patients), and not detected with a standard 30-min EEG. It is unclear whether ICU patients should receive continuous EEG monitoring, and whether this has an impact on clinical decision-making and outcome. We addressed these questions by doing 24-h video-EEG monitoring on ICU patients who would normally have received only a 30-min study.

Methods: During a prospective 2-year study, ICU patients, for whom medical staff requested a standard 30-min EEG at any point during their ICU stay, instead got 16–24 h of continuous video-EEG. Patients who initially needed long-term EEG monitoring were excluded from this study. Some patients were excluded for logistical reasons and received only a 30-min EEG. ICU nurses were asked to press the alarm button for clinical seizures, and all video-EEG data were reviewed by an epilepsy specialist. Abnormalities were noted and categorized. Hospital charts were reviewed for treatment decisions and outcomes.

Results: Altogether, 175 ICU patients got EEGs. Of these, 67 from the outset needed and received continuous video-EEG monitoring. Thirty one, for logistical reasons, had only a 30-min routine EEG. The remaining 77 patients, who were in the study, had continuous video-EEG for 16–24 h. In a few, this was continued for longer. All EEGs, except one, were abnormal. Non-epileptic abnormalities included generalized slowing (76), burst-suppression (4), triphasic waves (1).

Seventeen patients showed epileptiform EEG activity. Ten had structural pathology such as hemorrhage or tumor, 5 had suffered cardiac arrest, 2 had metabolic derangements. The most common finding was bilateral or lateralized periodic epileptiform discharges (BiPEDs or PLEDs) in 11 patients. Other abnormalities were myoclonus with generalized EEG discharges (2), subclinical generalized seizures (1), focal motor seizures (3).

Nine patients showed epileptiform activity in the first 30 min, of whom 1 had a clinical seizure. In 8 patients the epileptiform activity evolved overnight, with 5 patients showing definite seizure activity (1 electrographic, 4 clinical). No patient had non-convulsive status epilepticus. Thirty nine patients died. 38 went to a residential facility. Six patients with seizures were treated, and 4 were discharged.

Conclusion: This study suggests that in an unselected ICU population, overnight EEG monitoring, compared to a standard 30-min EEG, adds only a little information, and has little effect on treatment or outcome. Additional epileptiform abnormalities were detected in only 8 out of 77 patients, and only 1 of those had clinically undetectable seizures. 5 out of 6 patients with seizures were treated on clinical grounds. The benefit of treating purely electrographic abnormalities is unproven. Although prolonged monitoring for >24 h might lead to a different conclusion, we believe that routine long-term EEG monitoring of all ICU patients is not warranted.

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7. The effects of neonatal seizures on learning, memory, and behavioral flexibility in adult rats—Edie X. Wu¹, Jonathan K. Kleen¹, Alexandre Sesqué², Rod C. Scott^{1,3}, Pierre-Pascal Lenck-Santini¹, Gregory L. Holmes¹ (¹Neuroscience Center at Dartmouth, Dartmouth Medical School, Hanover, New Hampshire,

