Prim ing the motor system enhances the effects of upper limb therapy in chronic stroke

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After stroke, the function of primary motor cortex (MI) between the hemispheres may become unbalanced. Techniques that promote a re-balancing of MI excitability may prime the brain to be more responsive to rehabilitation therapies and lead to improved functional outcomes. The present study examined the effects of Active–Passive Bilateral Therapy (APBT), a putative movement-based priming strategy designed to reduce intracortical inhibition and increase excitability within the ipsilesional MI. Thirty-two patients with upper limb weakness at least 6 months after stroke were randomized to a 1-month intervention of self-directed motor practice with their affected upper limb (control group) or to APBT for 10–15 min prior to the same motor practice (APBT group). A blinded clinical rater assessed upper limb function at baseline, and immediately and 1 month after the intervention. Transcranial magnetic stimulation was used to assess MI excitability. Immediately after the intervention, motor function of the affected upper limb improved in both groups \( (P < 0.005) \). One month after the intervention, the APBT group had better upper limb motor function than control patients \( (P < 0.05) \). The APBT group had increased ipsilesional MI excitability \( (P < 0.025) \), increased transcallosal inhibition from ipsilesional to contralesional MI \( (P < 0.01) \) and increased intracortical inhibition within contralesional MI \( (P < 0.005) \). None of these changes were found in the control group. APBT produced sustained improvements in upper limb motor function in chronic stroke patients and induced specific and sustained changes in motor cortex inhibitory function. We speculate that APBT may have facilitated plastic reorganization in the brain in response to motor therapy. The utility of APBT as an adjuvant to physical therapy warrants further consideration.

Keywords: stroke; rehabilitation; upper limb; primary motor cortex; transcranial magnetic stimulation; inhibition; bilateral therapy

Abbreviations: APBT = Active–Passive Bilateral Therapy; BIT = bilateral isokinematic training; ECR = extensor carpi radialis; EMG = electromyography; FCR = flexor carpi radialis; FM = Fugl–Meyer; MEP = motor evoked potential; MSO = maximum stimulator output; NIHSS = National Institutes of Health Stroke Scale; RMT = rest motor threshold; SICI = short-latency intracortical inhibition; TCI = transcallosal inhibition; TMS = transcranial magnetic stimulation


Introduction

In healthy adults, the excitability of neurons within motor cortex is balanced between the two hemispheres, as measured with techniques such as transcranial magnetic stimulation (TMS). Each primary motor cortex (M1) actively inhibits the opposite M1 via pathways in the corpus callosum and this prevents mirror movements (Ferbert et al., 1992; Duque et al., 2007). After stroke, this mutual transcallosal inhibition (TCI) becomes asymmetric. The ipsilesional M1 generates less TCI (Boroojerdi et al., 1996; Shimizu et al., 2002), and this may contribute to the increased excitability and reduced intracortical inhibition observed in the contralesional M1 (Liepert et al., 2000; Manganotti et al., 2002; Shimizu et al., 2002; Butefisch et al., 2003). The contralesional M1 generates normal levels of TCI resulting in a net increase in inhibition acting on ipsilesional M1 (Murase et al., 2004). This in turn depresses ipsilesional M1 excitability and further suppresses the generation of TCI. These changes have been shown to be associated with reduced functional recovery in stroke (Rossini et al., 2003; Hummel and Cohen, 2006).
Better clinical outcomes following stroke are associated with increased excitability of the ipsilesional motor cortex (Catano et al., 1996; Traversa et al., 2000; Dobkin, 2004; Talelli et al., 2006a), and techniques that promote re-balancing of cortical excitability and TCI are likely to enhance stroke recovery (Rossini et al., 2003; Dobkin, 2004; Hummel and Cohen, 2006). Priming the motor system prior to physical therapy, with techniques designed to balance corticomotor excitability and TCI, is a promising new therapeutic strategy supported by a number of ‘proof of principle’ studies (Fregni et al., 2005; Hummel et al., 2005; Khedr et al., 2005; Mansur et al., 2005; Takeuchi et al., 2005). Priming of the brain can involve the use of neuromodulators such as drugs and non-invasive brain or somatosensory stimulation techniques (Dobkin, 2004; Hummel and Cohen, 2006; Ridding and Rothwell, 2007). The use of movement-based strategies that may prime the motor system for beneficial plasticity remains largely under-explored.

