The Proportional Recovery Rule for Stroke Revisited

Most motor recovery occurs in the first 3 months after stroke. This is often referred to as spontaneous biological recovery (SBR), a process that has been both underinvestigated in humans and underexploited with respect to neurorehabilitation.[1] Data from animal models suggest that SBR is attributable to a unique time-limited period of enhanced postischemic plasticity.[2–5] In 2008, we defined recovery as the difference (Δ) between impairment in the few days after stroke and at a later time point (3 months).[6] We reasoned that SBR, being a process, is best reflected in a change rather than in a final endpoint. Our original finding was that SBR, in the majority of patients, follows a proportional recovery rule.[6] Impairment was measured with the Fugl-Meyer Scale (FM), which assesses the ability of the patient to move individual joints out of synergy and therefore captures both motor control and strength.[7] For the upper limb, the maximal score is 66. The proportional recovery rule states that, at 3 months, patients should get approximately 70% of their maximum potential recovery back. So, for example, a patient with moderate hemiparesis of 46 will recover (66-46) $\times$ 0.7, which equals 60. This rule has since been validated for motor recovery in two subsequent studies,[8,9] and we have shown that it appears to also be true for aphasia recovery.[10] Interestingly, a subset of patients with severe hemiparesis (FM <20) fails to show proportional recovery. That is to say, whereas some patients with severe hemiparesis recover proportionally as all others, some are nonrecoverers. In contrast, patients with mild-to-moderate hemiparesis always recover to nearly the same degree. Thus these two findings—the rule itself and its failure in a subset of patients with severe hemiparesis—led us to two conclusions[4,6,8]: (1) The existence of the rule implies that current rehabilitation methods in the first 3 months after stroke have little or no impact on recovery from impairment above what is expected from SBR, and (2) there is something categorically different between severe patients who do recover and those who do not. Specifically, we conjectured that recovery requires reorganization, which takes time, but this reorganization ultimately requires access to muscles through the corticospinal tract (CST).[8] If the CST is interrupted too much, then no amount of cortical reorganization will make a difference. Accordingly, we predicted that the dichotomy between recoverers and nonrecoverers might map onto patients who do or do not have measurable motor-evoked potentials (MEPs) using transcranial magnetic stimulation (TMS).[8] In two studies published in this issue of *Annals of Neurology*, two approaches have been taken to find CST-based predictors of recovery versus nonrecovery in patients with severe hemiparesis.

Before describing the two studies, it is important to first examine the proportional recovery rule itself a little more carefully given that there are potential concerns when the same measure, initial impairment (FM_0), is correlated with itself plus another term, final impairment (FM_1), that is, the relationship between FM_0 and $FM_1 - FM_0$. Measuring FM_0 and FM_1 with error, $FM_0 + \varepsilon_0$ and $FM_1 + \varepsilon_1$, can induce positive correlations between initial impairment and the change in impairment, even when there is either no true recovery or true recovery that is unrelated to initial impairment. This correlation arises from the appearance of the error ε_0 in measured initial impairment, $FM_0 + \varepsilon_0$, and in the measured change in impairment, $\Delta = (FM_1 + \varepsilon_1) - (FM_0 + \varepsilon_0)$. However, the induced correlation will be small when the variability in true initial FM_0 impairment is large compared to the variance of the measurement error ε_0, as is the case for FM, which has good reliability.[11] Given low measurement error variance, it is reasonable to interpret Δ as true biological change. In contrast, high correlations between FM_1 and FM_0 are expected whether or not Δ is related to initial impairment. Although this correlation is not spurious, given that it accurately reflects the fact that patients with lower-than-average initial FM will have lower-than-average final FM, it does not directly address recovery. For this reason, we, and others subsequently, prefer to model Δ rather than FM_1. Finally, when using measurements that have a constrained range, it is important to consider ceiling effects. Thus far, such effects have not been observed: Substantial room for improvement remains for all but the least affected subjects. A related concern is that FM measures latent "true recovery" nonlinearly. For example, a change from $FM_0 = 56$ to $FM_1 = 61$ ($\Delta = 5$) may reflect the same degree of "recovery" as a change from $FM_0 = 36$ to $FM_1 = 51$ ($\Delta = 15$). In this hypothetical scenario, true recovery is constant (and therefore unrelated to initial impairment), but the observed data are consistent with proportional recovery. This possibility, however,

neither negates the usefulness of proportional recovery as an important predictor of clinical change nor suggests that proportional recovery is an artifact. Instead, the possibility of nonlinearity implies a potential explanation for how proportional recovery might arise and emphasizes the need for care when interpreting the rule mechanistically.

