Cerebellar Stimulation Fails to Modulate Motor Cortex Plasticity in Writing Dystonia

Anna Sadnicka, MD,[1,2] Masashi Hamada, MD, PhD,[1,2,3] Kailash P. Bhatia, MD, FRCP,[2] John C. Rothwell, PhD[2] and Mark J. Edwards, MD, PhD[2]*

[1]*Shared first authorship;* [2]*Sobell Department of Motor Neuroscience and Movement Disorders, University College London, London, United Kingdom;* [3]*Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*

ABSTRACT

Background: Primary dystonia is characterized neurophysiologically by reduced inhibitory mechanisms and abnormal regulation of plasticity responses. The potential of anodal cerebellar transcranial direct current stimulation as a therapeutic tool in writing dystonia was examined, after the observation that cerebellar stimulation reduces responses to an associative plasticity protocol in healthy subjects.

Methods: Ten patients with writing dystonia completed a two-part study (sham and anodal) in which cerebellar stimulation was given simultaneously with paired associative stimulation. Electrophysiological and clinical parameters were measured before and after stimulation.

Results: Clinical symptoms were unchanged by cerebellar stimulation. Patients exhibited much variability in the size and direction of their plasticity responses. Excessive or topographically abnormal plasticity responses were not observed. In the subgroup of patients with facilitatory responses to paired associative stimulation in the sham condition, anodal cerebellar stimulation retained its ability to reduce the magnitude of plasticity response.

Conclusions: Our limited understanding of intersubject variability of plasticity responses in writing dystonia currently undermines cerebellar stimulation as a novel treatment in this subset of dystonia. Cerebellar stimulation may be beneficial in other neurological disorders with consistently exaggerated plasticity. © 2014 International Parkinson and Movement Disorder Society

Key Words: writing dystonia; writers' cramp; plasticity; cerebellum; cerebellar stimulation

Despite increasing understanding of the pathophysiology of dystonia, defining novel treatments based on research findings has remained elusive. Historically considered a disorder of the basal ganglia, a wider sensorimotor network has been now been implicated.[1] One node within this network is the cerebellum, with its intimate structural and functional relationships to the basal ganglia.[2,3] In rodent models, modulating cerebellar function can cause or abolish dystonia.[4-6] In humans, pathological conditions of the cerebellum can produce secondary dystonia, and a growing literature links cerebellar dysfunction to primary dystonia.[7]

In parallel to work delineating the anatomical basis, electrophysiological studies demonstrate reduced inhibition throughout the central nervous system. Specifically, reduced cerebellar inhibition of the motor cortex is suggested by the finding of reduced cerebellar brain inhibition in focal dystonia (cerebellar brain inhibition tests the functional integrity of the cerebello-thalamocortical pathway).[8] In addition, abnormal plasticity regulation has been demonstrated, and responses to plasticity protocols are widely considered to be excessive and nonselective in the motor cortex and other sites within the dystonic network.[9]

When we (and others) found that plasticity responses of the motor cortex could be reduced by cerebellar stimulation in healthy subjects, exploring whether the excessive plasticity responses described in dystonia could be normalized by cerebellar stimulation was an intriguing hypothesis.[10,11] We chose to give patients with writing dystonia (WD) anodal cerebellar transcranial direct current stimulation (cDC), because this was the type of stimulation with the greatest block of plasticity in healthy subjects.[10] In addition, anodal cDC is thought to functionally increase cerebellar activity, increasing cerebellar inhibition of target structures, and thus is the intuitive choice in a disease in which the motor cortex is hyperexcitable. Proof of the concept that modulation of cerebellar activity is beneficial could provide exciting new treatment options for dystonia.

*Correspondence to: Dr Mark Edwards, Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Box 146, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, United Kingdom, E-mail: m.j.edwards@ucl.ac.uk

Funding agencies: This study was supported by grants from the Guarantors of Brain Clinical Fellowship Scheme (AS) and the Japan Society for the Promotion of Science Postdoctoral Fellowships for Research Abroad (MH).