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Neonates are particularly vulnerable to seizures, which can impair neurodevelopment and carry cognitive and behavioral consequences later in life. On a molecular level, neonatal seizures (NS) reduce cellular proliferation, differentiation, and migration; alter myelination; and affect the formation and stabilization of synapses. Prior research suggests that even a single neonatal seizure can produce these consequences. We hypothesize that these abnormal cellular and network changes can alter learning and memory processes later in life, and that these changes correspond to alterations in electrophysiological oscillation activity in the brain. We induced 100 flurothyl seizures in seven rats from days P15 until P29 (NS rats), while seven control rats experienced no flurothyl seizures. Later in adulthood, 5 control and 4 NS rats were trained in an operant behavior paradigm called delayed-nonmatch-to-sample (DNMS), a short-term memory task involving temporal delays which relies upon intact hippocampal function for accurate performance. Local field potentials were recorded *in vivo* during all training sessions via depth electrodes in three areas: the CA3 and CA1 areas of the hippocampus, and the prefrontal cortex (PFC). Learning curves revealed that control and NS rats performed comparably during the preliminary consecutive training steps of the task. However, NS rats showed impairments during the initial hippocampal-dependent stage of learning ($p < 0.05$, $F = 4.33$; repeated measures ANOVA). Later, impairments among trials with protracted delays indicated general cognitive impairment in NS rats, in addition to hippocampal-related learning deficits. In a separate pilot experiment, 2 control and 3 NS rats were trained in a behavioral flexibility task associated with PFC function. In brief, the rats were required to continuously switch between levers to maximize the number of rewards obtained, requiring a form of PFC-mediated strategy switching. Control rats performed 17.9 ± 3.6 lever switches in an hour-long session on average compared 11.9 ± 1.5 switches among NS rats ($p = 0.06$; Student's *t*-test), and took 34.6 ± 4.5 min to perform the first 10 switches compared to 42.3 ± 4.5 min among NS rats ($p = 0.13$; Student's *t*-test). These results imply that individuals with a history of NS may experience difficulty with cognitive abilities involving hippocampal- and PFC-dependent function, including impairments with learning and memory as well as behavioral flexibility. We plan to examine the corroboration of performance-related electrophysiological oscillation patterns with respect to task performance between control and NS rats to evaluate faulty brain rhythms as a potential mechanism for cognitive impairment in adulthood following NS.

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8. N complexes: An under-recognized normal EEG variant needing to be distinguished from generalized spike-waves—C. Deacon, A. Guillemette, J. Reiher (Service de Neurologie, Centre Hospitalier Universitaire de Sherbrooke, Canada)

Background: N complexes were described by Reiher and Carmant (1991). They are considered normal EEG variants and are associated with 14 and 6 per second positive spikes. In our opinion, they

may be easily mistaken for generalized spike-waves. A comparative study was undertaken.

Method: Two groups of EEGs from our EEG database were compared: N complexes and generalized spike-waves. N complexes were identified from EEGs done between February 2004 and January 2009. Age matched EEGs containing generalized spike-waves were randomly selected for comparison. All EEGs from both groups were blindly categorized by Dr. Jean Reiher has containing N complexes or generalized spike-waves. Several electrographic features were then assessed in the two groups.

Results: We identified 21 EEGs containing 63 N complexes, and selected 18 EEGs containing 52 generalized spike-waves. Features favouring N complexes over generalized spike-wave were: 14–6 Hz positive spikes preceding the complex (86% vs. 0%), multiple successive phase reversals of the slow wave on bipolar montage (66% vs. 10%), and oscillating amplitude of the slow wave in successive electrodes on referential montage (48% vs. 10%) while a frontal maximum amplitude of the negative spike favoured generalized spike-waves (52% vs. 5%). Exclusive occurrence during light sleep and drowsiness was also typical of N complexes.

Conclusion: In this study, several electroencephalographic features were identified to recognize N complexes and avoid misdiagnosis of generalized spike-waves. In our study, close association with 14 and 6 per second positive spikes was the most useful discriminating feature.

Reference

Reiher J, Carmant L. Clinical correlates and electroencephalographic characteristics of two additional patterns related to 14 and 6 per second positive spikes. *Can J Neurol Sci* 1991;18:488–91.

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9. Anti-convulsant doses of 5-alpha-dihydroprogesterone: Behavioural toxicity results and possible mechanisms of action—M. Jeffrey, D. Lonsdale, W.M. Burnham (Department of Pharmacology, University of Toronto, Canada)

The effects of the hormones on seizures have been recognized for decades. One third of all women with epilepsy experience catamenial seizure exacerbation, an increased risk of seizures when plasma progesterone levels are low, or the ratio of estradiol to progesterone is high. One of the most common seizure types is the complex partial seizure, which may secondarily generalize to a convulsive seizure. These seizures are notoriously refractive to conventional pharmacological treatments and remain a significant challenge in seizure therapy today.

A primary metabolite of progesterone, 5-alpha-dihydroprogesterone (5αDHP), was recently discovered by our laboratory to be the first compound to suppress the complex partial seizure focus at non-toxic doses in over 25 years:

Progesterone and allopregnanolone both confer seizure protection by activating GABA_A channels, which accounts for their highly sedative side effects. A different mechanism of anti-convulsant action is implicated for 5αDHP since it is the only compound to suppress the seizure focus, has a rapid onset of action, and subjects exhibit no ataxia or sedation. The discovery of 5αDHP's ability to control complex seizures so effectively at *non-sedating doses* deserves further research.

