Review

Bilateral Arm Training in the Chronic Phase of Stroke Rehabilitation: A Systematic Review and Meta-analysis

Rachel Mays[1,2], Amanda McIntyre MSc[1], Cecilia Kwok MSc[1], Robert Teasell MD[1,3,4]

[1]*Lawson Health Research Institute, St. Joseph's Parkwood Hospital, London, ON*

[2]*Department of Biological Sciences, Dalhousie University, Halifax, NS*

[3]*St. Joseph's Healthcare, St. Joseph's Parkwood Hospital, London, ON*

[4]*Department of Physical Medicine and Rehabilitation, Western University, London, ON*

Abstract

Objective: Bilateral arm training (BAT) is an intervention utilized in rehabilitating upper-extremity paresis. The objective of this study was to conduct a systematic review and meta-analysis on the evidence for BAT on upper-limb paresis in the chronic phase of stroke.

Methods: A literature search of multiple databases (MEDLINE, CINAHL, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, OT Seeker) was conducted for relevant randomized controlled trials (RCTs) published in the English language that met inclusion criteria. Studies must have included BAT as part of treatment and participants must have been ≥6 months post stroke. Methodological quality of each study was assessed using the PEDro scale (maximum score=10).

Results: Eight RCTs satisfied the inclusion criteria (PEDro scores 1-7) for a total pooled sample size of 131 subjects (88 males and 43 females). The mean age of subjects was 57.6±4.1 years (range 50.7-64.8 years) and the mean time since stroke was 43.8±34.8 months (range 13.9-114.0 months). Among study endpoints, only the Fugl-Meyer Assessment tool showed significant improvement in motor impairment whereby the BAT groups improved, on average, 3.77 points whereas the control group improved just 1.23 points (Difference of Means = 1.46±0.662; p=0.028).

Conclusion: Overall, BAT showed a general trend in improvement over standard therapy, although it was not statistically significant. Future studies with improved methodological quality (e.g., strict inclusion criteria, protocol standardization) and larger sample sizes are needed to appropriately assess the benefit of BAT in stroke patients.

Stroke is the number one cause of long-term disability in the United States[1] and 30-66% of stroke patients show motor deficits in the arm contralateral to the lesion after six months.[2] Lack of upper extremity control, specifically arm and hand movement, can directly affect quality of life.[3] Compensatory strategies and motor relearning have been used to progress plasticity-based motor performance following a stroke, specifically practice and repetition type exercises.[4-10] Passive movement is insufficient to alter motor recovery, so active engagement attempts that focus on coordination, rather than strengthening, have been proven most effective.[11]

Rehabilitation is key to minimizing disability after stroke; use of the affected body part for task-related challenges is critical for cortical neural reorganization in long-term rehabilitation for individuals with chronic stroke.[12] With the aid of a physiotherapist, rehabilitation can be effective in minimizing disability post-stroke, particularly on the hemiplegic (affected) side. Neurorehabilitation techniques, such as task-oriented bilateral arm training (BAT), allow individuals to practise activities with the upper limbs in a simultaneous manner. The basic premise of BAT is that symmetrical bilateral movements activate similar neural networks in both hemispheres as homologous muscle groups are simultaneously activated.[12,13] Consequently, bilateral symmetrical movements allow the activation of the undamaged hemisphere to increase activation of the damaged hemisphere to facilitate movement control of the impaired limb.[14] Therefore, BAT should promote neural plasticity.[15,16] Compared to BAT, unilateral movements (e.g., unilateral arm training, UAT) generate an interhemispheric inhibition in the ipsilateral hemisphere that prevents mirror movements in the opposite contralateral hemisphere.[17]

Evidence supporting the effectiveness of BAT, as compared to other therapies such as UAT, is conflicting.[13,14,18] While many of the reports have been generally negative, some report conflicting or inconsistent results, which may be attributed to a number of confounding variables including level of impairment, therapy intensity, and phase of stroke recovery. Historically, neurorehabilitation was thought to plateau in the chronic phase of stroke (≥6 months post stroke); however, Teasell et al.[19] report that functional gains can be made when therapies are provided during this time. There exists an abundance of literature which provides evidence for interventions long after the typical recovery phase which supports the notion that motor improvement beyond the acute/sub-acute phase may be possible.[20] Thus, the objective of the current study was to conduct a systematic review and meta-analysis of all randomized controlled trials (RCTs) examining BAT on motor function among individuals with chronic stroke (≥6 months).