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 16 September 2013; **Revised:** 4 February 2014; **Accepted:** 17 February 2014
Published online 5 May 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25881

TABLE 1. Statistical outcomes of the effect of anodal cDC on PAS25 response

		cDC (1,9)		TIME (2,18)		cDC x TIME (2,18)	
		F-value	*P*-value	*F*-value	*P*-value	*F*-value	*P*-value
RMT (%SI)	APB	0.207	0.660	1.75	0.202	2.10	0.151
AMT (%SI)	APB	0.152	0.706	0.518	0.604	1.26	0.309
30MEP (mV)	APB	0.002	0.965	0.301	0.744	1.55	0.239
	FDI	0.318	0.587	1.36	0.283	3.32	0.059
	ADM	1.24	0.294	0.154	0.859	2.56	0.105
*r*RC (mV/SI)	APB	0.078	0.789	0.208	0.814	0.624	0.547
	FDI	0.072	0.794	0.235	0.793	0.444	0.648
	ADM	0.214	0.655	0.444	0.648	0.293	0.749
CSP (ms)	APB	0.294	0.601	1.80	0.194	0.155	0.857

cDC, cerebellar transcranial direct current stimulation; RMT, resting motor threshold; SI, stimulus intensity; APB, abductor pollicis brevis; AMT, active motor threshold; MEP, motor evoked potential; FDI, first dorsal interosseous; ADM, abductor digiti minimi; *r*RC, linear regression of recruitment curve; CSP, cortical silent period.

Methods

Ten patients with WD/writers' cramp diagnosed at the National Hospital for Neurology and Neurosurgery, London, United Kingdom, were recruited. All completed a two-part study (sham and anodal cDC) in which cDC was given simultaneously to paired associative stimulation (PAS25). The first cDC stimulation type was randomized, and the patients were blinded. Experimental sessions performed a week apart at the same time.

Details of transcranial magnetic stimulation (TMS), PAS25, cDC, and electromyography are described in the Supplementary Data and in a recent publication in healthy controls.[10] In brief, resting and active motor threshold (RMT and AMT), motor cortex excitability (30 motor evoked potentials (MEPs)), recruitment curves (RC), and cortical silent period (CSP) were measured before (baseline) and at 0 min (T0) and 30 min (T30) after PAS25. Novel features of analysis were: (1) the analysis of RC for each muscle recorded (right: abductor pollicis brevis [APB], first dorsal interosseous [FDI] and abductor digiti minimi [ADM]); (2) linear regression of RC of each patient (*r*RC) for data points between 100% and 140% of the RMT as described by others for group data.[12] Patients were videotaped at the baseline and end of experiment. Assessors blinded to cDC type scored patients with the writing movement subscore of the Writer's Cramp Rating Scale[13] and the time taken to copy a standardized sentence or sentences. Patients rated change in symptoms using a visual analog scale (from −100% [deterioration] to +100% [resolution]).

To assess effect of cerebellar stimulation, RMT, AMT, and CSP (for APB) and 30MEP and *r*RC (for ABP, FDI, and ADM) were evaluated by repeated measures analysis of variance with factors 'cDC' (sham-PAS25, anodal-PAS25), 'TIME' (baseline, T0, T30), and 'cDC × TIME.' Patients were divided into facilitators to PAS25 (amplitude of 30MEP larger at T30 compared with baseline, >0) and inhibitors to PAS25 (amplitude of 30MEP smaller at T30 compared with baseline, <0) for each muscle in the sham condition. Change in amplitude at T30 for sham and anodal cDC were compared in both groups, using paired *t* tests.