Bilateral movement training has shown some promise in promoting recovery of upper limb function in chronic stroke patients (Cauraugh and Summers, 2005). Whitall and colleagues (2000) demonstrated that bilateral movements paced by an auditory metronome led to improved function of the weak or paretic arm in a study involving chronic patients. It has been argued that bilateral movements performed in synchrony can generate crossed facilitation between the non-paretic and paretic upper limbs. However, stroke patients may have difficulty actively moving the paretic upper limb due to weakness, or other complicating factors like spasticity. Here we explore a novel bilateral movement-based approach known as Active–Passive Bilateral Therapy (APBT). APBT relies upon a device which mechanically couples the two hands. Using APBT, stroke patients actively produce rhythmic flexion-extension of the non-paretic wrist, and mirror-symmetric movements of the paretic hand are generated through a mechanical linkage that confers an inertial advantage. During active–passive bilateral wrist flexion-extension movements, such as the kind produced by APBT, there is a reduction in short-latency intracortical inhibition (SICI) within the passive M1, as assessed using TMS (Stinear and Byblow, 2002, 2004b). This reduction in SICI may arise from a reduction in TCI due to synchronous somatosensory feedback such that the upper limbs become functionally coupled (Schnitzler et al., 1996; Stinear and Byblow, 2002; Carson et al., 2004; Vardy et al., 2007). Disinhibition within ipsilesional M1 may facilitate use-dependent plasticity (Hess and Donoghue, 1996). In a pilot study we found neurophysiological evidence that APBT promoted re-balancing of M1 excitability in a small sample of chronic stroke patients who showed improved upper limb function after a period of self-administered therapy (Stinear and Byblow, 2004c).

In the present study, we examined the effects of APBT combined with a programme of motor practice in patients at least 6 months after stroke. Changes in motor system function were measured with TMS, which was used to evaluate corticomotor excitability, TCI and intracortical function (Talelli et al., 2006a). We hypothesized that priming the motor system with APBT would result in a greater balancing of corticomotor excitability and TCI, and that this would enhance the functional benefits of motor practice.

**Methods**

**Participants**

Thirty-two patients (20 men, mean age 55.3 years, range 25–82 years) with first-ever stroke at least 6 months prior to enrolment were studied. Inclusion criteria included upper limb weakness, with an abbreviated Fugl–Meyer (FM) upper limb score of between 3 and 25. The abbreviated FM scale included the wrist, hand and coordination sections, which have been shown to be reliable [ρ 0.971–0.984, (Platz et al., 2005)]. Together, these sections comprise 16 items, each given a score of 0 (unable), 1 (incomplete) or 2 (normal), with a maximum total score of 32. Exclusion criteria included increased upper limb spasticity with a modified Ashworth Scale wrist spasticity score >2; severe sensory loss as assessed with the NIHSS and contraindications to magnetic resonance imaging (MRI) or TMS. All participants had MRI T1- and T2-weighted images, from which lesion location and extent were determined. Customized software was used by the study coordinator to randomly allocate each participant to the control or APBT group (Fig. 1). The software involved a minimization procedure which was used to constrain between-group differences in age, time since stroke and FM score. All participants gave written informed consent and the study was approved by the regional Ethics Committee. This study is registered with the Australian Clinical Trials Register, number ACTRN012605000261617.

![Fig. 1](http://brain.oxfordjournals.org/) Trial profile. Asterisk indicates inclusion of five eligible patients originally assigned to control who crossed over to APBT after a one-month wash-out.
Intervention
All participants were provided with a set of wooden blocks, and
instructed to perform two self-directed, home-based tasks with their
affected upper limb. The blocks were a variety of shapes, with the
dimensions of each side ranging from 2 to 9 cm. The container with
matching holes was 15 × 15 × 15 cm³ in size. The first task was to
pick up and transport each block 20 cm, using a visual distance
guide. The second task was to manipulate each block, by picking up
and slotting it through the appropriately shaped hole in the block
container. All participants were able to perform both tasks, though
with a range of speed and accuracy. The goal was to spend 10 min
performing these tasks with the affected hand three times per day
over 4 weeks. Transporting or manipulating all 12 blocks consti-
tuted one repetition of each task. Patients were asked to record the
number of repetitions performed of each task, and the total amount
of time, for each session. Patients were randomized to motor
practice alone (control group) or APBT for 10–15 min followed by
motor practice (APBT group).