Behavioural studies of male and female rats have tested behavioural toxicity of anti-convulsant doses of 5αDHP and allopregnanolone. Compounds were administered intraperitoneally (ip) at doses that had produced anticonvulsant effects in earlier studies. The presenter will introduce behavioural and pharmacological models and present results of the Elevated Plus Maze, a model of anxiety, the Morris Water Maze, a model of learning and memory, and the Forced Swim Test, a model of depression. Possible mechanisms of 5αDHP's anti-convulsant action will also be discussed.

5αDHP may control complex partial seizures. Future biomolecular experiments will produce data to elucidate the compound's novel mechanism of action. It is hoped that this body of animal work will improve our understanding of neurosteroid effects in epilepsy. It is also hoped that a better understanding of neurosteroids in epilepsy will lead to a better understanding of the pathophysiology of seizures.

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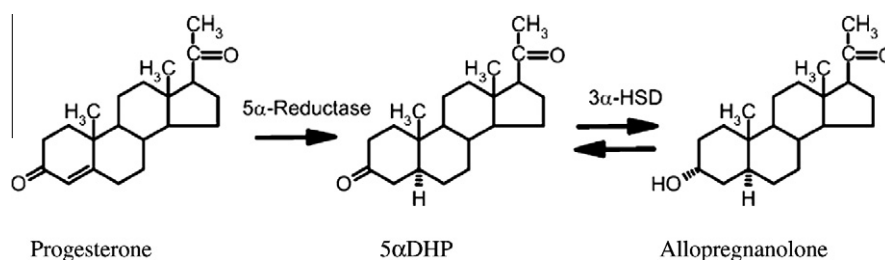
10. Musicogenic epilepsy with independent bilateral temporal seizures—Dina Amrom^{1,5}, Francesca Pittau^{2,5}, Benjamin Zifkin⁴, Francois Dubeau^{3,4,5}, Martin Veilleux^{3,4,5}, Michael Doherty⁸, Eva Andermann^{1,5,6}, Frederick Andermann^{3,4,5,7} (¹Neurogenetics Unit, ²EEG unit, ³Epilepsy Service, ⁴Seizure Clinic, Montreal Neurological Hospital and Institute, ⁵Department of Neurology & Neurosurgery, ⁶Human Genetics, ⁷Pediatrics, McGill University, ⁸Epilepsy Service and Seizure Clinic, Swedish Epilepsy Center, Seattle, WA, USA)

Rationale: A recent review of musicogenic epilepsy by Tinuper et al. included 110 patients studied since 1984. Most had unilateral epileptic discharges, with an overwhelming preponderance in the non-dominant hemisphere; only 3 had bitemporal discharges.

We present four female patients with musicogenic epilepsy who had bilateral temporal interictal discharges and seizure onsets. In these four patients, surgical treatment was not considered possible as they had no atrophy and no convincing lateralization. This conundrum is the reason for the presentation.

Methods: Review of medical records and investigations of four patients.

Results: Patient 1, a 52-year-old woman, has had temporal lobe seizures since the age of 8 years. Some of her attacks, those with an aura déjà vu, were precipitated by music and by a voice with emotional significance. She had normal hippocampal volumes. Stereotactic EEG recorded temporal seizures with onset mostly from



the right side but also independently from the left. It was not possible to decide whether musicogenic attacks originated on one side or both. Medication was not sufficiently effective.

Patient 2, a 51-year-old woman, had her first temporal seizure 3 months after hysterectomy. Attacks recurred cyclically once a month. Almost all were provoked by listening to certain types of music or to the news. Videotelemetry recorded two seizures originating from the left temporal region while listening to TV, and two from the right while listening to music. Brain MRI, hippocampal volumes and curvilinear reconstruction were normal. Medical treatment was unsatisfactory.

