Libraries and Learning Services

University of Auckland Research Repository, ResearchSpace

Version

This is the Accepted Manuscript version of the following article. This version is defined in the NISO recommended practice RP-8-2008 http://www.niso.org/publications/rp/

Suggested Reference

Byblow, W., Schlaug, G., & Wittenberg, G. (2016). What's the perfect dose for practice to make perfect?. *Annals of Neurology*, *80*(3), 339-341. doi:10.1002/ana.24735

Copyright

Items in ResearchSpace are protected by copyright, with all rights reserved, unless otherwise indicated. Previously published items are made available in accordance with the copyright policy of the publisher.

For more information, see General copyright, Publisher copyright, SHERPA/RoMEO.

Accepted Article

What's the Perfect Dose for Practice to make Perfect?

Neurologists and clinician-scientists interested in stroke recovery frequently do not know the details of the rehabilitative therapy that their patients receive. However, patient's and caregiver's expectations of getting the best possible therapy will put more demands on healthcare providers to understand not only the ingredients of rehabilitation but also the patient's potential for recovery. Some of the crucial questions are when to provide traditional and/or experimental therapy (acute vs subacute vs chronic phase), how intense it should be, its frequency and duration per session, how many sessions in total, what activities it should include (relearning of skills versus compensatory skill learning), and whether or not it is coupled with plasticity enablers and enhancers (such as pharmacological agents, brain stimulation, or multi-sensory feedback). Lang et al. in this issue of *Annals of Neurology* have taken up this challenge by rigorously investigating one of these variables, repetition of movements within a fixed number of sessions.

Lang and colleagues showed that gains in upper limb function did not improve as a function of dose for task specific therapy in patients, beginning six months or more after stroke. The treatment consisted of supervised practice of functional tasks that were graded and progressive for each participant by study therapists. Therapy dose was quantified in terms of repetitions of upper limb movement and delivered one hour/day, four days/week, for 8 weeks (a total of 32 hours). A strength of the study design was the provision of 4 levels of dose including an "individualized maximum" (IM) level. The IM group received the highest dose, 300 repetitions per session but also continued beyond 8 weeks until the outcome plateaued, which on average occurred about 1200 repetitions beyond the week 8 total. The lowest dose delivered was 3200 repetitions. Modest gains in function with improvements were realized at a rate of just under 1 point per week on the Action Research Arm Test, with no differences between groups (dose) to indicate that more movement training results in better functional outcomes. In fact, the group which performed 6400 repetitions did not improve over the study period. Within each group, there was considerable variation in response, characteristic of many stroke rehabilitation trials.

The Action Research Arm Test (ARAT) was the primary outcome. The ARAT measures the ability to perform tasks and is comparable to the Wolf Motor Function Test. Although there is a concern about practice effects with repeated assessments, advancing in the ARAT generally means ability to perform a new task, because of its hierarchical Guttman scale design [1]. The statistical analysis used for the main outcome was sophisticated, and mitigated the relatively small sample size in each group. Change in outcome over the course of the intervention was best modeled by a linear growth curve, and significance of group assignment on growth curves assessed with hierarchical linear modeling. Permutation tests and bootstrapping completed the rigorous analysis and provide some assurance of reliability. Of course, there is no guarantee that random differences among groups didn't mask in some way the specific effect of an intervention.

Since there was no dose-response effect, one might wonder if there was any effect of therapy, saturation of effects at the lowest dose, or if the improvements may reflect a practice effect from the weekly assessment alone or an expectation bias that therapy helps. A no-therapy control, and use of multiple baseline assessments before treatment, could

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ana.24735

This article is protected by copyright. All rights reserved.

Accepted Article

usefully be included in future trial designs. It is understandable that such a control was omitted in this study, as it had a singular goal of measuring the effect of dose, and it can be impractical to expect frequent visits for assessment when therapy is withheld. But if a null control had been included, it would have answered the interesting question of whether the 3200 dose was an effective and efficient treatment compared to no treatment.

The lack of improvement of the 6400 group is curious. For example, it is unknown whether this group by chance, had more patients with lower potential for therapy response, as might have been evident if biomarkers of functional or structural corticospinal tract integrity were obtained.[2, 3] Such biomarkers, which have been shown to correlate highly with clinical measures of impairment and recovery predictions[4-6], were not used to stratify patients at study inception, and may indeed have accounted for variation in treatment response within and across groups. In fact, in comparison to the other groups, the 6400 group was more heavily male, left-handed, disconcordant (non-dominant hand affected) and had the fewest purely subcortical strokes (only one) even though only concordance was significantly different by statistical comparisons. Stratification on multiple features cannot succeed when sample size is too small, but inclusion of biomarkers that help to stratify patients at the beginning and predict ability to recovery can be helpful in such trials.

The study reminds us of the potential value of "bursts" of therapy at the chronic stage, even if the functional gains achieved are modest for some. Lang and colleagues found that 90% of patients in their study reported a meaningful perception of change in performance and satisfaction over time - an effect that did not depend on dose, and was not borne out by differences in functional outcomes. How long these perceived benefits might last is questionable, and perhaps better answered once a robust treatment effect is found. The EXCITE trial, which included patients across a wider range of time since stroke, also demonstrated the effectiveness of a burst of therapy on functional ability [7].

