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PARADOXICAL FACILITATION: THE RESOLUTION OF FOREIGN ACCENT SYNDROME AFTER CEREBELLAR STROKE

Foreign accent syndrome (FAS) is a rare speech disorder characterized by a change in prosody and other speech variables yielding altered phonetic characteristics that are perceived as a foreign accent. Lesions associated with FAS typically involve left frontoparietal regions. However, 2 reported left-hemispheric stroke patients presenting with FAS also had hypoperfusion of the right cerebellum on ^{99m}Tc ECD SPECT imaging, presumably from diaschisis. In both cases, there was a close parallel between the normalization of the cerebellar perfusion and resolution of the clinical syndrome up to 3 years later despite continued hypoperfusion of left hemispheric structures.^{1,2} The authors argued that the temporal association between the clinical improvement and the right cerebellar perfusion suggested a functional role of the cerebellum in this speech disorder. We describe a unique case that provides convergent evidence for a causative role of the cerebellum in FAS.

Case report. A right-handed English-speaking woman was 58 years of age at the time of her left frontoparietal infarct (figure, A), presenting with right upper limb paresis and aphemia. Within hours, the patient's paresis resolved to a slight hand ataxia and her speech sounded like English spoken with an unlearned accent. Workup suggested an embolic event, and she was discharged on warfarin. The foreign accent persisted for approximately 3 years until she had a right inferior cerebellar hemorrhage (figure, B–D) from accidental excessive anticoagulation. Following this second stroke, the patient and her family noted that the foreign accent was no longer perceptible in her speech.

Analysis. Detailed acoustical analysis was performed on speech samples recorded prior to the patient's left frontoparietal infarct (CVA1), 4 and 20 days following this infarct, shortly after her cerebellar hemorrhage (CVA2), and later (BIMDC CVA2). Results indicated that post CVA1, she showed the constellation of impaired and spared speech production characteristics of FAS.³ She displayed pathologic patterns

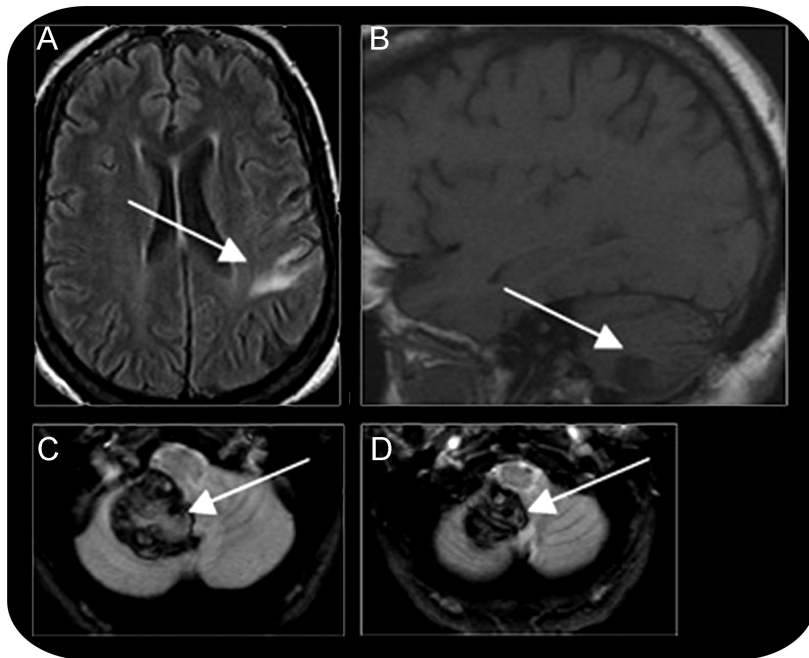
in prosody, vowel formant frequencies, vowel durations, and increased variability on these vowel measures, and she showed normal patterns in the production of voicing and place of articulation in stop consonants as well as preservation of the distinction between tense and lax vowels. Subsequent to her cerebellar stroke (CVA2), the patient's pathologic speech patterns resolved and she showed normal speech output (appendix e-1 and figures e-1 through e-4 on the *Neurology*[®] Web site at www.neurology.org).

