Published in final edited form as:

Ann Neurol. 2018 June ; 83(6): 1069–1071. doi:10.1002/ana.25265.

Repair after brainstem ischemia involves neurogenesis and the rubrospinal system

Theodor Rüber, MD and

Dept. of Epileptology, University of Bonn Medical Center, Bonn, Germany

Gottfried Schlaug, MD, PhD

Dept. of Neurology, Division of Stroke Recovery and Neurorestoration and Division of Cerebrovascular Diseases. Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

The investigation of predictors and facilitators of stroke recovery constitutes one of the new frontiers in clinical neuroscience, firmly placing stroke recovery and brain repair within the continuum of care for stroke patients. It is for this reason that the NIH has made *stroke recovery* one of the three pillars of the StrokeNet grant program.¹ In a study published in the most recent issue of *Annals of Neurology*,² Minnerup and colleagues used histological assessments, MRI as well as motor testing to examine motor recovery and its structural correlates in a novel rat model of brainstem stroke. Remarkable findings were the post-lesional activation of a newly described neurogenic site in the dorsal brainstem and the structural reorganization of the cortico-rubro-spinal system with its rubral relay station (possibly allowing crossed and uncrossed connections with the descending spinal system). Their findings are supported by previous studies showing evidence of neurogenesis in the floor of the IVth ventricle in rats³ and structural changes/remodeling of the red nucleus and its anatomical vicinity after lesion to the descending motor system.^{4,5} Both of their main findings deserve discussion to provide further perspective with regard to human stroke.

First, the last two decades of research have demonstrated that new neurons are produced in the adult brain and that their production is facilitated after damage to the brain.⁶ Neurogenesis has reliably been proven to subsist in two germinal niches of the mammalian brain across species: in the subventricular zone of the lateral ventricle and in the subgranular layer of the dentate gyrus.⁷ Studies with animal models of focal cortical ischemia have repetitively demonstrated an increased proliferation and neurogenic differentiation in the subventricular zone to generate neuroblasts which migrate to peri-infarct cortex where they mature into neurons. Neurogenesis in the dorsal brainstem has never been as convincingly shown as in the study by Minnerup and colleagues and falls in the midst of a renewed discussion about whether or not adult neurogenesis occurs in the human hippocampus, which has been sparked by two recent studies with contrary results.^{9,10} However, the classic neurogenic niches are not activated by brainstem lesion and the novelty of the current study

Author Contributions

T.R. and G.S. contributed equally to the writing of this invited commentary

Potential Conflicts of Interest

Nothing to report

is not only the discovery of an unknown neurogenic niche, but the observation that its lesion-induced activation follows the logic of anatomical proximity. Namely, lesion location not only seems to determine the deficit but also its potential recovery mechanisms.

Second, Minnerup and colleagues have shown that neuronal repair is facilitated by the compensatory recruitment of uninjured brain regions and motor pathways. Compensation occurs when systems mediating complementary functions in a physiologically functioning network exhibit substitutional functions in a lesioned one. While compensation in other systems of the brain such as the language system¹¹ or the swallowing system¹² relies on inherent capabilities of one hemisphere to take over function of the injured hemisphere or on its rudimentary bihemispheric organization, this process does not seem to apply to the motor system. One potential reason is the hemispheric specialization and localization of function in the human brain enabling speed and accuracy of volitional finger movements. Previous research has shown that most of the variability in motor outcome after a stroke is explained by the degree of injury to the descending pyramidal tract and initial motor impairment.^{13,14} Compensation and substitution has not been a major focus of this system in humans. However, the motor system might have some built-in redundancy such as the uncrossed pyramidal tract (which so far has only been shown to play a compensatory role in the developing, but not the adult brain)¹⁵ as well as more bilaterally organized extrapyramidal tracts such as the cortico-rubro-spinal system. The cortico-rubro-spinal system draws fibers from the primary motor cortex, premotor and supplementary motor areas and also allows for cross-talks between both rubral nuclei in the midbrain.¹⁶ It, thus, may play a compensatory role in motor recovery and has been suggested to do so based on its interactions with the corticospinal system during development.¹⁷ The evidence for plastic changes in the rubrospinal system is manifold: 1) Corticofugal fibers originating in the contralesional hemisphere have been shown to sprout into the ipsilesional red nucleus in animals after hemidecortation or pyramidotomy or other experimental manipulations.^{18–20} 2) Diffusion Tensor Imaging studies in humans indicate remodeling of the red nucleus during natural as well as experimentally facilitated recovery and found associations between diffusivity measures and the degree of functional motor recovery.^{4,21} 3) Benowitz and Carmichael have speculated that rubrospinal fibers at spinal cord level can sprout and potentially make connections with alpha-motoneurons that do no longer get input from the corticospinal tract.²²