Methods

Literature Search Strategy

Relevant articles were identified by a literature search of articles published from January 2000 to December 2013 using multiple databases (i.e., MEDLINE, CINAHL, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, OT Seeker). Key words used included stroke, cerebral vascular accident, hemorrhage, ischemic, bilateral arm training, bilateral upper limb training, upper limb, upper extremity, chronic and stroke bilateral/bimanual coordination/training, motor recovery/rehabilitation, motor control/coordination, and interlimb coordination. References of retrieved articles were also searched to identify additional articles that may have been missed in the primary database search.

Study Selection

Two authors (RM, AM) independently assessed titles, abstracts, and full length articles against inclusion criteria. Studies were included for analysis if the following six a priori criteria were met:

1) published in English;

2) included only human subjects;

3) research design was a RCT;

4) treatment group received bilateral arm treatment and the control group received a form of rehabilitation therapy representing 'typical' or 'usual' rehabilitation for the upper limb;

5) mean time since stroke was ≥6 months for both the treatment and control groups; and

6) functional improvement of the upper-extremity was assessed pre-treatment and post-treatment using a measurable outcome.

Studies were excluded from analysis if BAT was provided alongside another treatment (e.g., electrical stimulation) or if the control group provided a treatment not 'typically' used in a rehabilitation setting. Furthermore, studies were eliminated if data could not accurately be extracted from the article or if a complete explanation of the BAT protocol was not available.

Study Appraisal

Each RCT was assessed for methodological quality using the Physiotherapy Evidence Database (PEDro) scoring system. Scores were extracted from the PEDro website (www.pedro.org.au) where possible. Scores that were not available online were independently calculated by two authors (RM, CK). The PEDro scale consists of 11 questions that are answered with either a "yes" (1 point) or "no" (0 points). Since the first question is not included in the final score, a maximum score of 10 can be achieved. Strength of evidence was assessed using previously established guidelines for the Evidence-Based Review of Stroke Rehabilitation,20 (where "excellent" quality RCTs are scored as 9 or 10 on the PEDro, "good" quality studies as 6–8, "fair" quality studies as 4 or 5; and "poor" quality studies as 1-3). The PEDro was originally developed to assess physiotherapy trials however, the tool has subsequently been used to evaluate rehabilitation trials in the stroke population.[21] Additionally, it has demonstrated both good reliability[22] and validity.[23]

Data Synthesis

Extracted data included subject demographics (e.g., age, gender, time since injury), sample size, treatment and control methods, outcome measures, and study results. If data could be extracted, it was summarized in a table. Where necessary and when possible, authors of selected studies were contacted to collect additional raw data. If accurate data could not be extracted from the study or collected from the original author(s), it was not included in the meta-analysis on that particular outcome measure. Meta-analyses for individual outcome measures were conducted using the software Comprehensive Meta-Analysis Version 2 (Biostat Inc., Englewood, New Jersey, USA, 2007). Baseline (pre-treatment) and follow-up (post-treatment) scores in mean ± standard deviation form were extracted for both the treatment and control groups. In the event that a standard deviation was not available, standard errors were converted to standard deviations, or a p value or Cohen's d value was used. In the instance that there were two control groups, only the data from the control group receiving 'usual' care was included in the meta-analysis. To quantify the effect of heterogeneity, an I^2 value was calculated which provides a measure of the degree of inconsistency in study results.[24] I^2 is readily calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom.[25,26] A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.[27] A pooled mean difference (MD) ± standard error (SE: 95% confidence interval, CI) was calculated between the treatment and control groups. To enhance clinical relevance, effect sizes were converted into their original units. Statistical significance was set at $p<0.05$.

Five meta-analyses were conducted on the following outcome measures: Fugl-Meyer Assessment (FMA); Functional Independence Measure (FIM); Motor Active Log Amount of Use (MAL AOU); Motor Active Log Quality of Movement (MAL QOM); and the Modified Motor Assessment Scale (MAS). For each outcome measure assessed, the baseline (pre-treatment) and follow-up (post-treatment) mean ± standard deviation was extracted for both the treatment and control groups.

