"Mr. B" was a 54-year-old man with a history of hypertriglyceridemia as well as depression refractory to treatment in multiple antidepressant trials. He had undergone vagal nerve stimulator implantation in November 2006. The procedure was well tolerated, and no adverse effects were reported. He seemingly appreciated an improvement in mood.

The patient first came to our unit when his clinical course was complicated by meningitis. Culture from CSF revealed pan-sensitive *Staphylococcus aureus*. An infectious diseases consult raised the concern that vagal nerve stimulator presented an infection source, which prompted explantation of the device (including the generator, leads, and wire coil) in March 2008. Subsequently, the patient developed hoarseness and left vocal cord paralysis.

Electromyographic investigation revealed abnormalities limited to the left thyroarytenoid muscle, suggestive of an incomplete left recurrent laryngeal nerve lesion. Review of Mr. B's operative report was noteworthy for the observation that the vagus nerve was invested with scar tissue requiring "meticulous and tedious" excision. The etiology of the patient's vocal cord paralysis was presumed to be the result of direct trauma related to scar tissue and wire-coil removal impinging upon the recurrent laryngeal nerve.

After 5 months of intensive speech therapy, the patient manifested nearly complete functional recovery, with marked improvement in vocal fatigue. However, stroboscopic-video vocal cord examination and follow-up electrodiagnostic investigations revealed a residual and permanent neurologic injury, even at 9 months postinjury. The patient elected not to have another vagal nerve stimulation implant and instead pursued antidepressant pharmacotherapy, with adequate response.

Although deep-tissue infection arising after vagal nerve stimulator implantation is uncommon, there can be considerable morbidity in instances in which infection occurs (1, 4). The literature to date suggests that these problems are generally encountered within 1 month postimplantation (4).

The present case is the first, to our knowledge, in which meningitis in an adult patient prompted vagal nerve stimulation hardware removal and, most notably, scar tissue excision and hardware removal precipitated a permanent left recurrent laryngeal nerve injury. The most appropriate and efficacious approaches to treating deep-tissue infection and meningitis arising after implantation is limited in the available literature. Because of hazards encountered in the excision of scar tissue associated with explantation, treatment with intravenous antibiotics while retaining the wire coil in situ may be the most prudent first-line approach to the management of complications (1). Refractory, persistent infection, despite conservative treatment, might necessitate eventual device removal. Patients considering vagal nerve stimulation treatment will need to be made aware of the risks of infection and potential complications if explantation is ever required.

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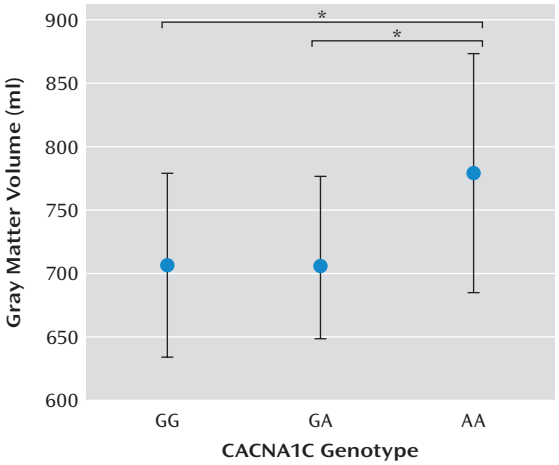
Effects of the CACNA1C Risk Allele for Bipolar Disorder on Cerebral Gray Matter Volume in Healthy Individuals

To the Editor: Recently, large genome-wide association studies in bipolar disorder have implicated a single nucleotide polymorphism (SNP) in intron 3 of the CACNA1C gene (rs1006737, G to A), which encodes for the voltage-dependent calcium (Ca^{2+}) channel L-type, alpha 1_c subunit (1). Voltage-dependent Ca^{2+} channels rapidly increase intracellular Ca^{2+} concentration when triggered by depolarization, initiating a host of responses, including neurotransmitter release and changes in gene expression. A known missense mutation (G406R) in CACNA1C causes Timothy syndrome, which is characterized by QT prolongation and autism spectrum disorder (2). The A allele is associated with bipolar disorder, but the effect of the rs1006737 polymorphism on brain function and structure is not known. To our knowledge, this is the first report of the potential effect of this polymorphism (or a functional variant in linkage disequilibrium with it) on cerebral volumes in healthy individuals.

Participants were 77 healthy adults of self-reported British, Caucasian ancestry without personal lifetime history of mental health disorders, head injury, or medical disorders (mean age: 34.9 years [SD=13.3]; female subjects: 35). DNA was obtained from buccal swabs using established procedures. The CACNA1C A/G (rs1006737) genotype was determined by a "TaqMan" allelic discrimination assay (Applied Biosystems, Foster City, Calif.). End-point analysis was performed on an ABI7900 DNA analyser, and genotypes were called using the SDS package, with a probability >95%. Structural images were acquired at the Maudsley Hospital, London, using a 1.5 Tesla General Electric Signa magnetic resonance imaging scanner (General Electric, Milwaukee). Images were acquired in the axial plane with a T1-weighted, three-dimensional spoiled-gradient-recalled echo protocol (echo time=5.1 ms, repetition time=18 ms, flip angle=20°, slice thickness=1.5 mm, in-plane resolution=0.9375 mm 0.9375 mm, number of excitations=1). Total, lobar, and subcortical gray matter (3) as well as white matter, CSF, and intracranial volumes were determined using voxel-based morphometry employing unified segmentation in Statistical Parametric Mapping-5. The effect of genotype was examined utilizing linear regression of the gene dose effect and analysis of variance (ANOVA) treating the three genotypes (AA, AG, GG) as independent groups.

FIGURE 1. Mean Gray Matter Volume in Healthy Carriers of Genotypes AA, AG, and GG of the CACNA1C Risk Allele[a]



[a] Data represent results from Tukey's honest significant difference post hoc test; Cohen's effect size=0.95 for both comparisons.
* $p<0.05$.

Allele frequencies did not violate the Hardy-Weinberg principle (p=0.53). Genotype groups were matched for age and gender (both p values >0.33). In the regression and ANOVA models, there was a significant effect of CACNA1C G to A mutation on total gray matter volume (both p values=0.03) but not regional gray matter volume and no effect on total white matter, CSF, or intracranial volumes (all p values >0.13). Total gray matter volume was largest in carriers of the AA allele (N=9,779 ml [SD=94]), followed by heterozygote carriers (N=31, 713 ml [SD=64]), and smallest in carriers of the GG allele (N=37, 707 ml [SD=73]) (Figure 1). The result remained significant after controlling for total intracranial volume and age (p=0.04).

There are two limitations to the present study. The rs1006737 polymorphism may not be a direct functional variant but a tagging SNP within a large block of linkage disequilibrium in intron 3. In addition, potential mechanisms underlying our findings are beyond the resolution of brain imaging. However Ca^{2+} voltage-gated channels are involved in neuronal development and connectivity both during early development and in adulthood (4).

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