All in all, human studies contrasting brainstem lesions with supratentorial lesion are necessary to examine whether this lesion type serves as particular triggers for activation of a neurogenic niche and rubrospinal plasticity to enhance recovery of function further than what is generally expected.^{23,24} In the pursuit of forming homogenous study populations, patients with brainstem stroke are often excluded from stroke recovery studies^{25,14} and detailed studies of natural outcomes or comparisons to hemispheric strokes are lacking. By describing the neuronal response to brainstem ischemia, Minnerup and colleagues have increased our attention to an understudied type of stroke and their findings of post-lesional remodeling might offer a new window into predictors and facilitators of stroke recovery. We hope that further studies will scrutinize the neuronal underpinnings of these newly mapped routes to recovery, relate structural changes (e.g., amount of precursor cells, amount of fiber outgrowth or rewiring) to functional improvement or recovery, and examine how novel

rehabilitative approaches can leverage them to enhance recovery beyond what can be expected from natural outcome.

References

1. Broderick JP, Palesch YY, Janis LS. National Institutes of Health StrokeNet Investigators. The National Institutes of Health StrokeNet: A User's Guide. II [Internet]. *Stroke*. 2016; 47(2):301–3. [cited 2018 May 9] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26715457>. [PubMed: 26715457]
2. Minnerup J, Strecker J-K, Wachsmuth L., et al. Defining mechanisms of neural plasticity after brainstem ischemia in rats. [Internet]. *Ann Neurol*. 2018. [cited 2018 May 5] Available from: <http://doi.wiley.com/10.1002/ana.25238>
3. Bauer S, Hay M, Amilhon B, et al. In vivo neurogenesis in the dorsal vagal complex of the adult rat brainstem. *Neuroscience*. 2005; 130(1):75–90. [PubMed: 15561426]
4. Ruber T, Schlaug G, Lindenberg R. Compensatory role of the cortico-rubro-spinal tract in motor recovery after stroke [Internet]. *Neurology*. 2012; 79(6):515–522. [cited 2018 Feb 28] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22843266>. [PubMed: 22843266]
5. Lawrence DG, Kuypers HGJM. The Functional Organization of the Motor System in the Monkey [Internet]. *Brain*. 1968; 91(1):1–14. Available from: <http://brain.oxfordjournals.org/cgi/doi/10.1093/brain/91.1.1>. [PubMed: 4966862]
6. Kempermann G, Gage FH, Aigner L., et al. Human Adult Neurogenesis: Evidence and Remaining Questions. [Internet]. *Cell Stem Cell*. 2018. [cited 2018 May 5] Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1934590918301668>
7. Alunni A, Bally-Cuif L. A comparative view of regenerative neurogenesis in vertebrates [Internet]. *Development*. 2016; 143(5):741–753. Available from: <http://dev.biologists.org/cgi/doi/10.1242/dev.122796>. [PubMed: 26932669]
8. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. *Lancet Neurol*. 2009; 8(5):491–500. [PubMed: 19375666]
9. Boldrini M, Fulmore CA, Tartt AN, et al. Human Hippocampal Neurogenesis Persists throughout Aging [Internet]. *Cell Stem Cell*. 2018; 22(4):589–599. e5. [cited 2018 May 5] Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1934590918301218>. [PubMed: 29625071]
10. Sorrells SF, Paredes MF, Cebrian-Silla A, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. II [Internet]. *Nature*. 2018; 555(7696):377–381. [cited 2018 May 5] Available from: <http://www.nature.com/doi/10.1038/nature25975>. [PubMed: 29513649]
11. Schlaug G. Even when right is all that's left: There are still more options for recovery from aphasia [Internet]. *Ann Neurol*. 2018; 83(4):661–663. [cited 2018 May 5] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29573028>. [PubMed: 29573028]
12. Kumar S, Schlaug G. Enhancing swallowing recovery after a stroke by harnessing its bihemispheric organization. [Internet]. *Ann Neurol*. 2018; 83(4):658–660. [cited 2018 May 5] Available from: <http://doi.wiley.com/10.1002/ana.25206>. [PubMed: 29572924]
13. Byblow WD, Stinear CM, Barber PA, et al. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol*. 2015; 78(6):848–859. [PubMed: 26150318]
14. Feng W, Wang J, Chhatbar PY, et al. Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. *Ann Neurol*. 2015; 78(6):860–870. [PubMed: 26289123]
15. Staudt M, Gerloff C, Grodd W, et al. Reorganization in congenital hemiparesis acquired at different gestational ages [Internet]. *Ann Neurol*. 2004; 56(6):854–863. [cited 2018 May 9] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15562409>. [PubMed: 15562409]
16. Canedo A. Primary motor cortex influences on the descending and ascending systems. *Prog Neurobiol*. 1997; 51(3):287–335. [PubMed: 9089791]
17. Williams PTJA, Kim S, Martin JH. Postnatal Maturation of the Red Nucleus Motor Map Depends on Rubrospinal Connections with Forelimb Motor Pools [Internet]. *J Neurosci*. 2014; 34(12):4432–4441. Available from: <http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.5332-13.2014>. [PubMed: 24647962]

