XXVII BRAZILIAN CONGRESS OF CLINICAL NEUROPHYSIOLOGY

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NON-INVASIVE BRAIN STIMULATION IN EPILEPSY

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As has been demonstrated by the other speakers, slow-frequency rTMS may be used to decrease abnormal cortical hyperexcitability in neurological disorders...

Epilepsy is the prototype of a neurological disorder with clear-cut cortical excitability abnormalities that might be treatable by neuromodulation techniques

rTMS and Epilepsy

Why try it in epilepsy? According to the review by Chen et al. (2018):

- Of 1,795 patients firstly treated for epilepsy, 1,144 were free from seizures for a year or more
- This represents only 63.7% of all patients
- Over a third of patients remain with uncontrolled seizures with pharmacological treatment
- The plethora of new drugs introduced in the past 20 years has not substantially changed this scenario

However, TMS was not initially thought of as a **treatment** for epilepsy, but rather as a possible diagnostic aid...

TMS and Epilepsy

In 1990 Andreas Hufnagel and colleagues proposed TMS as a tool to activate epileptic foci in the presurgical evaluation of epilepsy surgery :

Hufnagel, A., et al. “Activation of the epileptic focus by transcranial magnetic stimulation of the human brain.” Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 27.1 (1990): 49-60.

TMS and Epilepsy

In 1999, Frithjof Tergau and colleagues, based on animal studies, tried inhibitory (low-frequency) rTMS in cases on intractable epilepsy :

Tergau, Frithjof, et al. “Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy.” The Lancet 353.9171 (1999): 2209.

TMS and Epilepsy

William Theodore, at the NIH, studied 24 patients with intractable epilepsy, and found a mild and short-lived effect of low-frequency rTMS upon seizure frequency:

Theodore, W. H., et al. “Transcranial magnetic stimulation for the treatment of seizures: a controlled study.” Neurology 59.4 (2002): 560-562.

TMS and Epilepsy

In 2004, we tested the low-frequency rTMS method in 5 patients with intractable epilepsy; we also found a mild effect, best seen in a patient with a neocortical focus :

Brasil-Neto, Joaquim P., et al. “Experimental therapy of epilepsy with transcranial magnetic stimulation: lack of additional benefit with prolonged treatment.” Arquivos de neuro-psiquiatria 62.1 (2004): 21-25.

TMS and Epilepsy

In 2006, Felipe Fregni and colleagues, in a double-blind controlled study, treated 21 patients with cortical developmental malformations and refractory epilepsy and found significant reductions in seizure frequency (58% in the treated group) :

Fregni, Felipe, et al. “A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy.” Annals of neurology 60.4 (2006): 447-455.

TMS and Epilepsy

In 2007, Roberto Cantello and colleagues also performed a double-blind, placebo controlled study of 43 patients with refractory epilepsy and did not find a significant effect upon seizure frequency; however, they pointed out a significant reduction in EEG interictal epileptiform abnormalities :

Cantello, Roberto, et al. “Slow repetitive TMS for drug resistant epilepsy: clinical and EEG findings of a placebo controlled trial.” Epilepsia 48.2 (2007): 366-374.

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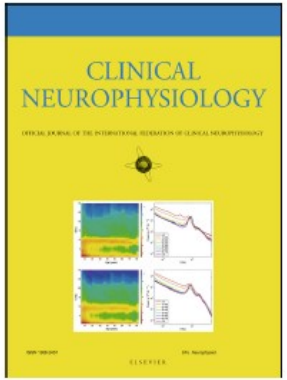

