Brain stimulation and treatment of motor impairments

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Brain stimulation and therapy

- Repetitive TMS (rTMS) of a cortical area activates the same synapses repeatedly
 - plasticity
- This may account for some of the changes in excitability that persist after rTMS
- Plasticity = learning; hence interest in rehabilitation
- BUT
- Is this the only way that rTMS might interact with learning?
- Could variability be a factor?
- Teo et al (2005) examined effect of iTBS on variability and learning



iTBS increased variability

As quantified by the variance in the direction of evoked thumb movements after pretreatment with iTBS

Teo et al. (Cerebral Cortex 2005)

iTBS also improved learning

- Give iTBS prior to learning thumb abduction task and participants increase their initial acceleration more rapidly during repeated practice
- Is the effect "plasticity" or variability?



Recent expt in cats: 10 Hz rTMS increases variability and improves response to orientation training (Kozyrev et al 2018)

- Examine visual orientation maps in V1 before and after rTMS
- Variability of maps increases after rTMS
- But the ability of repeated stimulation with a directional grating to change maps is increased after rTMS





Never mind the mechanism: does it work in stroke?

- Uncertain at moment
- Trials are too small with heterogeneous designs making them difficult to compare
- Response rate highly variable between participants
- AND conventional therapies can be remarkably efficient

• So lets ask another question that we might be able to answer more easily





Figure 5: Scatterplot showing the differences in scores obtained from admission with discharge, 6 weeks and 6 months in Fugl-Meyer. Mean changes of 6.32, 7.73 and 7.89 respectively.

TWO "contrasting" TDCS results (it all depends on how you measure outcomes)

A double-blinded randomised controlled trial exploring the effect of anodal transcranial direct current stimulation and uni-lateral robot therapy for the impaired upper limb in sub-acute and chronic stroke.

Tedesco-Triccas et al (2016) Neurorehabilitation

"Adding tDCS did not result in an additional effect on UL impairment in stroke." 22 patients, 18 sessions (2-3/week), 1mA, 20min, 1 hour training

Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke Allman et al (2016) <u>Science Translational Medicine</u>

"The addition of ipsilesional anodal tDCS to a 9-day motor training program (GRASP) improved long-term clinical outcomes relative to sham treatment in patients after stroke."

24 patients, 9 sessions (daily), 1mA, 20min, 1 hour training





Is there a "window" of increased plasticity after stroke?

- Data from stroke models in animals suggests that following resolution of ischaemic damage, there is a period in which nerve axons branch and new connections are formed between cells ("plasticity") at a much faster rate than in the normal adult brain
- In addition there is reduced inhibition (GABAa) and enhanced excitation (glutamate)
- The theory is that this window of qualitatively different plasticity underlies the period of "spontaneous biological recovery"
- These natural processes have to be combined with movement practice (i.e. therapy) in order to be functionally effective.



Rat model of stroke: Enhanced rehabilitation (i.e. enriched environment + daily task training) is more effective when given early after stroke.

Early treatment interacts better with the window of increased plasticity.



Plasticity window after stroke? (Duncan Austin & Brenton Hordacre)

- IN two parallel experiments in Adelaide and London
- Examine TMS-induced motor cortex plasticity in patients at 2, 4, 6 weeks and 6 months after stroke.
- Is there evidence of a period of increased plasticity?
- Use spaced continuous theta burst protocol, measuring MEPs up to 30min after second cTBS burst (Goldsworthy et al, 2012)
- London: test contralesional hemisphere
- Adelaide: test ipsilesional hemisphere
- All subjects had made a good functional recovery with FMUL > 58 or ARAT > 55 after 4 weeks
- Approx 30 patients each centre (calculated from a separate study looking at reproducibility of spaced cTBS over measurements made 6 months apart).





Evolution of "plasticity" changes after stroke

- There is a larger response to the paired cTBS protocol 2-4 weeks after stroke than at 6 months
- Suggests that plasticity may be enhanced (compared with a presumed baseline pre-stroke) after stroke
- If correct then does this mean that this is the optimal time to give rehabilitation therapy? (i.e. do not send patients home too soon)
- Data being analysed to see if changes in plasticity relate to improvement in outcome, but given the inter-individual variability it may be difficult to observe.