The APBT group were provided with an APBT device developed
in our laboratory that allows up to 135° rhythmic flexion-extension
of the unaffected wrist, which in turn drives the passive flexion-
extension of the affected wrist in a mirror-symmetric pattern. APBT
produces afferent input from the passive stretch of wrist
flexors and extensors, and long finger flexors and extensors, all of
which were engaged by the subsequent motor practice. Patients
were instructed to focus attention on the unaffected wrist at the
beginning of each APBT session, to establish smooth, rhythmic
movement. They were instructed to then shift their attention to the
affected wrist, and allow it to be passively driven. In the third week,
they were instructed to imagine that they were actively producing
the movements of their affected wrist, with progression towards
bilaterally active movements in the fourth week. This was intended
to ensure that all patients started the intervention using the device
in the same way, and then progressed towards active movement in
the fourth week, to the best of their abilities. Motor imagery was
included in the third week, as previous work has shown that it
activates cortical motor areas (Ehrsson et al., 2003; Hanakawa et al.,
2003), increases the excitability of M1 (Facchini et al., 2002; Stinear
and Byblow, 2003; Stinear et al., 2006), and can improve upper limb
function in chronic stroke patients (Dijkerman et al., 2004; Page
et al., 2007). Patients recorded the actual amount of time spent
using the device in each session. All control group patients were
offered the APBT intervention after a 1-month washout period.
Data from ‘cross-over’ patients were included in the APBT group
analysis if they had no change in FM score during the control
intervention and still met the study’s inclusion criteria at the time of
‘cross-over’. Patients were contacted every week to check com-
pliance with the intervention.

Assessments
Clinical assessments consisted of the abbreviated version of the
upper limb FM scale described above, the National Institutes of
Health Stroke Scale (NIHSS), and grip strength in each hand,
measured using a custom handgrip dynamometer. The lateraliza-
tion of grip strength was calculated: \( \frac{F_{\text{un}} - F_{\text{aff}}}{F_{\text{un}} + F_{\text{aff}}} \) where
\( F \) = maximal grip force (N) for the unaffected and affected hands.

Baseline assessments were performed on two occasions separated
by 1 month, prior to the intervention, to confirm a stable baseline.
Clinical assessments were performed by a trained clinical rater who
was blinded to the patients’ group allocation (control or APBT),
and to the results of previous assessments. Post-intervention
assessments were performed immediately and 1 month after the
intervention. For each clinical scale and grip lateralization, change
scores were calculated by subtracting the score at baseline from each
post-intervention score. FM change scores were also converted to
percentage change. The primary outcome measure was FM change
scores 1 month post-intervention, relative to baseline.

TMS was used to measure corticomotor excitability in each
hemisphere, TCI from ipsilesional M1 to contralesional M1 and
SICI within contralesional M1. These measurements were made
immediately before and after the intervention in both the control
and APBT patients, and again 1 month after the intervention. TMS
was delivered using two MagStim stimulator 200 stimulators and a
BiStim unit (MagStim Company, Dyfed, UK), via a figure-of-eight
coil (wing diameter 9 cm) oriented to induce current flow in a
posterior to anterior direction in the underlying tissues. Surface
electromyography (EMG) was recorded from the extensor carpi
radialis (ECR) and flexor carpi radialis (FCR) muscles of each
forearm. The coil was positioned over the scalp, at the optimal site
for producing responses in the resting ECR muscle.

In the pre-intervention session, the rest motor threshold (RMT;
Rossini et al., 1994) of each ECR was determined and the stimulus
intensity set to 110% RMT for mapping the ECR corticomotor
representation, as previously described (Stinear and Byblow, 2004c).
Briefly, mapping was carried out by delivering six stimuli at each of
18 pre-determined grid points over the scalp, in a different pseudo-
randomized order for each session. Trials were rejected online if
pre-trigger EMG in any of the four muscles exceeded 0.01 mV
(root-mean-square, calculated over 100 ms prior to the stimulus).
The area of each motor evoked potential (MEP, mV-s) was
calculated over a 15 ms window, beginning at the mean MEP
latency for the individual muscle. The stimulation intensity used for
mapping in the pre-intervention session was used for both post-
intervention sessions, to enable between-session comparisons of
map volume. RMT was determined at the beginning of each post-
intervention session, and 110% RMT calculated. If this intensity was
found to differ from that used in the pre-intervention session by
>5% RMT, mapping was also conducted at the new 110% RMT
intensity. This enabled between-session comparisons of map Centre
of Gravity (CoG). Transcallosal inhibition from the ipsilesional to
contralesional M1 was assessed by delivering 12 stimuli at 80% maximum
stimulator output (MSO) over the optimal site for eliciting MEPs in
the affected ECR. Patients were instructed to pronate their unaf-
fected forearm, and then extend their wrist with ~50% maximal
effort. Stimuli were delivered in blocks of four, separated by rest
periods, to prevent fatigue. TCI was defined as a silent period in the
EMG trace of the unaffected ECR (Chen et al., 2003; Avanzino et al.,
2007), below one-third of the pre-trigger value, in a window
between 30 and 60 ms following the magnetic stimulus. TCI
persistance was defined as the number of trials (max. 12) that
produced a silent period, and the latency and duration of each silent
period were calculated.