Discussion. Rather than further impairing her speech, a right cerebellar stroke paradoxically extinguished the FAS. This case demonstrates that abnormal right cerebellar activity can play a causal role in perpetuating the FAS rather than being merely an epiphenomenon of damage to the reciprocally connected left hemisphere. Many of the presenting features of FAS relate to alterations in timing and rhythm of speech,⁴ and a functional role of the cerebellum in FAS is consistent with the model that the cerebellum plays a generalized role in processing temporal information.⁵ The prosodic disturbances in FAS may reflect deficits in timing resulting in impairments in the control of speech melody, in maintaining the correct vocal posture for the production of vowels, in maintaining the correct durational patterns of speech, and in producing syllabic stress and quantity.

The occurrence of the paradoxical facilitation⁶ in this case suggests that normal cerebellar control mechanisms may involve competitive interactions between the 2 cerebellar hemispheres. When the right cerebellum is lesioned, however, the contralateral left cerebellum may be disinhibited and thus assume a functional role, in the current case controlling the rhythmic and prosodic patterns for speech output, resulting in the resolution of the FAS. The idea that damage in one area of the brain may result in a release from inhibition and activation of an alternative network has been described.⁷ In that case, fMRI demonstrated a shift of the cortical representation of speech motor control to the right rolandic cortex and left cerebellum during rapid recovery from dysarthria following an infarct in the left internal capsule. In the case of our patient, persistent maladaptive activation in the right cerebellum may have prevented a similar

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Figure MRI scans of the patient's strokes



The foreign accent syndrome patient's initial embolic middle cerebral artery stroke (A, axial image, fluid-attenuated inversion recovery sequence, lesion appears whiter than surrounding cortex) resulted in a lesion at the frontoparietal junction. The patient's second stroke was a hemorrhagic stroke (3 cm × 4 cm × 1–3 cm hematoma) in the inferior portion of the right posterior lobe of the cerebellum reaching the midline and impinging on the vermis (T1-weighted sagittal image B, lesion appears darker than surrounding cortex, and susceptibility axial images C and D, where blood appears black). All images are presented in radiologic convention with the left hemisphere appearing on the right-hand side of the image. The white arrows indicate the lesioned area.

type of shift and the failure of her speech abnormalities to resolve spontaneously.

Ultimately, the behavioral consequences of a brain insult reflect the capacity of the rest of the brain to cope with the injury. Thus, the findings from our patient reveal that the neural control mechanisms of speech production depend on maintaining a delicate balance between bihemispheric cerebral and cerebellar connections and that changes in these dynamics can have effects on the operation of the entire system. Furthermore, the findings of resolution of FAS following right cerebellar disruption raise the intriguing possibility of a therapeutic potential of neuromodulatory interventions.

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ACUTE HIPPOCAMPAL SCLEROSIS FOLLOWING ECSTASY INGESTION

We report 2 patients presenting with brief tonic-clonic seizures following ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) ingestion who initially showed hippocampal swelling and subsequently atrophy.

Case reports. *Case 1.* A 25-year-old right-handed man presented following 2 generalized tonic-clonic sei-

