LETTER TO THE EDITOR

Transcranial magnetic stimulation as a biomarker for epilepsy

Prisca R. Bauer,1,2 Annika A. de Goede,3 Esther M. ter Braack,3 Michel J. A. M. van Putten,3,4 Richard D. Gill5 and Josemir W. Sander1,2,6

1 NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Department of Clinical and Experimental Epilepsy, London WC1N 3BG, UK
2 Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands
3 Department of Clinical Neurophysiology, University of Twente, Enschede, The Netherlands
4 Department of Clinical Neurophysiology and Neurology, Medisch Spectrum Twente, Enschede, The Netherlands
5 Department of Mathematics, Leiden University, Leiden, The Netherlands
6 Epilepsy Society, Chalfont St Peter, UK

Correspondence to: Prof. Ley Sander
NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Department of Clinical and Experimental Epilepsy, London WC1N 3BG, UK
E-mail: l.sander@ucl.ac.uk

Sir,
We read with interest the report by Badawy et al. (2013a) highlighting changes in cortical excitability in subjects with epilepsy and their siblings. It adds to the body of work of this group consistently showing that cortical excitability, measured by transcranial magnetic stimulation (TMS) may have potential as an epilepsy biomarker (Badawy and Jackson, 2012; Badawy et al., 2013b, 2014, 2015).

Responses to TMS were shown to have a relatively large interindividual variability (see for example Valls-Sole et al., 1992; Du et al., 2014). Badawy et al’s. reports do not provide clear information on interindividual variability. To estimate the variability across these reports, we extracted the data from some of their figures and compared these.

Several questions arose:

(1) The long-interval intracortical inhibition (LICI) curves of several groups of people with epilepsy in this report (Badawy et al., 2013a) seem to overlap with LICI curves in other reports from the same authors. For example, (i) the curve of the new-onset juvenile myoclonic epilepsy group, based on seven subjects, appears the same as the one from a report based on 10 subjects (Badawy et al., 2013b). The re-digitalized curves are shown in Fig. 1A; (ii) The curve of the new-onset temporal lobe epilepsy group, based on six subjects (Badawy et al., 2013a), appears the same as the one from a report based on 10 subjects (Badawy et al., 2015) (Fig. 1B); and (iii) The curve from the group with new onset generalized epilepsy with tonic-clonic seizures only (n = 7) (Badawy et al., 2013a), appears the same as the curve of the same patient group with a different sample size (n = 12) (Badawy et al., 2013b) and as the curve of the new-onset generalized epilepsy group with tonic-clonic, myoclonic and/or absence seizures (n = 20) (Badawy et al., 2014) (Fig. 1C).

Were the results of the epilepsy groups reported by the authors obtained from overlapping subject groups? Given the large interindividual variability, we would not expect such similar curves for groups with such a different sample size (n = 7 and n = 20) and different pathologies (generalized epilepsy with tonic-clonic seizures only, and generalized epilepsy with tonic-clonic, myoclonic and/or absence seizures).

(2) Within the report, there is a difference between the LICI curve of non-epilepsy controls shown in Fig. 1 (the red line) and the LICI curve of the non-epilepsy controls shown in the other figures as a grey shaded area (Badawy et al., 2013a). In the middle panel of their Fig. 2, (‘Refractory’), the grey shaded area appears to be shifted down, below the x-axis in the first figure on the left (JME). In their Fig. 1, the response ratio at an inter-stimulus interval of 200 ms appears to be greater than 100%, but in Fig. 2, the curve does not seem to reach 100% (Fig. 1D). Do those figures show data from the same group of control subjects?

© The Author (2017). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved. For Permissions, please email: journals.permissions@oup.com
The effect sizes reported do not seem to fit with the error bars shown in the figures, leading us to wonder what the 'error bars' in the figures represent. For example in their Fig. 2, second frame from the top, first on the left (juvenile myoclonic epilepsy drug naïve new-onset) (Badawy et al., 2013). The accompanying text on p.1182 says: 'In the drug naïve new-onset groups, cortical excitability was higher in patients compared with their siblings at the 150, 250 and 300 ms interstimulus intervals (P < 0.01, effect sizes ranging 0.5–0.7; maximum in juvenile myoclonic epilepsy), [...] (Fig. 2').

The effect size was calculated as: (mean of epilepsy) – (mean of siblings) / standard deviation of siblings (p.1181). The sample size of the group of siblings of people with new-onset juvenile myoclonic epilepsy was 11.

(i) For the 150 ms interstimulus interval, based on the effect size of 0.5–0.7, the standard deviation (SD) should be between ±164 and ±230%, and the standard error of the mean (SEM) between ±49 and ±69%. The 'error bar' in the figure shows ±25%.
(ii) For the 250 ms interstimulus interval, based on the effect size of 0.5–0.7, the SD should be between ±250 and ±350%, and the SEM between ±75 and ±105%. The ‘error bar’ in the figure shows ±30%.

(iii) For the 300 ms interstimulus interval, based on the effect size of 0.5–0.7, the SD should be between ±192 and ±270%, and the SEM between ±58 and ±81%. The ‘error bar’ in the figure shows ±40%.

(4) Lastly, the mean resting motor threshold of the control group reported 55.4 ± 5.7% (Badawy et al., 2013a), is similar to the motor threshold of 55.2 ± 5.6% repeatedly reported by the same authors (Table 1, Badawy et al., 2012). Were these results obtained from the same groups of participants?

It is essential to clarify these questions, as the promise of any clinical biomarker critically depends on its interindividual variability, which ultimately influences its specificity and sensitivity.

**Funding**

P.R.B. and J.W.S. are based at NIHR University College London Hospitals Biomedical Research Centre. P.R.B. is supported by the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie (Nederland). A.A.dG. received funding from the Dutch TWIN Foundation for Neuromodulation. J.W.S. receives research support from the Dr. Marvin Weil Epilepsy Research Fund, Eisai, NEF, GSK, WHO and EU FP7.

**References**