In the article by Byblow et al in this issue,[12] upper-limb FM was measured in 93 patients at 2, 6, 12, and 26 days after first-ever ischemic stroke. The patients were divided into two groups. One group, called the Standardized Therapy cohort, received an extra 30 minutes of upper-limb therapy 5 days per week for 4 weeks, between 2 and 6 weeks poststroke, in addition to standard of care. The other group, called the Variable Therapy cohort, received varying degrees of regular care. The mean difference in the dose of upper-limb therapy between the two groups was 376 minutes.

MEPs and motor threshold were recorded from the extensor carpi radialis. There were four main findings in this study. First, patients with detectable MEPs at 2 weeks showed proportional recovery of 0.7 at 6 weeks; this was true even with patients with FM_0 as low as 5. Second, patients without MEPs made little recovery and those with absent MEPs and a fractional anisotropy (FA) value in the posterior limb of the internal capsule above 0.15 (a "point of no return"[13]), made no recovery at all. Third, the resting motor threshold (RMT) itself showed proportional recovery. Finally, the proportional recovery rule held equally for both therapy cohorts. These results are interesting for several reasons. They go beyond just validating the proportional recovery rule by also demonstrating what was before only speculated about, namely, that proportional recovery cannot be expressed if CST integrity is compromised beyond a certain threshold. The proportional recovery of the RMT is important because it suggests that there may indeed be a physiological basis for the rule and that it is not, in fact, attributable to an underlying nonlinearity in the FM. The authors make the interesting conjecture that the time course of reduction in the RMT may be due to reversible demyelination leading to transient axonal dysfunction, which might correlate with the degree of permanent axonal damage and initial impairment. This is an appealing speculation because it also explains why recovery takes time and is not immediately expressed for any given degree of CST integrity. Another possibility is that residual descending pathways need to be facilitated and trained by a process of cortical reorganization.[8] These are not mutually exclusive mechanisms, and future work will need to determine how processes in intact gray and white matter allow recovery to proceed. The authors state that it is possibly controversial that the two cohorts with differing amounts of upper-limb rehabilitation still obeyed the same 0.7 rule. It should not be controversial, however—indeed it is entirely expected, as we have previously predicted.[4] The difference between the two groups in the number of minutes of therapy received would equate to a number of

extra functional movement repetitions too small to trigger significant reorganization.[14] Therefore, as we have stated before, current dosing of therapy is likely to be ineffectual in augmenting what is expected from proportional SBR. Animal models suggest that the plasticity processes that mediate SBR also cause a short-lived increase in responsiveness to training,[15,16] which suggests that significant increases in therapy dose, as could plausibly be achieved with robotics, might indeed break through proportional recovery.

The study by Feng et al in this issue[17] nicely complements that by Byblow et al. In this study, two cohorts of patients (total of 76) were followed prospectively at two separate sites. They were assessed with the upper-limb FM at 2 to 7 days poststroke and at 3 months. The innovation was to take an approach that the authors had developed in chronic patients[18] and apply it to motor recovery in the first 3 months after stroke. FA values, used by Byblow et al. in the least interesting part of their study, are problematic in acute stroke because of edema and delayed Wallerian degeneration. Feng et al instead calculated a weighted CST lesion load (wCST-LL) for each patient by overlaying the patient's diffusion-weighted imaging (DWI)-based lesion map with a probabilistic CST derived from diffusion tensor images of age-matched healthy subjects. There were three main results. First, for patients with nonsevere hemiparesis (FM >10), wCST-LL correlated no better with the FM at 3 months than did initial FM. This is not surprising—the initial impairment is almost certainly largely owing to CST damage rather than infarct size, and so the initial FM and wCST-LL are measuring the same thing. Second, the nonsevere patients obeyed the proportional recovery rule. Third, for patients with severe hemiparesis (FM <10), the 3-month FM was correlated better with the initial sCST-LL than with the initial FM. Thus, unlike in the Byblow study, the emphasis here was not on Δ and recovery per se, but on the correlation between an initial measurement and a final FM. As we state above, this correlation can be positive even if what is initially measured is not itself correlated with Δ. The novelty then is that the wCST-LL may provide a more graded and sensitive measure of initial CST damage than initial FM—the improved dynamic range provided being the cause of the increased correlation reported. The authors also suggest that they can identify a wCST-LL cutoff below which minimal recovery is expected.