The threshold for SICI was determined for the contralesional
hemisphere, as previously described (Orth et al., 2003; Stinear
and Byblow, 2004a). Briefly, 16 MEPs were recorded in response to
a test stimulus set to produce a MEP of ~0.5 mV amplitude in the
resting unaffected ECR. The active threshold (AMT) for the
unaffected ECR was then determined while the patient maintained
isometric wrist extension against gravity (Rossini et al., 1994).
A range of conditioning stimulus intensities were used (50, 65, 80,
Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Control (n = 16)</th>
<th>APBT without cross-over (n = 16)</th>
<th>P</th>
<th>APBT with cross-over (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>579 (38–78)</td>
<td>52.6 (25–73)</td>
<td>&gt;0.2</td>
<td>53.7 (25–73)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Gender, male</td>
<td>10 (63%)</td>
<td>10 (63%)</td>
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<td>13 (62%)</td>
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<tr>
<td>Clinical syndrome</td>
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<tr>
<td>Time since stroke, months</td>
<td>28.8 (6–144)</td>
<td>20.2 (6–73)</td>
<td>&gt;0.5</td>
<td>24.7 (6–116)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Left hemisphere stroke</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td></td>
<td>12 (57%)</td>
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<tr>
<td>Lacunar infarct</td>
<td>5 (31.3%)</td>
<td>5 (31.3%)</td>
<td></td>
<td>7 (33.3%)</td>
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<tr>
<td>MCA territory, motor cortex spared</td>
<td>8 (50.0%)</td>
<td>9 (56.3%)</td>
<td></td>
<td>9 (42.8%)</td>
<td></td>
</tr>
<tr>
<td>MCA territory, motor cortex involved</td>
<td>3 (18.7%)</td>
<td>2 (12.4%)</td>
<td></td>
<td>5 (23.9%)</td>
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<tr>
<td>Pathology</td>
<td></td>
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<tr>
<td>Cerebral infarction</td>
<td>15 (93.8%)</td>
<td>15 (93.8%)</td>
<td></td>
<td>20 (95.2%)</td>
<td></td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
<td>1 (6.2%)</td>
<td>1 (6.2%)</td>
<td></td>
<td>1 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Stroke disability</td>
<td></td>
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<tr>
<td>Upper limb FM</td>
<td>17.6 (3–25)</td>
<td>15.0 (5–25)</td>
<td>&gt;0.1</td>
<td>14.0 (4–25)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>NIHSS</td>
<td>3.6 (1–10)</td>
<td>3.3 (1–8)</td>
<td>&gt;0.1</td>
<td>3.4 (1–8)</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Data are mean (range) or number (%).

95 and 110% AMT), with a condition-test interval of 3 ms. Eight responses were recorded at each conditioning stimulus intensity, in a randomized order. The %SICI produced by each conditioning stimulus intensity was calculated, and the threshold defined as the minimum intensity that produced at least 10% SICI with further increases as the intensity of stimulus increased (Stinear and Byblow, 2004a). Trials were rejected online if pre-trigger EMG in any of the four forearm muscles exceeded 0.01 mV (root-mean-square, r.m.s.). For offline analysis, the r.m.s. of the pre-trigger EMG in all four muscles was determined over a 75 ms period ending 5 ms prior to the stimulus.

We anticipated that contralesional M1 excitation would decrease in response to APBT (Stinear and Byblow, 2004c). To explore possible mechanisms for this, we examined two forms of inhibition acting on the contralesional M1: TCI from the ipsilesional M1; and SICI within the contralesional M1. TCI from the contralesional to the ipsilesional M1 was not determined, as it was expected to be near-normal (Talelli et al., 2006a). The threshold for SICI was not evaluated in the ipsilesional M1, as we anticipated small test MEP amplitudes, which make the interpretation of the effects of conditioning difficult (Roshan et al., 2003). While evaluation of TCI and SICI threshold bilaterally would have provided a more complete picture, these variables can only be reliably measured from the ipsilesional M1 in well-recovered patients.

