and PFS data were included; pediatric studies were excluded. The American Academy of Neurology level of evidence criteria (grade I, most robust, to grade IV, weakest evidence) was used to classify the strength of evidence of individual studies, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system was used to evaluate the overall body of evidence.

Thirty-seven studies were included in the meta-analysis, of which 36 studies were used for the analysis of OS and 8 studies for the analysis of PFS. The meta-analysis indicated a significantly improved OS after GTR compared with STR at 1 year (relative risk [RR], 0.62; 95% confidence interval [CI], 0.56-0.69; P < .01; number needed to treat [NNT] = 9) and after 2 years (RR, 0.84; 95% CI, 0.79-0.89; P < .01; NNT = 17). STR was superior to biopsy only in terms of 1-year OS (RR, 0.85; 95% CI, 0.80-0.91; P < .01). However, no significant difference in OS was observed between STR and biopsy after 2 years (RR, 0.99; 95% CI, 0.97-1.00; P = .09). At 6 months, GTR was better than STR in terms of PFS, but the differences were not statistically significant (RR, 0.72; 95% CI, 0.48-1.09; P = .12). However, GTR was indeed significantly better than STR in terms of PFS at 1 year (RR, 0.66; 95% CI, 0.43-0.99; P < .01; NNT = 26). The risk for progression was also significantly reduced by STR compared with biopsy alone at 6 months (RR, 0.72; 95% CI, 0.51-1.00; P = .05; NNT = 321); however, these differences were not significant at 1 year (RR, 0.96; 95% CI, 0.79-1.17; P = .69). None of the individual studies included in the analysis were graded class I; 4 were class II; 15 were class III; and 18 were class IV. However, with the inclusion of only class II studies, similar trends were observed compared with the larger meta-analysis for 1-year OS (RR, 0.62; 95% CI, 0.55-0.69; P < .01; NNT = 5) and 2-year OS (RR, 0.72; 95% CI, 0.49-1.07; P = .11; NNT = 7). Final assessment by GRADE criteria for quality of evidence was moderate for OS and the meta-analysis using only class II studies and low for all other analysis.

Certain limitations of this article acknowledged by the authors include the fact that GTR and STR were defined by the authors of the individual studies, introducing bias and limiting comparison between centers. GTR and STR cohorts were not matched according to prognostically important variables, and publication bias existed to exclude small studies favoring STR or biopsy over GTR. Importantly, surgical complications, adverse events, and quality of life were not compared between the GTR and STR cohorts. Despite these limitations, the article by Brown et al provides reasonable evidence, based on the sheer consistency of data across 41 unique patients, that GTR results in significant improvement in PFS and OS compared with STR or biopsy alone and that GTR should be preferred when clinically feasible.

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Long-term Training With a Brain-Machine Interface-Based Gait Protocol Induces Partial Neurological Recovery in Paraplegic Patients

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pineal cord injury (SCI) rehabilitation remains a major clinical challenge, especially in cases involving chronic, complete injury. Existing interventions for assisting patients with SCI in walking, including body weight support systems, robotic assistance, and functional electrostimulation of the legs, have not shown evidence of generating significant clinical improvement in somatosensory function below the level of the injury. In the past 2 decades, brain-machine interfaces (BMIs) have become popular tools for restoring limb function in paralyzed patients, although no study has suggested that long-term training with BMI-based paradigms and physical training could trigger neurological recovery, particularly in patients with complete SCI. However, the prospect of neurological recovery is supported by postmortem anatomical studies that have shown that 60% to 80% of patients with “complete” SCI show viable axons across the level of the SCI. In this study, Donati et al showed partial neurological and clinical improvement in patients with SCI subjected to long-term training with a multistage BMI-based gait protocol called the Walk Again Neurorehabilitation protocol (WA-NR).

Donati et al implemented WA-NR in 8 patients with chronic (>1 year) paraplegic SCI. Seven patients had complete SCI (American Spinal Injury Association Impairment Scale A), and 1 patient had partial SCI (American Spinal Injury Association Impairment Scale B). The 6-component protocol of WA-NR (Figure, A) started with seated virtual reality and progressed to gait training with a brain-controlled exoskeleton.