Guidelines

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

Jean-Pascal Lefaucheur, Nathalie André-Obadia, Andrea Antal, Samar S. Ayache, Chris Baeken, David H. Benninger, Roberto M. Cantello, Massimo Cincotta, Mamede De Carvalho, Dirk De Ridder, Hervé Devanne, Vincenzo Di Lazzaro, Saša R. Filipović, Friedhelm C. Hummel, Satu K. Jä äskeläinen, Vasilios K. Kimiskidis, Giacomo Koch, Berthold Langguth, Thomas Nyffeler, Antonio Oliviero, Frank Padberg, Emmanuel Poulet, Simone Rossi, Paolo Maria Rossini, John C. Rothwell, Carlos Schönfeldt-Lecuona, Hartwig R. Siebner, Christina W. Slotema, Charlotte J. Stagg, Josep Valls-Sole, Ulf Ziemann, Walter Paulus, Luis Garcia-Larrea

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TMS for Epilepsy (Lefaucheur et al., 2014)

Evidence Level: "C" (possible efficacy)

Coil type: butterfly

Coil position: over suspected neocortical focus

Frequency: equal to or lower than 1 Hz

Intensity: 90 percent of motor threshold

Nmber of sessions: 5 to 14

Pulses per session: 900 a 1500

rTMS and Status Epilepticus

Review by Zeiler et al. (2015):

- Very few data regarding GSE
- 80% response rate with FSE; only 50% for FRSE
- Evidence: Oxford level 4, Grade D
- Seizures may reccur after 72 hours

tDCS and Status Epilepticus

What about tDCS?

- Yook, Soon-Won, et al. “Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient-a case report.” Annals of rehabilitation medicine 35.4 (2011): 579-582.

- Grippe, Talyta C., et al. “Interruption of epilepsia partialis continua by transcranial direct current stimulation.” Brain Stimul 8.6 (2015): 1227-1228.

tDCS and EEG epileptiform activity

San Juan et al. (2015)

San-juan, Daniel, et al. “Transcranial direct current stimulation in epilepsy.” Brain stimulation 8.3 (2015): 455-464.

> We analyzed 9 articles with different methodologies (3 animals/6 humans) with a total of 174 stimulated individuals; 109 animals and 65 humans. In vivo and in vitro animal studies showed that direct current stimulation can successfully induce suppression of epileptiform activity without neurological injury and 4/6 (67%) clinical studies showed an effective decrease in epileptic seizures and 5/6 (83%) reduction of inter-ictal epileptiform activity.

Non Convulsive Status Epilepticus (NCSE)

According to Laroche and Haider (2018):

- NCSE is often seen with acute neurologic injury
- NCSE may also occur with sepsis, metabolic abnormalities
- NCSE has been reported with paraneoplastic syndromes
- Many drugs may precipitate NCSE
- Altered states of consciousness may be caused by NCSE

LaRoche, Suzette M., and M. D. Hiba Arif Haider, eds. Handbook of ICU EEG monitoring. Springer Publishing Company, 2018.

Neuromodulation in the ICU?

- Both TMS and tDCS have been reported to decrease EEG interictal epileptiform discharges
- NCSE is a known cause of altered states of consciousness
- NCSE may be caused by medications: neuroleptics, penicillins, cephalosporins (especially cefepime), fluoroquinolones, GABA antagonists, sedatives and anesthetics
- Once the diagnosis is made by EEG, a neuromodulation technique might conceivably be a useful add-on to treatment of NCSE
- Neuromodulation might prevent the use of still more drugs in a patient with NCSE

Generalized Periodic Discharges (GPD) due to cefepime neurotoxicity

Conclusions

- There is a lack of multi-center, double-blind controlled studies on possible uses of neuromodulation in epilepsy
- This also applies to other neurological disorders, such as dystonia and Parkinson’s disease
- In patients on multiple drugs, such as ICU patients, non-pharmacological treatments, when feasible, might offer a wise alternative

Conclusions-continued

- Industry R&D support is important for funding controlled multicenter studies
- Many physiological parameters already monitored in the ICU: EKG, metabolism, VCP, ICP, etc
- What about continous EEG?
- Dedicated c-EEG systems are being developed
- In the future: AI closed-loop system with built-in neuromodulation???

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THANK YOU!

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