Statistical analysis

The study sample size calculations were based on a previous finding that APBT is associated with decreased contralesional corticomotor excitability and FM score increases of at least 10% (Stinear and Byblow, 2004c). The FM and NIHSS are ordinal scales, and these data were not normally distributed, so non-parametric tests of statistical significance were used. The Wilcoxon signed-ranks test was used for within-group comparisons, and the Mann–Whitney U-test was used to test for an effect of group on the change in FM and NIHSS score. A mixed ANOVA, with factors Group (control, APBT), Side (affected, unaffected) and Time (baseline, immediately after intervention, 1 month after intervention) was used to assess changes in grip strength lateralization, pre-trigger EMG, corticomotor excitability (MEP latency, threshold, map CoG, map volume) and inhibitory function (TCI onset and duration, contralesional SICI threshold). For the expected effects of Group and Time, one-tailed t-tests were used to explore significant main effects and interactions. For all other significant effects or interactions, two-tailed t-tests were used for post hoc comparisons. Mean values are presented ± standard error of the mean (SEM). A Mann–Whitney U-test was applied to change in TCI persistence, and median values and inter-quartile range are presented. The analysis of clinical measures was conducted both with and without the inclusion of crossover patients. Neuropsychological measures were analysed with the inclusion of crossover patients, to gain adequate statistical power for non-parametric testing. Statistical significance was set at P < 0.05.

Results

Thirteen patients completed the control intervention, and 19 completed the APBT intervention (Fig. 1). The two groups were well matched at baseline (Table 1) and remained well matched following the crossover of five control patients to the APBT intervention after a 1 month washout period. The five crossover patients had a median FM change score of 0 points (range 0–1) at both assessments following the control intervention, and a median FM change score of 2 points (range 0–4) at both assessments following the APBT intervention. This demonstrates that the crossover patients did not benefit from motor practice alone, but did benefit when motor practice was preceded by APBT. The possibility that the motor practice intervention somehow influenced the crossover patients’ response to the APBT intervention (initiated after a 1-month washout period) cannot be completely ruled out, although this seems unlikely.
Table 2 Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>APBT with cross-over</th>
<th>P</th>
<th>APBT without cross-over</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
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<tr>
<td>Δ FM score, percentage (mean, SEM)</td>
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</tr>
<tr>
<td>Immediately post-intervention</td>
<td>12.7 (10.0)</td>
<td>21.2 (8.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>One month post-intervention</td>
<td>10.8 (8.5)</td>
<td>27.1 (6.9)</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
<td>Δ FM score, points (median, range)</td>
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<tr>
<td>Immediately post-intervention</td>
<td>2.0 (0, 4)</td>
<td>2.0 (–1, 5)</td>
<td>&gt;0.1</td>
<td>1.5 (–1, 5)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>One month post-intervention</td>
<td>1.5 (0, 5)</td>
<td>2.0 (–1, 6)</td>
<td>&lt;0.05</td>
<td>2.0 (–1, 6)</td>
<td>&lt;0.05</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>Δ NIHSS (median, range)</td>
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<tr>
<td>Immediately post-intervention</td>
<td>0.0 (–2, 2)</td>
<td>0.0 (–2, 2)</td>
<td>&gt;0.1</td>
<td>0.0 (–1, 2)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>One month post-intervention</td>
<td>0.0 (–2, 2)</td>
<td>0.0 (–2, 2)</td>
<td>&gt;0.1</td>
<td>0.0 (–2, 2)</td>
<td>&gt;0.1</td>
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<tr>
<td>Δ Grip lateralisation (mean, SEM)</td>
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<tr>
<td>Immediately post-intervention</td>
<td>–0.03 (0.16)</td>
<td>–0.01 (0.14)</td>
<td>&gt;0.2</td>
<td>0.01 (0.13)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>One month post-intervention</td>
<td>–0.02 (0.18)</td>
<td>–0.02 (0.19)</td>
<td>&gt;0.2</td>
<td>–0.01 (0.22)</td>
<td>&gt;0.4</td>
</tr>
</tbody>
</table>

Data are median (range) and mean (SEM). P-value for between-group comparison.

The control and APBT groups performed an equivalent number of repetitions of each motor practice task. The mean number of block transport repetitions per session was 3.1 (SD 1.7) for the control group and 3.0 (SD 2.5) for the APBT group. For the block manipulation task, the mean repetitions per session was 1.7 (SD 1.2) for the control group and 1.3 (SD 1.6) for the APBT group. There were no differences between the groups in the number of repetitions per session, for either Task (two-tailed t-test, both P > 0.4). Patients randomized to the APBT group spent a mean of 13.3 min (SD 6 min, range 4–31 min) performing APBT prior to each of the three daily motor practice sessions. Patients completed 93.7% of planned sessions, with the remaining sessions missed due to illness or travel. There were no adverse events or side-effects from the intervention.