Although the original goal of the study was to explore how much such a long-term BMI-based protocol could help patients with SCI regain their ability to walk autonomously using the brain-controlled exoskeleton, the scientists realized after the first 12 months of training that all patients experienced a significant clinical improvement in their ability to perceive somatic sensations and to exert voluntary motor control below the original SCI. Sensory recovery was more vigorous and consistent for nociceptive perception (>5 dermatomes on average) than for tactile, vibration, or proprioception (1-2 dermatomes) and temperature (no significant improvement). Improvements were clinically significant after 7 months, peaking at the 10th month of training. Figure, B summarizes improvements in walking ability as measured by the Walking Index Spinal Cord Injury.

The authors propose that even in SCI up to 27% of the total area of spinal cord white matter may be preserved. Direct brain control of virtual or robotic legs and a continuous stream of tactile stimulation feedback from the legs and robotic actuators may induce plasticity through activation of central pattern generators and cortical afferents in patients with SCI. The full extent to which this mechanism of recovery can occur is of course still unclear. Other factors such as the timing of intervention and plasticity modulators that are still ill defined are, of course, unanswered questions at the current time.
 Nonetheless, this is the first clinical study to report the occurrence of consistent, reproducible, and significant partial neurological recovery in multiple patients with chronic SCI. These findings suggest that long-term exposure to BMI-based protocols enriched with tactile feedback and combined with robotic gait training may induce cortical and subcortical plasticity even in patients diagnosed with chronic SCI. The results obtained in the study suggest that BMI applications should be upgraded from a type of assistive technology to improve mobility to a potentially new neuro-rehabilitation therapy. It is indeed an exciting time to be involved in the care of these complicated patients.

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**IL-21 Receptor Modulates Ischemic Severity in Stroke**

Multiple lifestyle-related risk factors, including smoking and diabetes mellitus, have been definitively associated with an increased incidence of ischemic stroke.1,2 Previous studies have analyzed genetic factors such as lipid metabolism that would alter stroke risk but not the traits that would affect pial collateral vessel anatomy or infarct size. The variability of vessel anatomy and time of symptom onset and the heterogeneity of treatment course have made it difficult to accurately pinpoint molecular targets responsible for post-ischemic injury. In the present study, Lee et al3 applied a forward genetic (phenotype-driven) strategy by mapping the natural allelic variation in inbred mouse strains to determine the genes involved in determining both infarct size and extent of pial collateralization. Through this approach, 12 genes that influence the extent of pial collaterals and infarct size were identified within the chromosome 7 loci, *Civq1* and *Canq1*. Of these 12 genes, the authors determined that the *IL-21 receptor* (*Il21r*), found on immune cells and neurons, plays a major role in modulating infarct volume in vivo.

To examine differences in the pial collateral vessel anatomy between the *Il21r* ^−/−^ (KO) and *Il21r* ^+/+^ (WT) mouse strains, the authors measured the number of connections between the anterior cerebral artery, middle cerebral artery (MCA), and posterior cerebral artery in P21 mice. To accomplish this, the skull and dura were removed, and the pial circulation was observed under a stereomicroscope. The numbers of pial collaterals between the KO and WT group were 16.2 and 20.7 between the anterior cerebral artery and MCA territories and 16.6 and 20.1 between the MCA and posterior cerebral artery, respectively, a difference that was not significant (Figure). The authors concluded that *IL21r* is not the major gene encoding pial vessel anatomy under the chromosome 7 *Canq1* locus.

To then determine the role that *IL21r* plays in influencing infarct volume after ischemic stroke, permanent MCA occlusion was achieved by cauterizing and transecting the MCA through a 2-mm burr hole. Using this model, the authors determined that there was no change in cerebral blood flow in the KO mice.

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**Figure.** A, the Walk Again Neurorehabilitation protocol (WA-NR): (1) Seated patient uses his/her brain activity, recorded via EEG, to control the movements of a human body avatar in an immersive virtual reality (VR) environment while receiving visuo-tactile feedback; (2) the same as phase 1 but the patient is upright, supported by a stand-in-table device; (3) training on a robotic weight support (BWS) gait system on a treadmill; (4) training with a BWS gait system fixed on an over-ground track; (5) gait training with a brain-controlled robotic BWS gait system on a treadmill; and (6) gait training with a brain-controlled, sensorized robotic exoskeleton. B, functional assessment of autonomy in walking given by the Walking Index for Spinal Cord Injury (WISCI) scale. All patients improved in functional walking ability after 12 months of WA-NR. BMI, brain-machine interface; EEG, electroencephalography; EMG, electromyography. Adapted from Donati ARC, Shokur S, Morya E, et al. Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. Sci Rep. 2016;6:30383 used under CC BY 4.0.