It is not surprising that patients improve slightly after re-engaging in therapy at the chronic stage. Over time deterioration of paretic upper limb function occurs alongside factors such as learned non-use. Although plasticity is increased in experimental stroke models at the acute and subacute phase, at the chronic stage plasticity seems to normalize to pre-stroke levels, such that task-specificity of both compensatory responses in chronic stroke, and skill learning in healthy individuals, possibly rely on the same "garden variety" plasticity.[8] However, it seems unlikely that task specific therapy alone, no matter how high the dose, will ever exceed the magnitude of effect observed. The jury remains out until the limitations of everyday plasticity are overcome by some other means. This is why pharmacological agents[9, 10], methods to provide multi-sensory feedback (e.g., auditory-, and visuo-motor coupling)[11], and interventions such as noninvasive brain stimulation[12, 13] continue to be explored as possible plasticity enhancers and adjuvants to stroke rehabilitation..

The form of therapy in chronic stroke may need to differ substantially from the current individually guided and supervised practice paradigm to produce a more robust treatment effect. There is some evidence in support of this idea from trials of robotic-guided therapy [14,15]. The number of repetitions in such trials is substantially higher than even the highest dose in this one, but repetitions of elementary movements using a robot may not be equivalent to practice of a relevant task and may not generalize to non-practiced activities.

This article is protected by copyright. All rights reserved.

Accepted Article

The patients who are motivated to enter a clinical trial are likely to be the ones that have already practiced activities of daily living (ADLs) on their own. For these patients, only a therapy substantially different than task-based practice could offer any hope of reversing impairment or improving function. This is analagous to plateaus commonly observed in sporting performance, where regular repetitive practice leads to no further improvement. In sport, as in rehabilitation, progression and variation are key concepts in continued improvement.

It has long been claimed that individual performance differences in music and sports reflects differences in the amount of deliberate practice, culminating in reports that musicians entering professional conservatories have practiced far more than 10,000 hours. However, a recent meta-analysis suggested that deliberate practice only explains 18-21% of the variance in performance in music and sports.[16] Clearly more is good, but it is not always better.

Lang's study does not encourage more trials of conventional supervised task-based practice in the chronic phase. A conceivable next step identified by the authors is to examine dosing along other dimensions, such as intensity and also frequency. For example, a recent secondary analysis of the AVERT trial suggested that more frequent, shorter intervention periods might have a beneficial effect[17]. Arguably intensity would be more difficult to quantify than repetition. Nevertheless, we envision that future recovery and rehabilitation trials will explore dimensions such as repetition, intensity, and frequency of novel therapies. These trials will need to use biomarkers of recovery potential, explore methods to enhance plasticity (such as pharmacological agents, multi-sensory feedback, and noninvasive brain stimulation) alongside therapy, and be conducted in a motivating and rewarding environment.

Acknowledgment
None

Authorship Contribution
W.B., G.S., and G.W. contributed equally to the writing of this editorial

Potential Conflicts of Interest
No conflicts to report.

Winston Byblow, PhD, [1]
Gottfried Schlaug, MD, PhD,[2]
George Wittenberg, MD, PhD, [3]

[1]Department of Exercise Sciences, and Centre for Brain Research, University of Auckland, Auckland, New Zealand
[2]Department of Neurology, Division of Stroke Recovery and Neurorestoration, Neuroimaging and Stroke Recovery Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

This article is protected by copyright. All rights reserved.

[3]Maryland Exercise and Robotics Center of Excellence, Geriatrics Research Educational and Clinical Center, Department of Veterans Affairs, Baltimore, MD, USA & Laboratory for Research on Arm Function and Therapy, Older Americans Independence Center, Departments of Neurology, Physical Therapy and Rehabilitation Science, and Medicine/ Division of Gerontology and Geriatric Medicine, University of Maryland, Baltimore, MD, USA

References:

1. Rosow I, Breslau N. A Guttman health scale for the aged. J Gerontol. 1966 Oct;21(4):556-9.
2. Lindenberg R, Zhu LL, Ruber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Human brain mapping. 2012 May;33(5):1040-51.
3. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain : a journal of neurology. 2007 Jan;130(Pt 1):170-80.
4. Feng W, Wang J, Chhatbar PY, et al. Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. Annals of neurology. 2015 Dec;78(6):860-70.
5. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. Annals of neurology. 2015;78(6):848-59.
6. Burke Quinlan E, Dodakian L, See J, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. Annals of neurology. 2015 Jan;77(1):132-45.
7. Wolf S, Thompson P, Winstein C, et al. The EXCITE stroke trial: comparing early and delayed constraint-induced movement therapy. Stroke. 2010 Oct;41(10):2309-15.
8. Zeiler SR, Krakauer JW. The interaction between training and plasticity in the poststroke brain. Current opinion in neurology. 2013 Dec;26(6):609-16.
9. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet neurology. 2011 Jan 7.
10. Ng KL, Gibson EM, Hubbard R, et al. Fluoxetine Maintains a State of Heightened Responsiveness to Motor Training Early After Stroke in a Mouse Model. Stroke; a journal of cerebral circulation. 2015 Oct;46(10):2951-60.
11. Altenmuller E, Schlaug G. Apollo's gift: new aspects of neurologic music therapy. Progress in brain research. 2015;217:237-52.
12. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010 Dec 14;75(24):2176-84.
13. Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. Stroke; a journal of cerebral circulation. 2010 Jul;41(7):1568-72.
14. Brokaw EB, Nichols D, Holley RJ, Lum PS. Robotic therapy provides a stimulus for upper limb motor recovery after stroke that is complementary to and distinct from conventional therapy. Neurorehabil Neural Repair. 2014 May;28(4):367-76.
15. Lo A, Guarino P, Richards L, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010 May 13;362(19):1772-83.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

16. Macnamara BN, Hambrick DZ, Oswald FL. Deliberate practice and performance in music, games, sports, education, and professions: a meta-analysis. Psychol Sci. 2014 Aug;25(8):1608-18.
17. Bernhardt J, Churilov L, Ellery F, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). Neurology. 2016 Jun 7;86(23):2138-45.

This article is protected by copyright. All rights reserved.