Each of the five outcome measures analysed in the meta-analyses were specific to evaluating functional motor ability of the upper limb. The FMA evaluates and measures recovery in post-stroke hemiplegic patients and is a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicap.[28] The FIM is similar to the FMA, and more specifically measures the level of patient disability and indicates the level of assistance that is required for the individual to carry out activities of daily living. The MAL is used to assess how stroke survivors use their more-impaired arm outside the laboratory.[29] Finally, the MAS is used to assess everyday motor function in stroke patients.

Results

Study Quality and Characteristics

Eight studies met inclusion criteria (Figure 1).[30-37] Table 1 displays study characteristics, interventions, outcome measures and results for the included studies. The RCTs were published from 2004 to 2011 and PEDro scores ranged from 1 to 7. Samples sizes ranged from 8 to 92 with a total pooled sample size of 274 subjects. On average, subjects were 48.31 months post stroke and had a mean age of 57.63 years. All patients were randomized to either a treatment group (BAT) or a control group. The control therapies included dose-matched UAT[32,33,36,37] neurodevelopmental techniques and physical therapy[34], constraint induced movement therapy[31] or physical therapy (PT).[30] The following outcome measures were most commonly reported by the included studies and were analyzed in the meta-analyses: FMA, FIM, MAL AOU, MAL QOM, and MAS. No adverse events were reported by any of the studies.

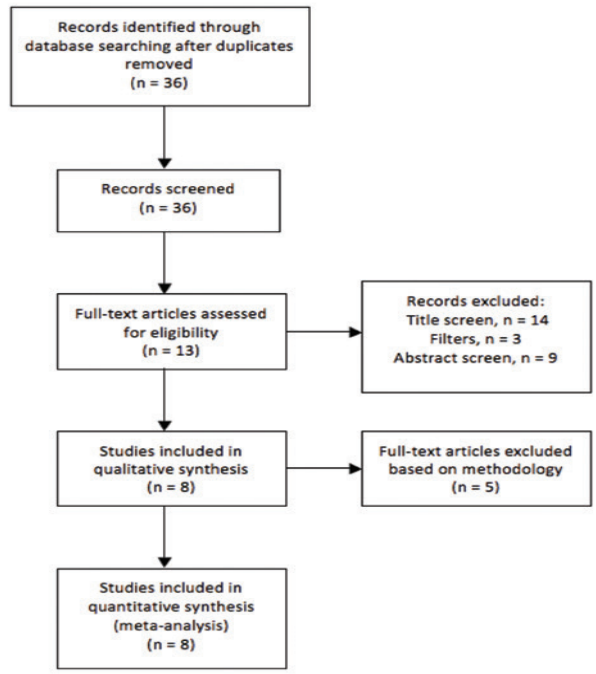


Figure 1. Study selection

Heterogeneity

The FMA used a fixed effects model due to the low I^2 value and the relatively small number of studies used to calculate the effect size (Q-value=6.625; df(Q)=4.000; I^2=39.619). The FIM (Q-value=0.038; df(Q)=2.000; I^2=0.000), MAL AOU (Q-value=0.163; df(Q)=2.000; I^2=0.000), MAL QOM (Q-value=0.105; df(Q)=2.000; I^2=0.000) and MAS (Q-value=0.005; df(Q)=1.000; I^2=0.000) analyses demonstrated complete homogeneity; therefore, a fixed effects model was used.

Analysis 1: FMA

Five studies[30,31,32,33,35] that used FMA to score upper limb impairment were included in a meta-analysis (Figure 2). The FMA showed significant improvement in motor impairment whereby the BAT groups improved, on average, 3.77 points whereas the control group improved just 1.23 points (MD=1.46; SE=0.662; p=0.028).

Table 1. Summary of results from eight studies included.