Breakthroughs from clinical trials for stroke recovery have been disconcertingly unsuccessful to date. Lack of efficacy across many therapeutic modalities has occurred both because of a poor understanding of the underlying mechanisms of SBR, as discussed above, but perhaps more importantly, the early time period after stroke has been a "moving target" because of SBR. To address this, many investigators have opted to run trials in the chronic phase of stroke where baselines are stable even though plasticity

is less active. There is an opportunity, however, to take advantage of the proportional recovery rule to solve the moving target problem by using the recovery rule of 0.7 as a robust and reliable benchmark against which to test interventions. Specifically, a treatment arm would be required to show a statistically different recovery proportion from the nonintervention group over the course of the study period.

In summary, the two studies in this issue of *Annals of Neurology* add further confirmation of the proportional recovery rule after stroke and begin to probe its physiology. In the Byblow et al study, the absence of MEPs in patients with severe hemiparesis identifies those who will not show proportional SBR, although validation in another cohort is required. The Feng et al study is more preliminary, but nevertheless suggests that the wCST-LL may be a sensitive measure for identifying nonrecoverers and be a more direct test of the CST integrity hypothesis for proportional recovery put forward by Byblow et al, given that MEPs can be absent or diminished for reasons other than because of disrupted CST integrity. Finally, the use of the proportional recovery rule may turn out to be most useful in design of future stroke recovery clinical trials, as proposed above. It is to be hoped that the identification of recoverers and nonrecoverers early after stroke will allow for more effective triage and stratification for neurorehabilitation (eg, emphasizing impairment vs. compensation) and will assist in the development of new interventions for mild-to-moderate as well as severe hemiparesis while the postischemic sensitive period is open.[2]

Potential Conflicts of Interest

Nothing to report.

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References

1. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci 2004;22:281–299.

2. Zeiler SR, Krakauer JW. The interaction between training and plasticity in the poststroke brain. Curr Opin Neurol 2013;26:609–616.

3. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol 2006;59:735–742.

4. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair 2012;26:923–931.

5. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci 2009;10:861–872.

6. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair 2008;22:64–71.

7. Fugl-Meyer AR. Post-stroke hemiplegia assessment of physical properties. Scand J Rehabil Med Suppl 1980;7:85–93.

8. Zarahn E, Alon L, Ryan SL, et al. Prediction of motor recovery using initial impairment and fmri 48 h poststroke. Cereb Cortex 2011;21:2712–2721.

9. Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. Neurorehabil Neural Repair 2015;29:614–622.

10. Lazar RM, Minzer B, Antoniello D, et al. Improvement in aphasia scores after stroke is well predicted by initial severity. Stroke 2010;41:1485–1488.

11. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair 2002;16:232–240.

12. Byblow W, Stinear CM, Barber PA, Petoe M, Ackerley S. Proportional recovery after stroke depends on corticomotor integrity. Ann Neurol 2015 Jul 7. doi: 10.1002/ana.24472. [Epub ahead of print]

13. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The prep algorithm predicts potential for upper limb recovery after stroke. Brain 2012;135:2527–2535.

14. Lang CE, Macdonald JR, Reisman DS, et al. Observation of amounts of movement practice provided during stroke rehabilitation. Arch Phys Med Rehabil 2009;90:1692–1698.

15. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J Neurosci 2004;24:1245–1254.

16. 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 2015;46:2951–2960.

17. Feng W, Wang J, Landsittel D, et al. Corticospinal tract lesion load—an imaging biomarker for stroke motor outcomes. Ann Neurol 2015 Aug 20. doi: 10.1002/ana.24510. [Epub ahead of print]

18. Lindenberg R, Zhu LL, Ruber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum Brain Mapp 2012;33:1040–1051.