

Bilateral priming accelerates recovery of upper limb function after stroke: A randomized controlled trial

Introduction: The ability to live independently after stroke depends on the recovery of motor function, particularly of the upper limb.¹ Techniques that ‘prime the brain’ for a more plastic response to therapy may accelerate motor recovery after stroke. Increasing excitability and reducing inhibition are important precursors for neural plasticity,² which may allow surviving neural elements to more easily reorganise in response to therapy.³ Active-passive bilateral priming (APBP) is a pattern of coordinated movement that disinhibits the M1 contralateral to the assisted (paretic) limb,⁴ and facilitates its excitability for at least 30 minutes after a 15 minute session.⁵ In patients at least six months after stroke, daily APBP followed by motor practice led to increased ipsilesional corticomotor excitability and a greater improvement in upper limb function compared to motor practice alone.⁶ The aim of this study was to determine the immediate and longer-term effects of bilateral priming with stroke patients at the sub-acute stage. We hypothesized that APBP (bilateral priming) before upper limb therapy would accelerate the recovery of hand and arm function, with a greater proportion of primed participants reaching maximum recovery by 12 weeks.

Methods: A single-centre randomized controlled trial of bilateral priming was conducted with 57 patients randomized at the sub-acute stage after first-ever ischemic stroke. The priming group made device-assisted mirror symmetric bimanual movements before upper limb physiotherapy, every weekday for 4 weeks. (Fig 1). The control group were given intermittent cutaneous electrical stimulation of the paretic forearm before physiotherapy. Assessments were made at baseline, 6, 12 and 26 weeks. Blinding was carefully maintained by having three groups of therapists who primed, treated and assessed participants. The primary endpoint was the proportion of patients who reached their plateau for upper limb function at 12 weeks, measured with the Action Research Arm Test.

Results: All participants began the intervention within 26 days of stroke. The groups’ clinical baseline characteristics were

well-balanced, as was their potential for recovery based on neurophysiology, neuroimaging and BDNF genotype. Odds ratios indicated that primed participants were 3 times more likely than controls to reach their recovery plateau by 12 weeks. (Fig 2) Intention to treat and per protocol analyses showed a greater proportion of primed participants achieved their plateau by 12 weeks (ITT: $\chi^2=4.25$, $P=0.039$; PP: $\chi^2=3.99$, $P=0.046$). ANOVA of per protocol data showed primed participants had greater re-balancing of corticomotor excitability than controls at 12 and 26 weeks and interhemispheric inhibition at 26 weeks (all $P<0.05$)

Conclusions: Bilateral priming before upper limb therapy accelerates the recovery of upper limb function after stroke, and increases the odds of reaching the recovery plateau by 12 weeks for equivalent therapy dose. Bilateral priming is a neuromodulatory adjuvant rather than a therapy, and is therefore distinct from bilateral isokinematic training or bilateral arm training with auditory cueing, which have been found to have no additional benefits by a recent Cochrane review.⁷ The neurophysiological effects of APBP are the most likely mechanism underlying the observed acceleration of recovery. Excitability increased for both descending and transcallosal projections from the ipsilesional M1 in the primed group, but not the control group. The successful primed treatment of a heterogeneous sample of patients in a busy clinical setting indicates that bilateral priming is feasible in the ‘real world’ and that these findings are generalisable.

References

1. Kwakkel G, Kollen BJ. *Int J Stroke*. 2013;8:25-32
2. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. *Annu Rev Neurosci*. 2000;23:393-415
3. Murphy TH, Corbett D. *Nat Rev Neurosci*. 2009;10:861-872
4. Stinear JW, Byblow WD. *J Physiol*. 2002;543:307-316
5. Byblow WD et al. *PLoS One*. 2012;7:e33882
6. Stinear CM et al. *Brain*. 2008;131:1381-1390
7. Coupar F et al. *Cochrane database of systematic reviews (Online)*. 2010:CD006432



Figure 1. Active-passive bilateral priming. The patient rhythmically flexes and extends the non-paretic wrist, while the device assists movement of the paretic wrist in a mirror-symmetric pattern via a mechanical coupling. The device confers an inertial advantage such that little force is required from the active wrist to maintain repetitive flexion-extension of both wrists. Participants in the primed group completed several hundred movement cycles, during each 15 minute priming session, prior to 30 minutes of upper limb therapy.

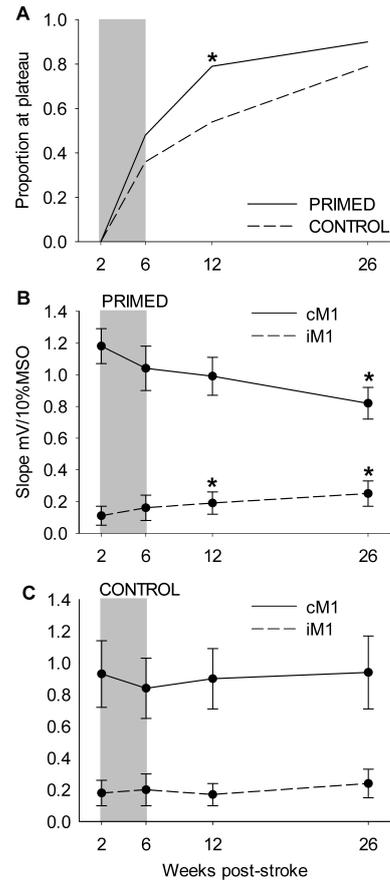


Figure 2. A. Primary endpoint. ITT analysis of the proportion of patients who reached their recovery plateau at 6, 12 and 26 weeks post-intervention. A significantly greater proportion of the primed patients achieved the plateau at 12 weeks, the primary endpoint. * $P=0.039$. Error bars=standard deviation. B & C. Corticomotor excitability increased in ipsilesional M1 (iM1), and decreased in contralesional M1 (cM1), for the primed group, but not the control group. Error bars = standard error; * $P<0.05$, two-tailed t -test comparison with baseline. The grey area indicates the 4 week period of primed therapy.