Study PEDro-Evidence Country	Treatment Group Sample Size Protocol	Treatment Group [1]Age X±SD [2]Stroke Onset X±SD	Control Group Sample Size Protocol	Control Group [1]Age X±SD [2]Stroke Onset X±SD	[3]Outcome Tool	[4]Result
Lin et al.[30] 6-Good Taiwan	BAT (n=16) 2hr/d, 5d/wk for 3wk	52.0±9.6 13.9±12.7	Occupational Therapy (n=17) 2hr/d, 5d/wk for 3wk	55.5±13.2 13.1±8.1	FMA FIM AOU/QOM	+ -- --/--
Lin et al.[31] 7-Excellent Taiwan	BAT (n=20) 2hr/d, 5d/wk for 3wk	51.6±8.7 18.0±17.4	Therapeutic Activities (n=20) 2hr/d, 5d/wk for 3wk	50.7±13.9 21.9±20.5	FMA* FIM* AOU/QOM*	++ -- --/--
Luft et al.[32] 5-Good USA	BAT (n=9) 1hr/d, 3d/wk, for 6 wk	63.3±15.3 75.0 (median)	Dose-Matched Exercise (n=12) 1hr/d, 3d/wk, for 6 wk	59.6±10.5 45.5 (median)	FMA	--
Whitall et al.[33] 6-Good USA	BAT (n=42) 1hr/d, 3d/wk for 6 wk	59.8±9.9 54.0±49.2	Dose-Matched Exercise (n=50) 1hr/d, 3d/wk for 6 wk	57.7±12.5 49.2±62.4	FMA	-- --
Wu et al.[34] 6-Good Taiwan	BAT (n=22) 2hr/d, 5d/wk for 3wk	52.2±10.7 15.9±13.7	Neurodevelopmental Techniques (n=22) 2hr/day, 5d/wk for 3wk	55.2±2.5 17.8±12.5	AOU/QOM*	--/--
Rosa et al.[35] 1-Poor Portugal	BAT (n=4) 3d/wk for 6 wk	55.0±5.9 55.3±52.3	Unilateral Arm Training (n=4) 3d/wk for 6 wk	57.5±12.1 32.5±27.4	FMA FIM	-- --
Summers et al.[36] 6-Good Australia	BAT (n=6) 50 trials/d for 6d	63.5±15.9 76.2±68.7	Unilateral Arm Training (n=6) 50 training trials/d for 6d	59.8±14.0 48.2±50.4	MAS	++
Stoykov et al.[37] 7-Excellent USA	BAT (n=12) 1hr/d, 3d/wk for 8 wk	63.8±12.6 114.0±64.8	Unilateral Arm Training (n=12) 1hr/d, 3d/wk for 8 wk	64.8±11.1 122.4±121.2	MAS	--

[1]Age is measured in years
[2]Stroke Onset is measured in months
[3]FIM: Functional Independence Measure; FMA: Fugl-Meyer Assessment; MAL AOU: Motor Activity Log-Amount of Use; MAL QOM: Motor Activity Log-Quality of Movement; MAS: Modified Motor Assessment Scale; *BAT versus Con 2 group only
[4]++ $p<0.01$; + $p<0.05$; -- Not significant ($p>0.05$)

