

# Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

## Editors' note: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

In the article “Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain,” Dr. Galhardoni et al. compared the analgesic effects of repetitive transcranial magnetic stimulation (rTMS) of the anterior cingulate cortex (ACC) or the posterior superior insula (PSI) against sham deep rTMS in 98 patients with central neuropathic pain (CNP) after stroke or spinal cord injury in a randomized, double-blinded, sham-controlled, 3-arm parallel study. They found that ACC- and PSI-rTMS were not different from sham-rTMS for pain relief despite a significant increase in heat thresholds after insular stimulation and anxiolytic effects after ACC-rTMS and concluded that different dimensions of pain can be modulated noninvasively by directly stimulating deeper structures without necessarily improving clinical pain. In response, Dr. Zugaib et al. point to their recent work suggesting that PSI-/ACC-rTMS involves more intense stimulation of superficial structures. They argue that the use of linear projection to estimate the stimulation targets—as was the case in the trial—does not correspond to the region of maximum-induced electrical field, which is more superficial, and therefore caution against interpreting the clinical findings as resulting from the stimulation of deep structures as opposed to a combination of stronger superficial and deeper stimulation. They suggest using electric field modeling to guide the coil positioning and adjustment of stimulation intensity. Responding to these comments, Dr. de Andrade et al. defend the precision of their approach, noting that in addition to linear projection-guided PSI stimulation providing antinociceptive effects in patients with CNP and healthy volunteers, direct cortical stimulation of the PSI during stereo-EEG in a previous study showed the same heat-pain changes as described by linear projection-target deep TMS. They also note that stimulation intensity was calculated using the tibialis anterior muscle as a parameter, represented medially in the primary motor cortex, suggesting that a measurable current was likely delivered to the PSI. They argue that computing electric fields would not solve the issue of stimulation intensity, and instead propose that future field models should account for the data from linear projection, validated against sham and active controls, in their algorithms. This exchange highlights the important points of debate in the field of rTMS regarding the most reliable means of targeting deeper structures in the brain, and conversely, identifying the responsible structural mediators of observed stimulation effects.

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## Reader response: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

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Galhardoni et al.<sup>1</sup> evaluated the effect of repetitive transcranial magnetic stimulation (rTMS) on the anterior cingulate cortex (ACC) and posterior superior insula (PSI) of patients with central

neuropathic pain (CNP). Multidimensional aspects of pain were evaluated with psychophysical tests, electrophysiologic recordings, and scales. rTMS in PSI increased the threshold for heat pain, whereas in ACC improved anxiety scores. It is plausible that the neuromodulation of these structures has a therapeutic potential for CNP.<sup>2</sup> On the other hand, we recently pointed out that rTMS over PSI and ACC involve greater stimulation of superficial rather than deeper structures.<sup>3</sup> In addition, estimation of the stimulation targets was based on a linear projection from the center of the coil.<sup>4</sup> Linear projection does not correspond to the region of maximum induced electric field on internally folded cortical structures, which is always on the more superficial tissue<sup>5</sup>; therefore, the clinical findings should not be regarded as the resultant of deep structures' stimulation instead of an ensemble of stronger spread superficial stimulation combined with deeper stimulation. Accordingly, electric field modeling may be used to guide the coil positioning and adjustment of stimulation intensity to achieve a significant pain relief. Certainly, there is great importance in the development of new therapeutic strategies for CNP.

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2. Peyron R, Fauchon C. The posterior insular-opercular cortex: an access to the brain networks of thermosensory and nociceptive processes? *Neurosci Lett* 2019;702:34–39.
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## Author response: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

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We thank Dr. Zugaib et al. for the interest in our work.<sup>1</sup> It has been suggested that modeling electric fields within the deep cortical structures would provide more reliable, target-effect conclusions. So far, the use of linear projection to target<sup>1</sup> the posterior superior insula (PSI) has provided antinociceptive effects as measured by increases in the heat-pain threshold in patients with central pain<sup>2</sup> and in healthy volunteers.<sup>3o</sup> Importantly, in a unique study,<sup>4</sup> direct cortical stimulation of the PSI during stereo-EEG showed exactly<sup>4</sup> the same heat-pain changes described by the linear projection-targeted deep transcranial magnetic stimulation (TMS). Taken together, these are very strong arguments for the precision of such an approach. In addition, in the setups cited above, stimulation intensity was calculated using the anterior tibialis muscle as a parameter (with the leg representation buried medially within the primary motor cortex), which attests that a measurable amount of induced electric current was indeed delivered to the PSI. As pointed out by Zugaib and Souza,<sup>5</sup> computing electric field would not solve the issue of intensity of stimulation. Because the linear projection-based deep TMS approach proved itself accurate on

psychophysical terms, we propose a pragmatic “reverse-modeling” perspective that future electric-field models should take into account the data from linear projection in their algorithms because they have been validated against sham and active controls and provided information on the intensity of stimulation all at once.