**Clinical outcomes**

The NIHSS score was stable between the first and second baseline assessments for both groups (both P > 0.1), with no between-group difference at the second baseline assessment (P > 0.1). The NIHSS score did not change from baseline at either the immediate or 1 month post-intervention assessments, in either group (P > 0.05). Maximal grip strength was less in the affected hand (Affected = 83.6 ± 5.9 N, Unaffected = 234.1 ± 7.5 N, mean lateralization index = 0.51 ± 0.2), with no between-group differences or changes over time (all P > 0.2, Table 2). The stability of the NIHSS score and grip strength suggest that patients’ response to the interventions was specific to the affected upper limb, and not due to a simple increase in muscle strength.

The FM score was stable between the first and second baseline assessments for both groups (both P > 0.4), with no between-group difference at the second baseline assessment (P > 0.2). The FM score increased at the immediate post-intervention assessment compared to baseline (P < 0.005), with similar FM score increases in both the control and APBT groups (P > 0.1, Table 2). The FM score increased to a greater extent at the 1-month post-intervention assessment in the APBT group than the control group compared to baseline (P < 0.05). These effects were observed in the APBT group both with and without the inclusion of the five crossover patients (Table 2). Patients who spent more time performing APBT (as recorded in the treatment diaries) exhibited a greater increase in FM score at the 1-month post-intervention assessment (R^2 = 0.28, P = 0.035). There was no association between baseline FM score and subsequent change in FM score in either group (all R^2 < 0.14, P > 0.1).

**Neurophysiological outcomes**

At baseline, the ipsilesional M1 was less excitable than the contralesional M1, with higher rest and active motor thresholds, smaller map volume and longer MEP latency (all P < 0.01). There were also no differences between the groups in TCI persistence, onset or duration or SICI threshold (all P > 0.3). Following the intervention, transcallosal and intracortical inhibitory function improved, and ipsilesional ECR map volume increased, in the APBT group but not the control group (Table 3). Specifically, the persistence of TCI increased, and SICI threshold decreased in the contralesional M1, immediately and 1 month after the intervention (all P < 0.05). Also, in the APBT group only, ipsilesional M1 ECR map volume increased 1 month after the intervention (P < 0.025). In both groups, contralesional M1 map volume decreased, at both post-intervention time points (Table 4). In general, motor thresholds increased in contralesional M1, and decreased in ipsilesional M1, in both groups. Specifically, contralesional AMT increased immediately after the intervention, and RMT increased 1 month after the intervention. Ipsilesional AMT decreased at both...
post-intervention time points, while RMT decreased immediately after the intervention (Table 4).

Some neurophysiological measures remained stable across all sessions. MEP latency was stable (contralateral 19 ± 1 ms, *P > 0.8; ipsilateral 23 ± 1 ms, *P > 0.5). The centres of gravity for the ipsilateral and contralateral maps were stable, remaining within 0.4 ± 0.02 cm of baseline (*P > 0.2). The voluntary activation of the unaffected ECR during TCI testing was consistent (90.8 ± 9.2 µV, *P > 0.3), as were TCI latency (38.6 ± 0.4 ms, *P > 0.2) and duration (21.1 ± 1.0 ms, *P > 0.1). The amplitude of the non-conditioned ECR MEP was stable across sessions (0.39 ± 0.02 mV, *P > 0.7), and the tested upper limb remained at rest throughout data collection (ECR 3.1 ± 0.3 µV, FCR 5.4 ± 0.7 µV, both *P > 0.3).

**Discussion**

This study examined the effects of priming the motor system with a movement-based neuromodulation strategy in chronic stroke patients. All patients were stable at baseline and improved immediately after the intervention. However, only those patients primed with APBT before motor practice showed sustained improvement in upper limb motor function. The APBT group had specific neurophysiological changes in motor cortex function previously shown to be associated with improved outcome (Catano et al., 1996; Traversa et al., 2000; Talelli et al., 2006a).

At baseline corticomotor excitability was asymmetric between the hemispheres, as expected (Talelli et al., 2006a). Immediately after the intervention, the APBT group exhibited an increase in TCI from the ipsilateral to contralateral hemisphere. This group also had a decrease in contralateral SICI threshold to normal values (Orth et al., 2003), indicating that excitability of contralateral inhibitory intracortical networks increased. The changes in inhibitory function in the APBT group are likely related to the bimanual and mirror-symmetric nature of APBT, which is known to reduce SICI within the passively-driven M1 (Stinear and Byblow, 2002). Repeated exposure to APBT may have increased the capacity of the ipsilesional M1 to inhibit the contralateral M1, thereby promoting a re-balancing of TCI. This may have created a neurophysiological state allowing for an increase in ipsilesional

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### Table 3 Neurophysiological outcomes unique to the APBT group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>APBT</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Immediately after intervention</td>
<td>One month after intervention</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>ECR corticomotor excitability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilesional map volume</td>
<td>2.9 (0.9)</td>
<td>2.9 (0.7)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Inhibitory function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCI persistence</td>
<td>6.5 (5.0)</td>
<td>6.0 (4.0)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>SICI threshold,%AMT</td>
<td>84.1 (5.0)</td>
<td>81.8 (6.2)</td>
<td>&gt;0.6</td>
</tr>
</tbody>
</table>

Data are mean (SEM) or median (inter-quartile range). ECR = extensor carpi radialis; P-values = different from Baseline, 95% CI; Group P-values = significant interaction between Group and Time.