18. Papadopoulos CM, Tsai S-Y, Alsbie T, et al. Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat. [Internet]. *Ann Neurol*. 2002; 51(4):433–41. Available from: <http://www.mendeley.com/catalog/functional-recovery-neuroanatomical-plasticity-following-middle-cerebral-artery-occlusion-in-1-antibo/>. [PubMed: 11921049]
19. Z'Graggen WJ, Fouad K, Raineteau O, et al. Compensatory sprouting and impulse rerouting after unilateral pyramidal tract lesion in neonatal rats. [Internet]. *J Neurosci*. 2000; 20(17):6561–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10964961>. [PubMed: 10964961]
20. Villablanca JR, Fómez-Pinilla F, Sonnier BJ, Hovda DA. Bilateral pericruciate cortical innervation of the red nucleus in cats with adult or neonatal cerebral hemispherectomy. [Internet]. *Brain Res*. 1988; 453(1–2):17–31. [cited 2018 May 5] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3401755>. [PubMed: 3401755]
21. Zheng X, Schlaug G. Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS and physical therapy [Internet]; *Front Hum Neurosci*. 2015. 9 Available from: <http://journal.frontiersin.org/article/10.3389/fnhum.2015.00229/abstract>
22. Benowitz LI, Carmichael ST. Promoting axonal rewiring to improve outcome after stroke. *Neurobiol Dis*. 2010; 37(2):259–266. [PubMed: 19931616]
23. Turney TM, Garraway WM, Whisnant JP. The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. [Internet]. *Stroke*. 1984; 15(5):790–794. Available from: <http://stroke.ahajournals.org/content/15/5/790%5Cnhttp://stroke.ahajournals.org/content/15/5/790.full.pdf%5Cnhttp://stroke.ahajournals.org/content/15/5/790.short%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/6474528>. [PubMed: 6474528]
24. Chua KS, Kong KH. Functional outcome in brain stem stroke patients after rehabilitation. [Internet]. *Arch Phys Med Rehabil*. 1996; 77(2):194–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8607746>. [PubMed: 8607746]
25. Stewart JC, Dewanjee P, Tran G, et al. Role of corpus callosum integrity in arm function differs based on motor severity after stroke. *NeuroImage Clin*. 2017; 14:641–647. [PubMed: 28348955]