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### Editors' note: Clinical manifestations of homozygote allele carriers in Huntington disease

In the article “Clinical manifestations of homozygote allele carriers in Huntington disease”, Dr. Cubo et al. examined the phenotypic differences between patients who were homozygous for Huntington disease (HD)—with both alleles carrying  $\geq 36$  CAG repeats—and those who were heterozygous with only one allele carrying such repeats, in 10,921 participants with HD in an international, longitudinal, case-control study (European Huntington's Disease Network Registry database). They found that homozygotes were infrequent (0.3%) and that the age at onset, HD phenotype, and disease progression did not differ significantly between homozygotes and heterozygotes. In response, Dr. Da Prat et al. noted a previous study that reported a more severe and rapid progression in homozygotes. They suggest using the term biallelic HD to refer to these patients to acknowledge the differences in the number of repeats that may exist between the 2 expanded alleles and cite a previous abstract from their group that also reported no differences in age at onset, cognition, motor capabilities, or disease evolution between a small sample of 7 patients with biallelic HD and heterozygous patients. Responding to these comments, Drs. Ramos-Arroyo and Cubo highlighted the potential drawbacks of using the term biallelic HD, noting the differences between patients with 2 expanded alleles carrying  $\geq 36$  CAG repeats vs those with one intermediate allele (27–35 repeats) who may have later-onset disease (both groups are combined under the biallelic definition), and noting the exclusion of compound heterozygotes with 2 nonfully penetrant repeat expansions from the conventional biallelic definition. They argue that these issues lead to imprecise categorization of patients with HD and potential noise in the analysis of clinical effects. This exchange illustrates the potential challenges that can arise in the interpretation of genotypic-phenotypic correlation studies from the use of what may appear at the first glance to be superficially discrepant definitions.

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## Reader response: Clinical manifestations of homozygote allele carriers in Huntington disease

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We read with interest the article by Cubo et al.<sup>1</sup> Patients with homozygous Huntington disease (HD) are rare—considering a patient as homozygous when presenting with repetitions greater than 36 in both alleles. Differences in age at onset, clinical characteristics, and evolution have been hypothesized because the gain function of the mutation is due to both alleles. Nevertheless, it has been shown that these patients have a similar clinical evolution. However, a very early study conducted by Squitieri et al.<sup>2</sup> reported a more severe and rapid progression in homozygotes.

The term biallelic HD (B-HD) was introduced to describe those individuals with 1 mutated allele ( $\geq 40$  CAG repeats) and one with  $\geq 27$  CAG repeats to differentiate them from individuals with 2 identical CAG repeats (true homozygous) or 1 fully expanded heterozygous ( $\geq 40$  CAG repeats) allele. For this reason, we suggest the categorization of B-HD instead of “homozygous,” as a more appropriate nomenclature.<sup>3</sup>

In our database, we identified 7 patients with B-HD among 150 patients with HD from June 2003 to May 2019. Coinciding with Cubo et al.,<sup>1</sup> we found no differences regarding the age at onset, cognition, motor capabilities, or disease evolution in patients with B-HD compared with the heterozygous patients with HD.<sup>4</sup>

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## Author response: Clinical manifestations of homozygote allele carriers in Huntington disease

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We appreciate the comments of Da Prat et al. comparing the results of our study<sup>1</sup> with their conclusions on the assessment of additional cases with 2 expanded HTT gene copies.<sup>2</sup>

Regarding terminology, we agree that “biallelic HD/mutations/expansions” might be an alternative term for the carriers of 2 expanded HTT alleles. By definition, biallelic carriers have a mutation in both maternal and paternal gene copies. For Huntington disease (HD), it could, therefore, include homozygotes for a particular CAG expansion and compound heterozygotes, carrying 2 different pathogenic alleles.

However, the term biallelic HD, as defined by Da Prat et al., presents, in our opinion, some major drawbacks. First, it is not useful in the analysis of genotype/phenotype relationships of the carriers

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Author disclosures are available upon request ([journal@neurology.org](mailto:journal@neurology.org)).

with 1 and 2 expanded ( $\leq 36$  CAGs) HTT copies (homozygotes and compound heterozygotes), as in our study.<sup>1</sup> Second, sequences of 27–35 CAG repeats are considered mutated/expanded alleles. We and others have observed that intermediate alleles (IAs) might confer late-onset abnormal motor and/or cognitive phenotype.<sup>3</sup> However, at present, IAs are considered unstable but are seen as non-HD–causing alleles.<sup>4</sup> Thus, their inclusion in the mutation range of the HTT gene seems premature and confusing. Third, the term excludes the compound heterozygotes in patients with HD carrying 2 nonfully penetrant CAG repeats.

In conclusion, we think that the term biallelic mutations leads to imprecision in grouping and categorization of patients with HD, adding “noise” to the analysis of their clinical effects. In fact, it has not been previously used in other diseases caused by repeat expansion mutations.

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## CORRECTIONS

### Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases

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In the Clinical/Scientific Note “Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases” by Neumann et al.,<sup>1</sup> Dr. Schneider’s first name should be listed as Hauke. The authors regret the error.

#### Reference

1. Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. *Neurology* 2020;94:e299–e313.

### Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease

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In the article “Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease” by Meza et al.,<sup>1</sup> the videos should be swapped so that the first video corresponds with the second legend and vice versa. The authors regret the errors.

#### Reference

1. Meza RM, Schulz H, Correa J, et al. Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease. *Neurology* 2019;93:e1410–e1411.

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## **Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases**

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