Results

The RMT, AMT, and CSP (for APB) and 30MEP and *r*RC (for ABP, FDI, ADM) did not change with the factors 'cDC' or 'TIME,' and we did not find an interaction of 'cDC x TIME' (Table 1). The reason for lack of plasticity response at the group level was a high degree of variability of PAS25 response at the individual level. Some patients facilitated to PAS25, and some patients inhibited to PAS25 in the sham condition. In several previous studies of PAS, participants have been specifically chosen on their ability to produce facilitation after PAS25, and "non-responders" or inhibitors to PAS were not included in these studies.[14] When we followed a similar rationale, grouping patients as facilitators or inhibitors, anodal cDC significantly reduced the facilitatory PAS25 response in FDI and ADM ($p = 0.032$, $p = 0.038$ respectively), with a nonsignificant reduction in APB ($p = 0.054$) (Figure 1). A weak tendency for cDC to reduce the amount of suppression was found in patients who showed inhibition of MEPs after PAS25, suggesting that anodal cDC might reduce the magnitude of PAS25 in either direction. In both stimulation settings, a moderate subjective improvement in writing occurred, which is likely to be a placebo effect (visual analog scale, 12% and 13% improvement in sham and anodal cDC, respectively, with no statistical difference between stimulation conditions). No significant change was found in the Writer's Cramp Rating Scale score or the timed writing assessments in either condition (Table 3, Supplemental Data).

Discussion

This study has examined the role of cDC as a potential therapeutic tool in WD. Our experimental design