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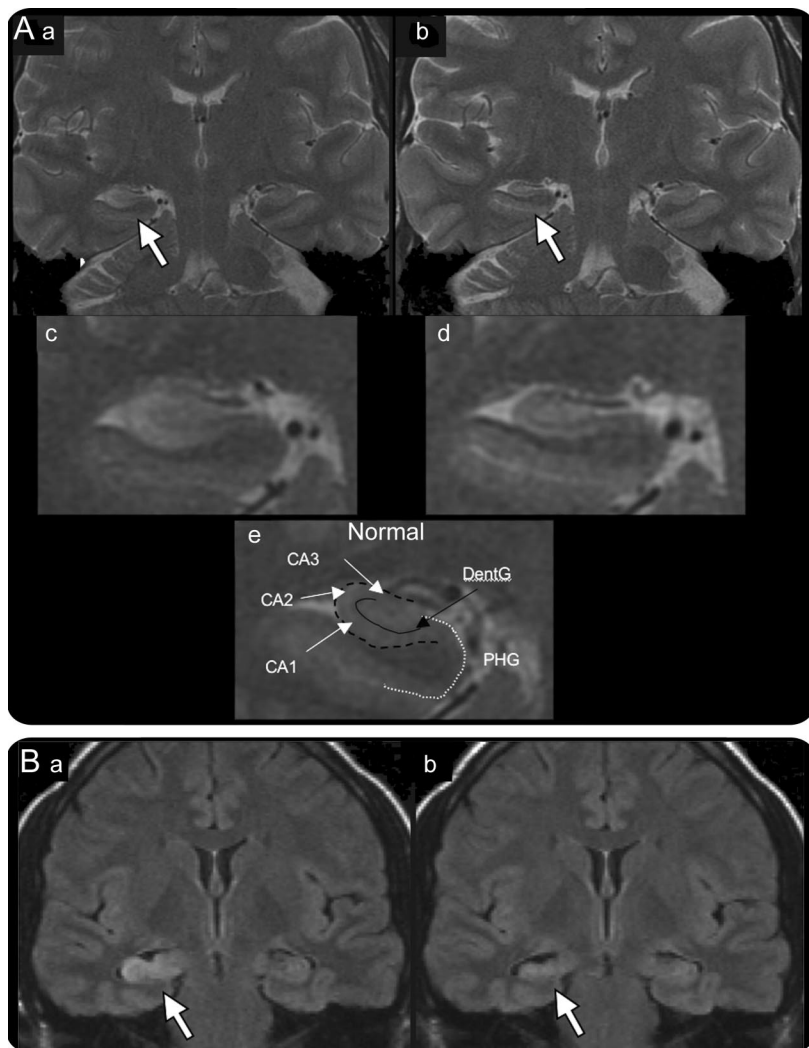
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1. Mariën P, Verhoeven J, Engelborghs S, Rooker S, Pickut BA, De Deyn PP. A role for the cerebellum in motor speech planning: evidence from foreign accent syndrome. *Clin Neurol Neurosurg* 2006;108:518–522.
2. Mariën P, Verhoeven J. Cerebellar involvement in motor speech planning: some further evidence from foreign accent syndrome. *Folia Phoniatr Logop* 2007;59:210–217.
3. Kurowski KM, Blumstein SE, Alexander M. The foreign accent syndrome: a reconsideration. *Brain Lang* 1996;54:1–25.
4. Blumstein SE, Kurowski K. The foreign accent syndrome: a perspective. *J Neurolinguistics* 2006;19:346–355.
5. Ivry R. Cerebellar timing systems. *Int Rev Neurobiol* 1997;41:555–573.
6. Kapur N. Paradoxical functional facilitation in brain-behaviour research: a critical review. *Brain* 1996;119:1775–1790.
7. Riecker A, Wildgruber D, Grodd W, Ackermann H. Reorganization of speech production at the motor cortex and cerebellum following capsular infarction: a follow-up functional magnetic resonance imaging study. *Neurocase* 2002;8:417–423.

zures (GTCS). The first, lasting 30 seconds, occurred 5 hours after taking 2 ecstasy tablets and 8 units of alcohol. The following day he felt unwell and vomited several times but his partner did not report any other unusual behaviors until the afternoon when he had a further 2-minute GTCS, and presented to hospital.

In the days prior to the ecstasy ingestion, he had been well. There was no past history or family

Figure Acute hippocampal damage following ecstasy (MDMA) ingestion



T2-weighted coronal images from subject 1 (A) 2 days (a), expanded in (c), and 3 months (b), expanded in (d), after ecstasy ingestion and 2 clinically brief seizures. Hippocampal anatomy of the normal left hippocampus (e), displayed with the image horizontally flipped. The CA1 region of the right hippocampus is initially of high signal and slightly swollen, subsequently becoming atrophic. Fluid-attenuated inversion recovery coronal images from subject 2 (B) 2 days (a) and 3 months (b) after ecstasy ingestion and a solitary brief seizure. DentG = dentate gyrus, dark line; PHG = parahippocampal gyrus, white dotted line tracing pial surface; CA1 (Sommer sector), CA2, and 3 of the hippocampus, arrowed; outer edge of hippocampus delineated by dark dashed line.

history of seizures. There was a history of IV heroin and amphetamine use from age 17 until 22. More recently, he used ecstasy, approximately “half a tablet” every few months. Examination revealed the patient to be oriented, agitated, and febrile (38.5°C), but with no focal neurologic deficits and no neck stiffness.