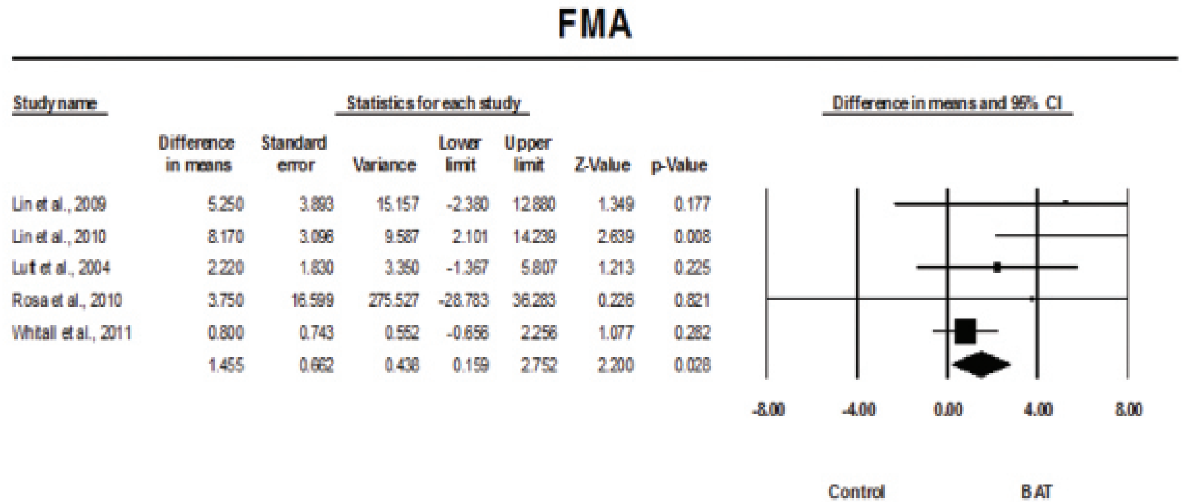


Figure 2. Meta-analysis of five studies examing the Fugl-Meyer Assessment

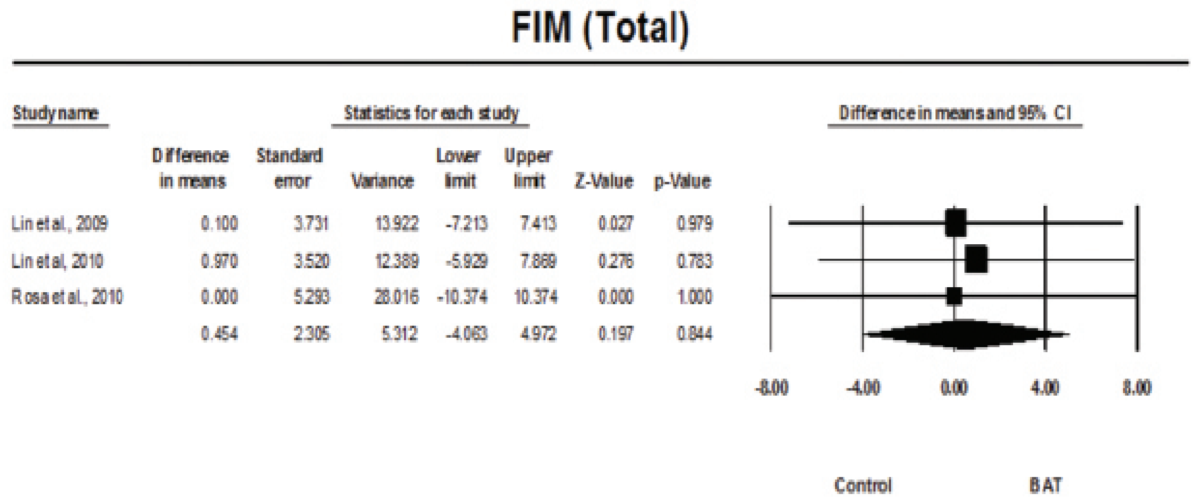


Figure 3. Meta-analysis of three studies examining the Functional Independence Measure

Analysis 2: FIM

Three studies were included in the meta-analysis of total FIM scores (Figure 3).[30,31,35] While the BAT group improved, on average 1.41 points on the FIM and the control group by 0.96 points, there was no significant improvement in total FIM scores (MD=0.454; SE=2.305; p=0.844).

Analysis 3: MAL AOU and QOM

Three studies were included[30,31,34] in the analysis of the MAL (Figure 4). The BAT group improved by 0.47 points on the MAL-AOU and the control improved by 0.32 points; however, overall there was no significant improvement demonstrated (MD=0.150; SE= 0.176; p=0.494). On average the BAT group improved by 0.61 points on the MAL-QOM whereas the control improved by 0.46 points. Similarly, MAL QOM scores also did not improve significantly (MD=0.154; SE= 0.195; p=0.431).

Analysis 4: MAS

Two studies included MAS[36,37] in their analysis and only the total scores were examined (Figure 5). MAS total scores reported no significant improvement (MD=0.658; SE=1.023; p=0.520) despite an average improvement by the BAT group of 0.95 points and by the control group, 0.29 points.

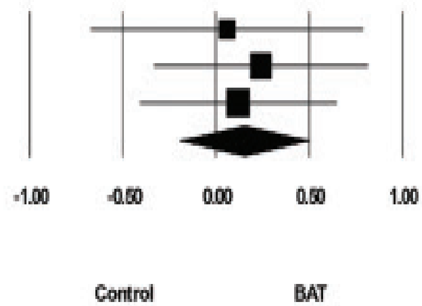
Discussion

This systematic review included eight RCTs that compared the effect of BAT versus standard rehabilitation on upper limb functioning and activities of daily living among chronic stroke survivors. Although multiple studies have shown BAT as a viable stroke rehabilitation technique[13,14,18,30-34,36,38,39] , the findings