### Table 4 Neurophysiological outcomes common to APBT and control groups

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>ECR corticomotor excitability</td>
<td></td>
</tr>
<tr>
<td>Ipsilesional RMT</td>
<td>72.3 (6.1)</td>
</tr>
<tr>
<td>Contralateral RMT</td>
<td>45.0 (1.3)</td>
</tr>
<tr>
<td>Ipsilesional AMT</td>
<td>48.2 (3.4)</td>
</tr>
<tr>
<td>Contralateral AMT</td>
<td>32.8 (1.5)</td>
</tr>
<tr>
<td>Contralateral map volume</td>
<td>5.3 (0.8)</td>
</tr>
</tbody>
</table>

Data are mean (SEM); ECR = extensor carpi radialis; P-values = different from Baseline, 95% CI.
excitability over the follow-up period, seen with increased ipsilesional TMS map volume. These underlying changes in neural function were associated with sustained improvements in upper limb motor function that were only observed in the APBT group. In contrast, the control group did not exhibit any changes in SICI, TCI or ipsilesional map volume, and had less improvement in upper limb motor function 1 month after the intervention.

In addition to the specific changes in neural function observed in the APBT group, both groups showed changes in corticomotor excitability immediately after the intervention. Motor thresholds decreased in the ipsilesional M1, and increased in the contralesional M1, while contralesional ECR M1 map volume decreased. These changes were associated with increases in upper limb motor function and we speculate that this improvement may be the result of an amelioration of learned non-use (Taub et al., 2006). A shift towards greater use of the affected upper limb, and less use of the unaffected upper limb, may have produced the partial balancing of asymmetries in corticomotor excitability, observed in both groups immediately after the intervention. However, changes in inhibitory function and ipsilesional M1 excitability were only observed in APBT group patients, and were associated with sustained improvements in motor function at follow-up.

We propose that priming with APBT gives rise to changes in synaptic efficacy, and this supports the sustained improvement seen in the APBT group. Motor practice can alter synaptic efficacy within motor cortex, and this use-dependent plasticity is essential for motor re-learning during stroke recovery. Plastic reorganization within M1 is promoted by down-regulation of intracortical inhibition (Jacobs and Donoghue, 1991; Ziemann et al., 2001; Chen et al., 2002; Butefisch, 2004). For these reasons, APBT was developed to disinhibit the ipsilesional M1. We contend that repeated exposure to mirror-symmetric patterns can influence corticomotor excitability and TCI. In neurophysiological studies, we have described how excitability of M1 increases, and excitability of intracortical inhibitory networks decrease, in the passively driven hemisphere when the wrists are flexed and extended in a mirror-symmetric pattern (Stinear and Byblow, 2002, 2004b). This phenomenon may be due to synchronous somatosensory feedback generated by the bilateral movements, and a reduction in TCI in both directions so that the two limbs become functionally coupled (Schnitzler et al., 1996; Stinear and Byblow, 2002; Carson et al., 2004; Vardy et al., 2007).

APBT is only one of many potential priming modalities. Drugs such as amphetamines and levo-DOPA have been shown to alter motor cortex function (Ziemann et al., 1997, 2006; Boroojerdi et al., 2001; Tegenthoff et al., 2004; Ziemann, 2004a). Non-invasive magnetic and electrical stimulation of the brain or peripheral nerves can also lead to temporary changes in motor cortex function (Stefan et al., 2000; Lang et al., 2004; Siebner et al., 2004; Ziemann, 2004b; Huang et al., 2005; Quartarone et al., 2006). Recent studies have also shown that the modulation of cortical excitability induced by magnetic and electrical stimulation of the brain may be reversed or abolished by voluntary activity or subsequent priming (Huang et al., 2007; Muller et al., 2007). A number of studies have shown that these priming techniques can result in a better response to physical therapy following stroke (Hummel et al., 2005; Kheddar et al., 2005; Mansur et al., 2005; Takeuchi et al., 2005; Fregni et al., 2006; Talelli et al., 2006b).