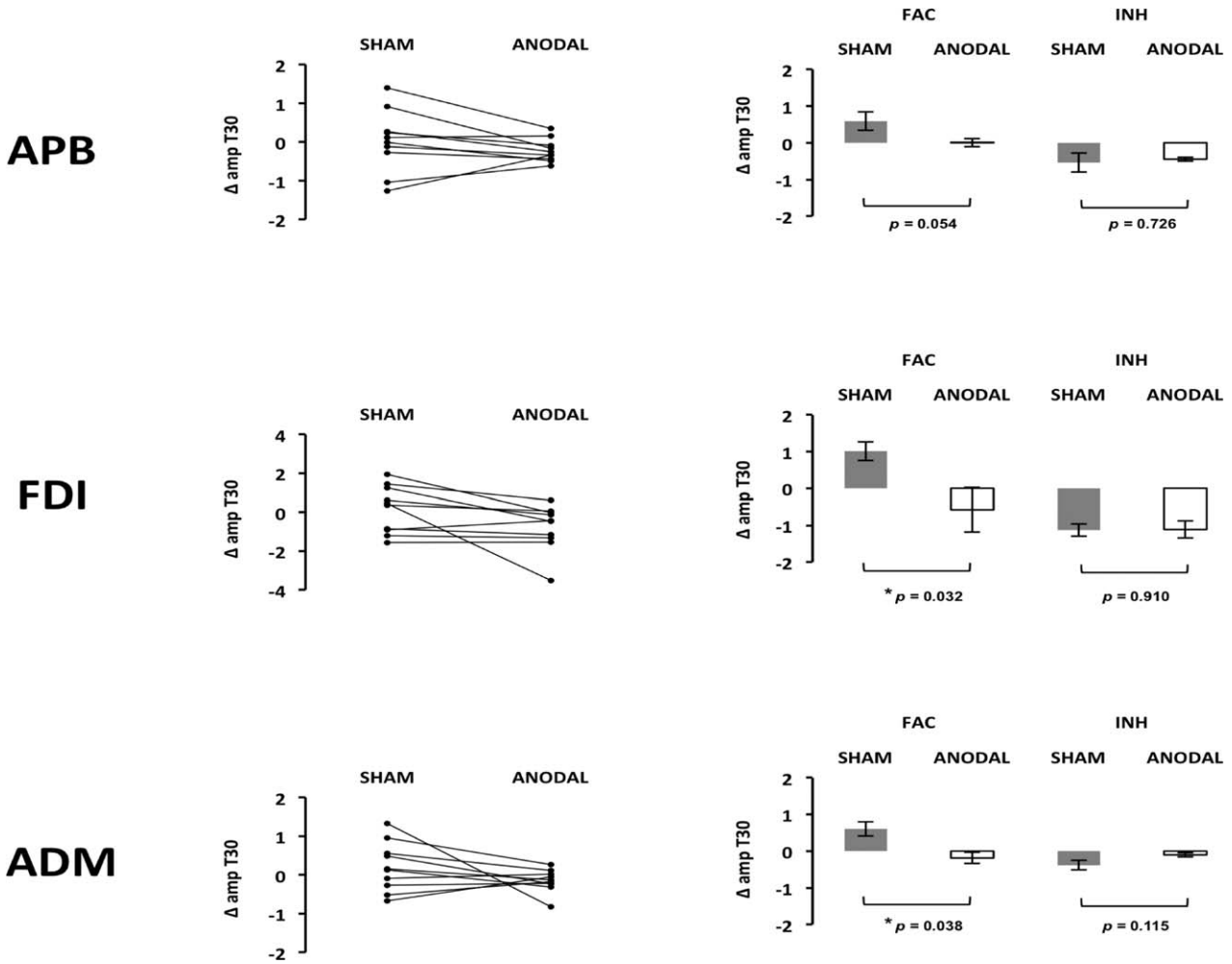

FIG. 1. Effect of cDC on PAS25 response. For each of the hand muscles tested, linked individual PAS25 responses without (sham) and with anodal cDC are shown. Responses are shown as change in the amplitude at T30 (Δ amp T30). To the right, patients are grouped as either facilitators (FAC) or inhibitors (INH) to PAS25 in the sham condition. Overall these data suggest a stabilizing effect of cDC on PAS25 response and a significant reduction in the size of PAS25 response in facilitators for the FDI and ADM muscles.

incorporated converging evidence from animal and human research. Our study was negative and does not provide evidence that anodal cDC is beneficial for patients after a single session. We discuss the importance of these results alongside recent publications from this currently topical field of dystonia research.

Modulating Cerebellar Function as a Potential Treatment for Dystonia

We have previously demonstrated that cDC reduces the response to PAS25 in healthy subjects.[10] We had reasoned that because cortical plasticity has been reported to be increased in dystonia, application of cDC might reduce and normalize the overactive response to PAS. In fact, we found that cDC had no effect when all patients were grouped together. At first sight this is a disappointing result, and similar to a recent finding by Hubsch et al.[15] This group had previously found that conditioning the cerebellar cortex with intermittent theta burst stimulation (excitatory) reduced the PAS25 response of the contralateral motor cortex. As in this study, at the group level, this modulatory effect of the cerebellum over PAS response was not observed in subjects with focal hand dystonia.[11,15]

We believe these negative findings obscure a more important feature. In both studies, considerable variation occurred in the response to PAS between individuals. In some patients corticospinal excitability after PAS25 was facilitated (i.e., long-term potentiation–like response), and in some patients it was inhibited (i.e., long-term depression–like response). In fact, no net plasticity response was seen at the group level to PAS25 in our present group. We do not think this is attributable to specific methodological problems, because the situation is similar in healthy volunteers: PAS paradigms produce facilitatory effects in

approximately 50% of participants.[16] We hypothesize that the response to PAS25 is, as in healthy people, highly variable in patients with dystonia.

Previous studies on healthy participants have circumvented the variability of PAS by preselecting individuals who have a facilitatory response.[14] When we followed the same logic and separated the patients into "responders" who showed facilitation after PAS25 and "nonresponders" or inhibitors, we found that cDC reduced facilitation in "responders," as described previously in healthy individuals. Indeed, there was a weak tendency for cDC to reduce the amount of suppression in "inhibitors" to PAS25, suggesting that cDC might stabilize the response to PAS25.

Clinically we did not see any behaviorally relevant improvement in measures of WD severity. Possibly the WD scores we employed were insensitive to clinical changes; however, subjective change was also negative, and thus we do not think we have missed subtle changes in writing kinematics. In addition, the negative electrophysiological data, which motivated our study design, are also against this.

Will the exciting work in animal models of dystonia translate into new therapeutic avenues in humans with dystonia? In rodent models, modulating cerebellar function (i.e., cerebellectomy, functional block of output) is sufficient to abolish dystonia. In humans, noninvasive stimulation techniques have been unable to achieve this. Clearly, cDC and TBS paradigms are by necessity weaker modulators. Furthermore, any study employing a single session of stimulation is ambitious, because one is attempting to undo dystonic processes within the brain, which have presumably been strongly consolidated through many years of symptoms. Repeated sessions of stimulation (as used in the treatment of depression,[17]), phasic cDC, or more invasive cerebellar stimulation sites are just a few of the potential tools that could be employed in future work. Our view is that cerebellar stimulation with the aim of modulating plasticity responses of the motor cortex in focal hand dystonia is not a useful avenue of research, because not all patients have increased plasticity. However, further characterization of pathophysiological changes in dystonia and characterization of cerebellar dysfunction in humans may well yield the development of new therapeutic options using cerebellar modulation, via different underlying mechanisms.