MAL AOU

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lin et al., 2009	0.060	0.374	0.140	-0.674	0.794	0.160	0.873
Lin et al., 2010	0.240	0.295	0.087	-0.337	0.817	0.815	0.415
Wu et al., 2011	0.120	0.271	0.073	-0.411	0.651	0.443	0.658
	0.150	0.176	0.031	-0.195	0.494	0.850	0.395

Difference in means and 95% CI



MAL QOM

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lin et al., 2009	0.050	0.385	0.148	-0.704	0.804	0.130	0.897
Lin et al., 2010	0.210	0.325	0.105	-0.427	0.847	0.647	0.518
Wu et al., 2011	0.170	0.316	0.100	-0.448	0.788	0.539	0.590
	0.154	0.195	0.038	-0.229	0.536	0.787	0.431

Difference in means and 95% CI

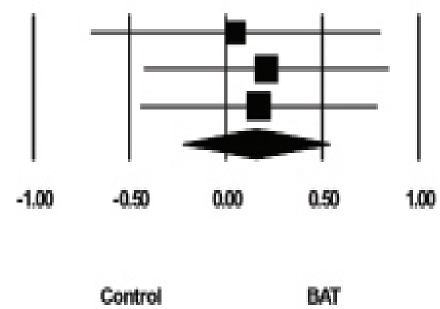


Figure 4. Meta-analysis of three studies examining the Motor Assessment Log amount of use (AOU) and quality of movement (QOM)

MAS

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Stoykov et al., 2009	0.563	1.719	2.956	-2.807	3.933	0.327	0.743
Summers et al., 2007	0.710	1.272	1.618	-1.783	3.203	0.558	0.577
	0.658	1.023	1.046	-1.346	2.662	0.643	0.520

Difference in means and 95% CI

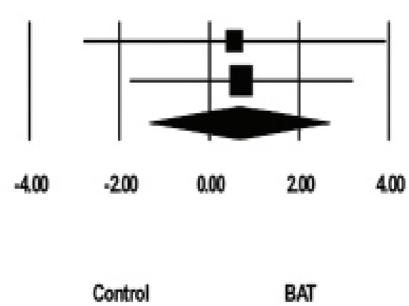


Figure 5. Meta-analysis of two studies examining the Motor Assessment Scale

from all but one outcome measure, FMA, indicated that BAT showed a general trend in improvement over standard therapy, although it was not statistically significant. This finding has been supported by previous meta-analyses and systematic reviews examining BAT at all stages of stroke recovery.[38]

Individually, the included studies were generally underpowered to detect significant differences between groups due to their small sample sizes. The claims made were overly positive with wide confidence intervals for treatment effect. The current meta-analysis adds to the body of literature by combining multiple study samples in an attempt to remove statistical error to report accurate relationships between BAT and upper limb recovery. Thus, the pooled sample in this meta-analysis allows for a more accurate assessment of BAT's role in upper limb recovery. Additionally, considering that individuals who are ≥6 months post-stroke experience different needs than those in earlier phases of recovery, this review adds knowledge to the existing gap in stroke rehabilitation literature as it specifically examined BAT during the chronic phase. A previous Cochrane review[39] was published in 2010 but all patients were included in the analysis without consideration for time since stroke; that is, patients in the acute, sub-acute, and chronic phase of stroke grouped together and analyzed.

Stroke survivors are not only interested in motor functioning, but activities of daily living and quality of life outcomes as well. Interestingly, neither motor function nor activities of daily (FIM) was found to improve with BAT; this finding is consistent with the Cochrane review as well.[39] It has been reported that the FIM is not suited to ongoing, long-term assessment in the community-based setting.[40] Given that the included subjects were in the chronic phase, the FIM was administered in a community-based setting, not a hospital or in-patient rehabilitation setting. These chronic patients are in a unique phase of stroke recovery whereby the FIM alone may not capture subtle changes in daily functioning. In addition to the FIM, quality of life measures that examine subjective health and wellbeing are an extremely important outcome to assess that should be considered for future studies.