APBT offers some advantages over other techniques; medications used for the purpose of priming can have systemic and unwanted effects; and electrical and magnetic stimulation techniques require specialized equipment and cannot be used with all patients (Fauth et al., 1992; Wassermann, 1998; Poreisz et al., 2007). In contrast, APBT is simple, inexpensive and can be used by the patient while at home. It therefore has the potential for broader clinical application. Furthermore, since APBT requires voluntary motor activity, it may produce changes in synaptic efficacy that are less likely to be compensated for by homoeostatic mechanisms compared with stimulation techniques applied to the resting motor system. APBT does have disadvantages. It cannot be used by those with spasticity that prevents passive wrist flexion and extension, and may not be appropriate for those with moderate-severe sensory impairments, although this has not been studied systematically.

Bimanual motor practice alone, as opposed to APBT in which there is bilateral movement-based priming, has been investigated as a rehabilitation strategy in stroke (Mudie and Matyas, 2000, 2001; Whitall et al., 2000). However, such bilateral active interventions have not been designed as a priming modality and few have been shown to produce any beneficial changes in neural function (Cauraugh and Summers, 2005). In a recent study, Luft et al. (2004) showed that bilateral arm training used in isolation resulted in no differences in functional outcome between treatment and control groups. Mudie and Matyas (1996, 2000) examined the effectiveness of a bilateral isokinematic training intervention (BIT), involving the practice of synchronous bilateral actions. BIT produced significant and rapid improvements in the kinematic patterns of unilateral hemiplegic limb performance. The gains observed during therapy were maintained at 6 months indicating some permanent reorganization of the motor system. The advantage of APBT over some other forms of bilateral arm training is that the APBT device is designed to permit hundreds and even thousands of movement cycles in each session because it offers an inertial advantage, preventing fatigue normally associated with active movement of the stroke-affected upper limb. While other home-based devices may guide the movement of the affected upper limb, they usually provide little assistance for fully passive movement. APBT is a potentially beneficial priming modality for patients with a wide range of impairment, as it allows the mirror-symmetric movement pattern to be achieved with varying degrees of voluntary drive to the affected upper limb. The level of...
voluntary drive to the affected upper limb during APBT is not a critical factor. Of course, the movements produced during APBT are not meaningful in isolation. Rather, they are used to generate sustained afferent input in a mirror-symmetric manner that has previously been shown to reduce excitability of M1 inhibitory networks.

There are a number of limitations to our study. First, no specific sham (of APBT) was given to the control group before motor practice. As such, APBT participants spent more time in structured activity each day. However, the intention was to evaluate the effect of adding APBT to a standardized motor practice regimen. Future studies need to devise an effective sham control for APBT, which has a similar session duration but does not engage the sensorimotor system. It seems unlikely that the difference in time spent in structured activity could wholly account for the neurophysiological changes and better clinical outcomes of the APBT group, that were sustained 1 month after the intervention, although the possibility that this may have contributed to some of the differences between groups cannot be ruled out entirely. Second, there was no quantitative recording of self-directed therapy with the use of goniometers or accelerometer-based devices. Instead, we relied upon the use of logbooks and weekly phone calls to check compliance. Third, data from patients who crossed-over from the control to the APBT group (after 1 month washout) were included in the analysis but only if they had no change in FM score following the control intervention. This may have reduced the likelihood of detecting a between-group difference, and a beneficial effect of APBT. However, the significant between-group differences in motor function remain when the crossover patients are removed from analysis, indicating that their inclusion does not confound these results. We cannot rule out the possibility that completing the motor practice intervention influenced the crossover patients’ response to the subsequent APBT intervention, initiated after the washout period, though this seems unlikely. Fourth, the intensive neurophysiological and imaging assessment of participants meant that a number of clinically suitable volunteers had to be excluded. However, the aim was to obtain both proof of principle of APBT as a potential therapeutic strategy and to determine underlying neurophysiological mechanisms. Fifth, participants in the APBT group were instructed to attempt bimanual voluntary wrist movement while using the device in the final week of the intervention, though no direct measure of their compliance with this was made. The effect on priming of progressing to active movement of the affected upper limb has not been directly studied, and warrants further investigation. Finally, as with many studies of this type, our sample was somewhat heterogeneous, although all had a first-ever stroke and upper limb weakness.

In conclusion, these results lend support to the notion that stroke patients can benefit from self-directed, home-based motor practice, particularly when their motor system is primed by a neuromodulator such as APBT. We have shown that APBT alters inhibitory function within and between hemispheres. These changes may, at least in part, create a neurophysiological state for lasting improvements in motor function.

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