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mGrid: A Load-Balanced Distributed Computing Environment for the Remote Execution of the User-Defined Matlab Code

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FOCUS

Transcranial magnetic stimulation: a stimulating new method for treating depression, but saddled with the same old problems

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When Dr Tony Barker designed and built the first modern TMS device in 1985 in Sheffield, England, he probably could not have predicted then how things would evolve with his 'fancy gadget' (Barker et al., 1985). For the first time he had built a machine powerful enough to non-invasively induce currents within the brain and spinal cord. Because TMS can create focal transient lesions, as well as measure brain excitability and regional connectivity, neuroscientists all around the world are now busily using it to understand the brain. TMS research is shown at every major neuroscience meeting now, with articles constantly sprinkled in many issues of prominent journals. Dr Barker's gadget is also evolving as a potentially important new therapy – especially for depression. However, as is often the case, technology has outpaced real understanding, and we have run into a wall. TMS is like the fancy new sports car sitting in our driveway. It looks pretty and can really move fast, however, because we lack true understanding of important brain questions, we cannot drive the sports car (TMS) to its maximum potential. Because our understanding of psychiatric diseases is still lagging, it is as if the roads are unpaved, and we do not have good maps. We are only using the technology in its crudest fashion. The fancy sports car is still in first gear, going 10 mph, with lots of stops, asking for directions.

TMS is really an amazing technology. For the first time ever, researchers and clinicians have a method for focally stimulating the brain in an alert awake adult who can immediately give feedback about what regional brain stimulation is doing to their thoughts, behaviours, wishes and desires (George and Belmaker, 2006). How very exciting! Surely this powerful tool, combined with modern imaging methods, and placed in the hands of legions of dedicated researchers, will quickly allow us to locate, surround and then conquer depression. We should be able to seek out the regions of the brain that are dysfunctional and reset them magically with the flick of a switch. And drive off into the sunset.

Well, the cold reality is that while TMS really is an important high-tech innovation, we are still forced to slowly slug it out in the clinics, trying to perfect it as a treatment. Three papers in this edition of *IJNP* simultaneously show the eventual promise of TMS, as well as highlight the very hard work it will take to perfect it as an antidepressant treatment.

TMS was first proposed as an antidepressant in case series of single-pulse TMS applied over the vertex (Grisaru et al., 1994; Hoflich et al., 1993; Kolbinger et al., 1995). The next round of antidepressant work involved focal stimulation of the prefrontal cortex in a dosing paradigm largely mimicking ECT (George et al., 1995, 1996, 1997). Dr Robert Post and I, both then at the NIMH, had to make a host of assumptions when we treated the first patients with prefrontal TMS. The basic paradigm we chose has now been tested for replication in over 20 prospective

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See Fitzgerald et al. (this issue). A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression; Fregni et al. (this issue). Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation; Rosa et al. (this issue). Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized single-blind study.

randomized controlled trials and appears to have antidepressant effects (Burt et al., 2002; Holtzheimer et al., 2001; Kozel and George, 2002; Martin et al., 2002). However, most of the parameters remain unexamined; and, unfortunately, we still do not understand the pathophysiology of the depressions.

In this issue, Fitzgerald and colleagues continue their important work in perfecting how TMS is delivered as an antidepressant, this time taking on one of the oldest paradigms in the field – the valence theory of mood or emotion (Fitzgerald et al., 2006; Wheeler et al., 1993). The valence theory of mood regulation has taken many different incarnations, but basically holds that mood disorders arise out of an imbalance between hemispheres, with right hemisphere hypoactivity driving mania, and left hemisphere hypoactivity driving depression (Bowers et al., 1991; George et al., 1993; Sackeim et al., 1978, 1982; Silberman and Weingartner, 1986). This approach would argue that a way to treat depression would be to inhibit the right hemisphere (low-frequency stimulation driving long-term depression) or activate the left hemisphere [high- frequency stimulation producing long-term potentiation (LTP)]. High-frequency TMS does excite the brain (Speer et al., 2000), and low-frequency TMS inhibits (Di Lazzaro et al., 2005; Fitzgerald et al., 2002; Gerschlager et al., 2001; Tsuji and Rothwell, 2002; Wassermann et al., 1998). In this issue, Fitzgerald and colleagues (2006) demonstrate that there is no difference in two different right hemisphere low frequencies despite doubling the dose, and that some patients later respond to left high frequencies. Unfortunately, in order to best address this issue one needs a huge trial with a totally randomized and balanced design with four cells – left or right prefrontal cortex, high or low frequency. Further work is still needed to determine the best prefrontal location and frequency.

The article by Rosa and colleagues (2006) in this issue builds on the work first started by Dr Saxby Pridmore. Early on, he used TMS in his outpatient practice and boldly stated that TMS and ECT had roughly similar antidepressant effects (Kirkcaldie et al., 1997; Pridmore, 2000; Pridmore et al., 1998). Few believed him at the time. There have now been several single-blind studies directly comparing ECT and TMS, and most have found no difference in efficacy, while there are large differences in side-effects and costs (Dannon et al., 2002; Dannon and Grunhaus, 2001; Grunhaus et al., 2000, 2003; Janicak et al., 2002; Pridmore et al., 2000). It is important to remember that showing similar efficacy in small sample studies is not the same thing as establishing equivalence. Most clinicians believe that bilateral ECT is a more powerful antidepressant than TMS. But this study and others like it certainly demonstrate that TMS is clinically effective in the range of other medications and ECT.

A further TMS paper in this issue tackles the most important issue of who responds to TMS (Fregni et al., 2006). This international team found that younger age and less treatment resistance are positive response predictors. This makes sense on multiple levels. ECT is a real salvation for elderly depressed patients who cannot tolerate medications. There was thus initial hope that TMS might fill this clinical niche, without a risk of cognitive side-effects. Unfortunately an early study found that elderly patients did not respond to TMS (Figiel et al., 1998). Later work shed some light on this by noting that, because of larger prefrontal atrophy, elderly patients might need higher doses to actually reach the brain (Kozel et al., 2000; Nahas et al., 2001). More work is needed to determine whether elderly depression is less likely to respond to TMS, or whether as some have claimed we simply have to age-adjust the dose (Nahas et al., 2004). Reassuringly almost, TMS is like all other antidepressants in that prior treatment resistance predicts poorer outcome. Unfortunately, in this area at least, TMS is no different than other antidepressants.

So, TMS really is 'something new under the sun' and is opening up novel avenues for research and innovative ways of treating patients. However, without a full understanding of the pathophysiology of the depressions, we really cannot use TMS in its most powerful way to treat our patients. We have a Ferrari of a technique (TMS), but the roads are still filled with potholes (the translational neurobiology of depression). We have a great new car in TMS, but we still lack a roadmap of depression. The going is still slow, even with the shiniest and fastest of new toys. We need much more high-quality research, like the articles in this issue.

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Statement of Interest

The author and his immediate family members have no equity stake in any device or pharmaceutical company. Within the past 3 years, the Brain Stimulation Laboratory has received research grant funding from GSK, Jazz, Cyberonics, Neuronetics, and Neuropace. The author holds several TMS-related patents. These are not in the area of TMS therapeutics, but rather are for new TMS machine designs as well as combining TMS with MRI. Dr George serves or has served within the past 3 years as a paid consultant to, or paid speaker for, several device companies (Aspect, Cephos, Cyberonics, Neuronetics, Neuropace) and pharmaceutical companies (Abbott, Argolyn, Aventis, Cortex, Darpharma, GSK, Jazz). His entire yearly compensation for consulting and speaking is less than 10% of his university salary.

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