It is important to note that the average age of a stroke patient in Canada is 69 years old and prevalence increases with age.[41] Studies included in this analysis were, on average, much younger than the typical stroke patient, reporting a mean age of 51.4 years and a median of 57.4 years. This discrepancy could be due to the increasing number of strokes affecting more young persons as all eight of the studies included in the analysis were published within the last ten years and six in the last five years. The reasons for this trend could be a rise in risk factors such as diabetes, obesity, and high cholesterol as well as improved diagnostic methods for the identification of younger stroke sufferers. Future studies should consider examining BAT among those who suffered a stroke at varying ages.

It is possible that BAT has not been shown to be significantly more beneficial in improving upper limb recovery compared to standard therapy due to the low intensity with which it is provided. To elicit a significant neuroplastic change in behaviour, high numbers of repetitions of task-specific activity are crucial. Animal studies in neuroplasticity have shown that 400 to 600 repetitions per day of challenging fine-motor exercises are required to promote significant structural neurological changes following stroke.[42] Thus, future studies should aim to better determine the effects of varying levels of BAT intensity on outcomes. At present, BAT is a low-intensity training regime which, although advantageous as it can appeal to a wide post-stroke audience, may come at a cost of slower recovery. Examining intensity effects could aid in our understanding of specific treatment regimens and protocols for unique stages of stroke recovery. It may also be beneficial to examine the combined effects of BAT and UAT in sequence to further understand the differences, similarities, or additive advantage of the two therapies. Future trials should include large, homogenous samples that receive varying intensities of BAT over a longer period of time.

It is important to note an important limitation associated with this study. A mean time since stroke of ≥6 months was chosen to allow the greatest number of studies to be eligible for inclusion; setting the minimum cut-off for all subjects would have limited the pool of studies with which to choose from. Based on the mean, subjects may be in either the acute or subacute phase, and consequently induce some amount of variability into the results.

Conclusion

Our results, along with the associated literature, demonstrate that BAT showed a general trend in improvement over standard therapy, although it was not statistically significant. This suggests that therapists have another tool available for upper limb rehabilitation and that, at minimum, it is as effective as normal standard of care. It should be noted that there was great variability in methodology, sample size, and outcome measures used among the studies included. We suggest that future studies improve methodological quality by implementing strict inclusion/exclusion criteria, controlling for confounders, standardizing BAT protocols, and recruiting a suitable sample size.