Investigations revealed renal impairment (serum creatinine 213 mmol/L; normal range 30–110 mmol/L), but otherwise normal electrolytes (serum sodium 139 mmol/L). There was leucocytosis (white cell count $19.0 \times 10^6/L$, lymphocytes $16.3 \times 10^6/L$; normal ranges 4–11 and 2–7.5 \times

$10^6/L$). C-reactive protein was 9 mg/L (normal <8 mg/L). Cerebral CT was unremarkable. Chest x-ray, urine, and blood cultures showed no evidence of infection. Lumbar puncture was not performed. Cerebral MRI 2 days after the seizures (figure, A, a) revealed swelling and high signal in the right hippocampus, on T2-weighted and fluid-attenuated inversion recovery sequences.

The patient was treated with IV fluids and phenytoin, but not commenced on long-term antiepileptic medication. Three months later, the patient remained seizure free and cerebral MRI (figure A, b) revealed right hippocampal atrophy with ongoing high signal, consistent with hippocampal sclerosis.

Six months after ecstasy ingestion, the patient remains seizure free, asymptomatic, and has returned to work. He denies further ecstasy use.

Case 2. A 25-year-old right-handed woman presented following a 1-minute GTCS, having taken 1 ecstasy tablet 11 hours prior and 5 units of alcohol. The patient had used ecstasy previously without incident. Several friends using ecstasy that evening from the same supplier remained well. Following the seizure, the patient vomited, reported headache, and was confused for 5 minutes.

There had been no previous seizures. Her sister had neonatal seizures thought to be the result of perinatal difficulties. The patient took the oral contraceptive pill but no other medications. On examination, she was afebrile but confused (Mini-Mental State Examination score 25/30; errors in orientation, recall [2/3], language). Neurologic examination was otherwise normal. Electrolytes and glucose were normal. EEG 2 weeks after the seizure was normal.

For the next few days, she felt tired and reported memory difficulties but no further seizures occurred. After 3 days, her boyfriend reported she was cognitively normal and she returned to work. Three months later, the patient reported no further seizures and normal memory.

MRI 48 hours following the seizure (figure B, a) showed signal change and swelling in the right hippocampus. Repeat MRI at 3 months (figure B, b) showed right hippocampal atrophy with ongoing high signal.

Discussion. In both patients, the clinical and imaging presentation is consistent with acute hippocampal damage following ecstasy ingestion. Ecstasy is a synthetic compound structurally similar to amphetamines. It causes release of endogenous catecholamines (noradrenaline, dopamine) and blocks reuptake into presynaptic vesicles. It also binds to a serotonin transporter, diminishing serotonin reuptake. Acute intoxication, as well as the desired euphoria, can cause agitation, anxiety, hyperactivity,

and occasionally seizures. The mechanism by which MDMA causes seizures is unclear, but may relate to chronic depletion of brain serotonin.^{1,2} Mice pretreated with MDMA have reduced thresholds for kainic acid–induced seizures.

There is increasing evidence that moderate chronic ecstasy use is associated with memory impairment.^{3,4} Users of the related compound methamphetamine show memory impairment that correlates with reductions in hippocampal volume.⁵ Thus it appears that chronic ecstasy use may damage the hippocampus. Our cases suggest ecstasy can cause acute hippocampal toxicity.

The evolution from increased hippocampal signal to hippocampal atrophy over several months is consistent with an acute hippocampal insult evolving to sclerosis. Although acute hippocampal damage has been observed within days of isolated prolonged seizures,^{6,7} these patients' seizures appear too brief. Thus, although we cannot completely exclude an infectious encephalitic cause, or prolonged subclinical seizure activity, we postulate that in these cases ecstasy ingestion caused an acute toxic insult to the hippocampus, leading to the MRI changes, and initial seizures.

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1. Green AR, Mehan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* 2003;55:463–508.
2. Giorgi FS, Lazzeri G, Natale G, et al. MDMA and seizures: a dangerous liaison? *Ann NY Acad Sci* 2006;1074:357–364.
3. Laws KR, Kokkalis J. Ecstasy (MDMA) and memory function: a meta-analytic update. *Hum Psychopharmacol* 2007;22:381–388.
4. Rendell PG, Gray TJ, Henry JD, Tolan A. Prospective memory impairment in "ecstasy" (MDMA) users. *Psychopharmacology (Berl)* 2007;194:497–504.
5. Thompson PM, Hayashi KM, Simon SL, et al. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci* 2004;24:6028–6036.
6. Jackson GD, Chambers BR, Berkovic SF. Hippocampal sclerosis: development in adult life. *Dev Neurosci* 1999;21:207–214.
7. Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain* 2003;126:2551–2557.

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