Patient 3, a 31-year-old woman, had onset at the age of 23 years of symptoms that were later identified as episodes of *déjà vu*. At the age of 24 years, she had a single generalized tonic–clonic seizure during sleep. Since then, she has *déjà vu* auras recurring once a week or in bursts of about 5 a day. These may be followed by loss of contact, oral automatisms and eventually by an atonic fall. Although these attacks first occurred spontaneously, they progressively, over a course of 6 years, were triggered by complex musical pieces like jazz and voices, rhythmic percussion or techno, or simply by voices. In response to medical treatment she still had one attack/month, but more recently has been seizure free when avoiding these triggers. EEG telemetry recorded bitemporal foci. The brain MRI was normal.

Patient 4, a 38-year-old woman, has had temporal lobe seizures since the age of 19. Some of her attacks, those starting with an unsafe feeling, a *déjà vu* aura and a rising epigastric sensation, were characteristically triggered by music, especially Johnny Cash's song Ring of Fire. The patient also had complex partial seizures with lip smacking, fumbling automatisms and inability to respond, as well as convulsive seizures. The first videotelemetry showed left-sided onset of four seizures, and one simple partial seizure from the right. One year later, intracranial monitoring showed bilateral onset of seizures. MRI scans showed subtle loss in internal architecture and increased T2 signal in the left hippocampus. An ictal SPECT scan, performed with injection immediately after onset of a seizure, showed abnormal tracer increase in the right temporal lobe. The seizures were intractable to medication.

Conclusion: Unlike the great majority of patients with musicogenic epilepsy described in the recent review, these four women had seizures arising independently from both temporal lobes. Their seizures were not exclusively triggered by identifiable musical or other auditory stimuli. Reliable distinction between reflex versus spontaneous seizures was not possible. Despite the intractability of the seizures, surgical treatment was not considered appropriate in these four patients with no atrophy of mesial temporal structures nor obvious neocortical changes.

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11. Psychosurgery: A lesson from history—J. Wark (Pediatric Neurology, Cooper University Hospital, New Jersey, USA)

Psychosurgery has a bad reputation. The odour of quackery dates from the fifties. Finding that he could tranquilize difficult patients by scrambling their frontal lobes, the ice-pick neurologist ran outpatient clinics in which he would, without anaesthesia or sterile technique, ameliorate the lot of asylum keepers all over America by lobotomizing as many as a hundred patients in a session. His efforts also extended to children who upset their step-mothers or frightened the neighbours' cat. A stark tale, from a cruel era before the arrival of neuroleptics.

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12. Human hippocampal theta oscillations show performance-dependent phase-locking during a working memory task—Jonathan Kleen, Barbara Jobst, Kandan Kulandaivel, Terrance Darcey, Gregory Holmes, Krzysztof Bujarski, Vijay Thadani, Pierre-Pascal Lenck-Santini (Dartmouth Medical School, Hanover, NH, USA)

Rationale: Depth electrodes implanted for pre-surgical monitoring can provide remarkable insight into the electrophysiological oscillation patterns of deep brain areas, since many of these structures cannot be reliably recorded using conventional scalp or subdural electrodes. These measurements can shed new light on mechanisms of cognitive processing, particularly in the hippocampus due to its heavy involvement in learning and memory. In addition, numerous transient epileptiform abnormalities occur in the hippocampus of patients with temporal lobe epilepsy, which may potentially disrupt cognitive processes via interference with normal functional brain rhythms.

Method: We analyzed the hippocampal oscillatory activity of 2 patients implanted with depth electrodes for medically refractory temporal lobe epilepsy, while they performed the Sternberg task of working memory. Both patients had bilateral depth electrodes oriented occipito-temporally, including 5–6 linear recording sites within each hippocampus. During the task, a combination of four random letters was shown to the patient (encoding), followed by a 5-s delay, and a subsequent presentation of a single letter (retrieval). The patient then had to decide whether the single letter was in the previous sequence and respond yes or no via computer mouse clicks. EEG signals from 600 of these trials between two patients were time-locked to these events via pulses sent by the computer that ran the memory task, to determine whether the phase of theta oscillations (4–8 Hz) could be reset relative to these events. Hippocampal theta phase was calculated using the Hilbert transform on the theta-filtered EEG, and analyzed using the Rayleigh test for circular data.

Results: Theta oscillations were differentially phase-locked (i.e. the cycle of theta was reset) relative to the encoding and retrieval components of the task, for multiple subsequent cycles (approximately 1 s; $p < 1^{-10}$). Limited phase-locking was exhibited among lure trials, in which information did not need to be retained by the subject ($p < 1^{-10}$). However, theta phase-locking was not shown during incorrect trials for either encoding or retrieval components. When EEG signals were time-locked to patient responses, strong phase locking occurred 500–750 ms after incorrect clicks ($p < 1^{-10}$, Bonferroni-corrected for multiple comparisons). Behaviorally, many of the incorrect responses were accompanied by a delayed corrective response by the patient (i.e. subsequently clicking the other button), which may relate to this particular delayed phase-locking.

Conclusion: These results suggest that phase locking of hippocampal theta oscillations is involved in both encoding and retrieval of accurate short-term memory information, and may reflect recognition of errors. Future work will examine whether transient epileptiform abnormalities such as interictal spikes can disrupt this phase-locking process, which might provide a potential mechanism for the phenomenon of transient cognitive impairment in epilepsy.

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13. Homozygosity mapping of Mabry syndrome: Identification of loci associated with alkaline phosphatase (ALP) gene over-expression or ALP protein over secretion—Miles D. Thompson¹, Marjan M. Nezarati^{2,3}, Gabriele Gillissen-Kaesbach⁴, Peter Meinecke⁵, Etienne Mornet⁶, Isabelle Brun-Heath⁷, Catherine Prost Squarcioni⁸, David E.C. Cole^{1,2,9,10,11}, Kathy Siminovitch^{11,12}, Paul A. Hwang¹³, W. McIntyre Burnham¹⁴, Arnold Munnich¹⁵, Han

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The impact of seizures associated with childhood onset metabolic disorders is considerable even though they account for 1% of live births. Like many infantile metabolic storage disorders, hyperphosphatasia with neurologic deficit (Mabry syndrome), has its onset starting in the first year of life – commencing with seizures followed by developmental disability (DD). At first considered rare, the disorder was first described by Mabry et al. in 1970 a single family (OMIM#239300) [1970]. Both the frequency and nosology of this condition, however, remained uncertain until the present study. Initially, our work involved patient and family recruitment and a thor-

ough description of the disorder and its differentials. In addition to the seizures and elevated serum alkaline phosphatase (ALP) levels, our work resulted in the recognition of several other salient features of the disorder including: a characteristic facial dysmorphism, nerve abnormalities (plaques disrupting Schwann cells) and subtle bone abnormalities in the hand (brachytelephalangy – shortening of terminal phalanges). Since the metabolic marker for Mabry syndrome is ALP elevation, our initial objective was to identify mutation(s) in gene(s) that determine the elevated levels of ALP in Mabry syndrome. This study was simplified partly because the syndrome is likely to be inherited in an autosomal recessive manner (based on sibling recurrence and the frequency of consanguinity). As a result, we used high density SNP genotyping to map regions of homozygosity in Mabry syndrome cases. This method is powerful since many of the families recruited are consanguineous. Among those not consanguineous, a French Canadian family provided useful data due to the presence of a founder effect. This whole genome analysis has identified portion(s) of chromosome 1p36 that are mutated in Mabry syndrome – the region to which the ALP gene maps – allowing us to correlate the role of ALP over-expression/secretion with the pathogenesis of Mabry syndrome. Candidate gene sequence analysis will now be used to identify the mutation(s) that result in the disorder. We hypothesize that Mabry syndrome will be found to be the result of mutations associated with either ALP gene over-expression or ALP protein over secretion. This work will elucidate the inborn error of metabolism that underlies Mabry syndrome – tease apart the mechanisms that regulate ALP expression/secretion – and provide insight into the how ALP associated pathways are involved epileptogenesis. Most importantly, understanding the molecular cause of Mabry syndrome may reveal novel pathways for treatment – and will result in better counseling for families regarding parental and childhood therapeutic choices.

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