References

1. The Internet Stroke Center. Stroke Statistics. 2013. Available from http://www.strokecenter.org/patients/about-stroke/stroke-statistics/.
2. Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation: A critical review of the literature. Physiotherapy 1999;85(7):377-91.
3. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke 2000;31:2390-95.
4. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: A systematic review. Lancet Neurol 2009;8(8): 741-54.
5. Cameiro MS, Badia SB, Verschure PF. Virtual reality based upper extremity rehabilitation following stroke: A review. J Cyber Ther Rehabil 2008;1(1):63-74.
6. Krakauer JW. Motor learning: Its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol 2006;19(1): 84-90.
7. Krouchev NI, Kalaska JF. Virtual worlds and games for rehabilitation and research. Virtual Rehabil 2008:113-20.
8. Kwakkel G , Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: A systematic review. Neurorehabil Neural Repair 2007;22(2):111-21.
9. Sveistrup H. Motor rehabilitation using virtual reality. J Neuroeng Rehabil 2004;1(1):10.
10. Woldag H, Hummelsheim H. Evidence-based physiotherapeutic concepts for improving arm and hand function in stroke patients: A review. J Neurol 2002;249(5):518-28.
11. Krebs HI, Volpe B, Hogan N. A working model of stroke recovery from rehabilitation robotics practitioners. J Neuroeng Rehabil 2009;25(6):6.
12. Staines RW, McIlroy WE, Brooks D. Functional Impairments Following Stroke: Implications for Rehabilitation. Toronto, CA; 2013.
13. Stewart KC, Cauraugh JH, Summers JJ. Bilateral movement training and stroke rehabilitation: a systematic review and meta-analysis. J Neurol Sci 2006;244(1-2):89-95.
14. Latimer CP, Keeling J, Lin B, Henderson M, Hale LA. The impact of bilateral therapy on upper limb function after chronic stroke: a systematic review. Disabil Rehabil 2010;32(15):1221-1231.
15. Wenderoth N, Debaere F, Sunaert S, van HP, Swinnen SP. Parieto-premotor areas mediate directional interference during bimanual movements. Cereb Cortex 2004;14(10):1153-1163
16. Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: A rehabilitation approach for chronic stroke. Prog Neurobiol 2005;75(5):309-320.
17. Carson RG. Neural pathways mediating bilateral interactions between the upper limbs. Brain Res Brain Res Rev 2005;49(3):641-662.
18. Cauraugh JH, Lodha N, Naik SK, Summers JJ. Bilateral movement training and stroke motor recovery progress: a structured review and meta-analysis. Hum Mov Sci 2010;29(5):853-870.
19. Teasell R, Mehta S, Pereira S et al. Time to rethink long-term rehabilitation management of stroke patients. Top Stroke Rehabil 2012;19(6):457-462.
20. Teasell R. Evidence-Based Review of Stroke Rehabilitation. 2013. http://www.ebrsr.com/.
21. McIntyre, A., Richardson, M., Janzen, S., Hussein, N., & Teasell, R. The evolution of stroke rehabilitation randomized controlled trials. International Journal of Stroke 2014;9(6):789-792.
22. Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., & Elkins, M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Physical therapy 2003; 83(8), 713-721.
23. de Morton, N. A. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Australian Journal of Physiotherapy 2009; 55(2), 129-133.
24. Petitti, D. B. Approaches to heterogeneity in meta-analysis. Statistics in medicine 2001; 20(23), 3625-3633.
25. Higgins, J., Thompson, S. G., Deeks, J. J., & Altman, D. G. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414), 557-560.
26. Higgins, J., Thompson, S., Deeks, J., & Altman, D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. Journal of health services research & policy 2002; 7(1), 51-61.
27. Higgins, J., & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002; 21(11), 1539-1558.
28. Simeonsson RJ, Lollar D, Hollowell J, Adams M. Revision of the International Classification of Impairments, Disabilities, and Handicaps: developmental issues. J Clin Epidemiol 2000;53(2):113-124.
29. Hammer AM, Lindmark B. Responsiveness and validity of the Motor Activity Log in patients during the subacute phase after stroke. Disabil Rehabil 2010;32(14):1184-1193.
30. Lin KC, Chen YA, Chen CL, Wu CY, Chang YF. The effects of bilateral arm training on motor control and functional performance in chronic stroke: a randomized controlled study. Neurorehabil Neural Repair 2010;24(1):42-51.
31. Lin KC, Chang YF, Wu CY, Chen YA. Effects of constraint-induced therapy versus bilateral arm training on motor performance, daily functions, and quality of life in stroke survivors. Neurorehabil Neural Repair 2009;23(5):441-448.
32. Luft AR, McCombe-Waller S, Whitall J et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. JAMA 2004;292(15):1853-1861.
33. Whitall J, Waller SM, Sorkin JD et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. Neurorehabil Neural Repair 2011;25(2):118-129.
34. Wu CY, Chuang LL, Lin KC, Chen HC, Tsay PK. Randomized trial of distributed constraint-induced therapy versus bilateral arm training for the rehabilitation of upper-limb motor control and function after stroke. Neurorehabil Neural Repair 2011;25(2):130-139.
35. Rosa M, Vasconcelos O, Marques A. The influence of two rehabilitation protocols in upper-limb fucntion of stroke patients. Int J of Therapy and Rehabil 2010.
36. Summers JJ, Kagerer FA, Garry MI, Hiraga CY, Loftus A, Cauraugh JH. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: A TMS study. J Neurol Sci 2007;252(1):76-82.
37. Stoykov ME, Lewis GN, Corcos DM. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. Neurorehabil Neural Repair 2009;23(9):945-953.
38. McCombe WS, Whitall J. Bilateral arm training: why and who benefits? NeuroRehabilitation 2008;23(1):29-41.
39. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. Clin Rehabil 2012;26(4):291-313.
40. Gurka JA, Felmingham KL, Baguley IJ, Schotte DE, Crooks J, Marosszeky JE. Utility of the functional assessment measure after discharge from inpatient rehabilitation. J Head Trauma Rehabil 1999;14(3):247-256.
41. Wilson, E., Taylor, G., Phillips, S., Stewart, P. J., Dickinson, G., Ramsden, V. R., & Strauss, B. (2001). Creating a Canadian stroke

system. Canadian Medical Association Journal, 164(13), 1853-1855.
42. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. Stroke 2005;36(11):2493-2496.