Based on the results of this study, cerebellar stimulation may have a role in regulating the responsiveness of the motor cortex to plasticity-inducing protocols. Aside from dystonia, other important conditions such as brain recovery after stroke would greatly benefit from a noninvasive brain stimulation method that regulates plasticity response. In other conditions, if exaggerated plasticity is more consistently seen, a therapeutic effect may be possible, especially if stimulation is repeated and given alongside targeted physical rehabilitation. ■

Acknowledgment: We thank the patients for their participation in this study.

References

1. Neychev VK, Gross RE, Lehericy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. Neurobiol Dis 2011;42:185-201.
2. Bostan AC, Strick PL. The cerebellum and basal ganglia are interconnected. Neuropsychol Rev 2010;20:261-270.
3. Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A 2010;107:8452-8456.
4. Campbell DB, North JB, Hess EJ. Tottering mouse motor dysfunction is abolished on the Purkinje cell degeneration (pcd) mutant background. Exp Neurol 1999;160:268-278.
5. LeDoux MS, Lorden JF, Ervin JM. Cerebellectomy eliminates the motor syndrome of the genetically dystonic rat. Exp Neurol 1993;120:302-310.
6. Fan X, Hughes KE, Jinnah HA, Hess EJ. Selective and sustained alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activation in cerebellum induces dystonia in mice. J Pharmacol Exp Ther 2012;340:733-741.
7. Sadnicka A, Hoffland BS, Bhatia KP, van de Warrenburg BP, Edwards MJ. The cerebellum in dystonia: Help or hindrance? Clin Neurophysiol 2012;123:65-70.
8. Brighina F, Romano M, Giglia G, Saia V, Puma A, Giglia F, Fierro B. Effects of cerebellar TMS on motor cortex of patients with focal dystonia: A preliminary report. Exp Brain Res 2009;192:651-656.
9. Quartarone A, Pisani A. Abnormal plasticity in dystonia: Disruption of synaptic homeostasis. Neurobiol Dis 2011;42:162-170.
10. Hamada M, Strigaro G, Murase N, Sadnicka A, Galea JM, Edwards MJ, Rothwell JC. Cerebellar modulation of human associative plasticity. J Physiol 2012;590:2365-2374.
11. Popa T, Velayudhan B, Hubsch C, et al. Cerebellar processing of sensory inputs primes motor cortex plasticity. Cereb Cortex 2013;23:305-314.
12. Cirillo J, Lavender AP, Ridding MC, Semmler JG. Motor cortex plasticity induced by paired associative stimulation is enhanced in physically active individuals. J Physiol 2009;587:5831-5842.
13. Wissel J, Kabus C, Wenzel R, et al. Botulinum toxin in writer's cramp: objective response evaluation in 31 patients. J Neurol Neurosurg Psychiatry 1996;61:172-175.
14. Korchounov A, Ziemann U. Neuromodulatory neurotransmitters influence LTP-like plasticity in human cortex: a pharmaco-TMS study. Neuropsychopharmacology 2011;36:1894-1902.
15. Hubsch H, Roze E, Popa T, et al. Defective cerebellar control of cortical plasticity in writer's cramp. Brain 2013;136:13.
16. Muller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp Brain Res 2008;187:467-475.
17. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry 2013;26:13-18.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Language Impairment in Cerebellar Ataxia

Judith van Gaalen, MD,[1]* Bert J.M. de Swart, PhD,[2]
Judith Oostveen,[2] Simone Knuijt, MA,[2]
Bart P.C. van de Warrenburg, MD, PhD[1] and
Berry (H.) P.H Kremer, MD, PhD[3]

Departments of [1]Neurology and [2]Rehabilitation, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen