lateral OFC (Figure, C), suggesting a behavioral link to differential lateral OFC activity.

Along with processing of the context of pain in the lateral OFC, the authors found that bid value, ie, the amount offered to avoid another painful stimulus, was negatively correlated with activity in a region in the right OFC more medial to that activated contralaterally by the context of the painful stimulus. Distinct regions of processing for stimulus context and bid value could be linked by a pathway through which context-dependent pain processing influences bidding behavior. Although this potential pathway needs further elucidating, one can appreciate the influence that the context of pain has on the activity of different brain regions that ultimately govern specific behaviors.

From a clinical perspective, given the presence of an integrated, objective pain matrix and higher-order contextual processor, there is potential for a deficit to arise in the communication between these processes. In concrete terms, deficits would manifest as differences between objective stimuli and perceived symptomatology, similar to what might be seen in somatic symptom disorder or chronic pain syndrome. Specifically, the patient processes an objective stimulus (be it visceral, somatic, or neuropathic), but the higher-order cognitive representation of that stimulus is transmuted so as to be immensely problematic for the patient. Patients with somatic symptom disorder, with prevalence estimates ranging from 10% to 20%,[10] may experience pain that does not respond to a long list of conventional medical therapies. For these patients, the lateral OFC may represent a target for therapy. Along with processing contextual correlates of pain as demonstrated by Winston and colleagues, the lateral OFC performs related higher-order functions such as the reception of integrated afferent sensory information[11] and the processing of alterations in expected outcome values.[12] Neurosurgically, the convergence of these higher-order functions in the lateral OFC presents a node with therapeutic potential for disorders such as somatic symptom disorder or chronic pain syndrome that possess troublesome, hard-to-treat cognitive components. Neuromodulation of the lateral OFC (and other associated nodes in the circuit as they are delineated) may thus provide logically defined therapeutic avenues for patients suffering from debilitating disorders who have exhausted all other options.

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A Novel Vehicle for the Delivery of Exogenous Neurotrophic Factors in Spinal Cord Injury

The relatively permanent nature of central nervous system injury is a great scientific dilemma, specifically as it pertains to spinal cord injury (SCI). Over the past several decades, significant advances have been made in the understanding of the pathophysiological mechanisms of SCI. Furthermore, the basic science literature is rife with promising studies investigating the effects of novel therapeutic interventions targeted to alter the disease process and to restore neurological function. Unfortunately, translating this progress into effective clinical treatment modalities has proved to be a major challenge and lags far behind. Despite the advances in basic science research, severe SCI continues to carry a poor prognosis with respect to restoration of neurological function and creates a major burden on our society.

As is the case for any disease process, to develop effective therapeutic interventions for SCI, it is first necessary to gain a thorough understanding of the pathophysiology of SCI. In broad terms, neurological recovery after SCI is impeded by a multitude of processes that occur both immediately after the injury and in a delayed fashion. Such processes include myelin-associated inhibitors, a paucity of neurotrophic factors, the inability of mature neurons to overcome inhibitory signals, and delayed formation of glial scar. No single process is responsible for blocking neuronal regeneration; therefore, effective therapies should be multimodal. Methods to promote neuronal regeneration range from genetic alterations and stem cell transplantation to administration of exogenous neurotrophic factors. However, the lack of feasible and realistic strategies for successful administration of these interventions in humans has limited their translation to clinical medicine.

In a recent article, Wang et al[1] explored the advantages and effectiveness of administering exogenous neurotrophic factors, specifically ciliary neurotrophic factor (CNTF), to promote neuroregeneration after SCI. The development of realistic application strategies for genetic and stem cell–based therapies, although potentially effective, is rather challenging. Comparatively, delivery of exogenous neurotrophic factors is theoretically less complicated. The authors have focused on the cytokine CNTF because dramatic increases in expression of CNTF after central nervous system injury have been detected and because it may play an important role in neuroregeneration. Simple injection of exogenous compounds generally leads to poor results owing to rapid diffusion, insufficient concentration at the site of injury, and systemic side effects. One solution to this dilemma involves implantation of a pump to deliver high concentrations of the desired cytokine to the injury site. Alternatively, the authors used sodium hyaluronate as a vehicle for sustained CNTF release by implanting gelatinous

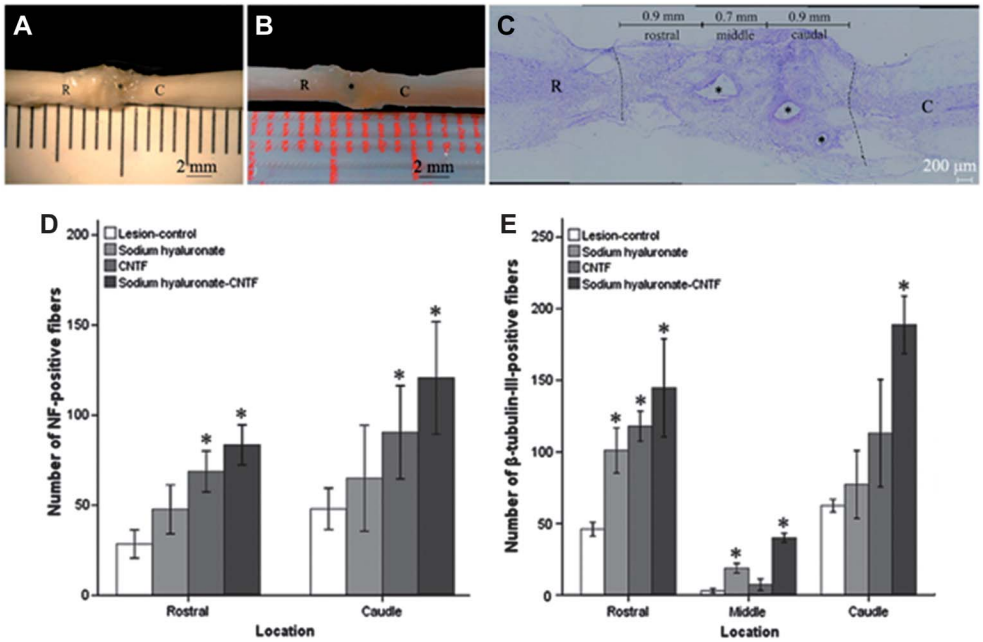

Figure. Quantification of neurotrophic factor- and β-tubulin III–positive neuronal fibers in the lesion area at 2 months postoperatively. **A** *and* **B**, *macroscopic images of the dorsal surfaces of the lesion control (***A***) and sodium hyaluronate-ciliary neurotrophic factor (CNTF;* **B***) cords at 2 months postoperatively.* **C**, *Nissl staining of the sodium hyaluronate-CNTF cord showed that the complete resection operation had made no neural residue left in the lesion area. The sodium hyaluronate-CNTF gelatinous particles are indicated by an asterisk.* **D** *and* **E**, *quantification of neurotrophic factor- (***D***) and β-tubulin-III–positive (***E***) neuronal fibers in the rostral, middle, and caudal segments of the lesion area at 2 months postoperatively. Error bars represent ±2 SE. Scale bars:* **A** *and* **B**, *2 mm;* **C**, *200 μm.* Reprinted by permission from Macmillan Publishers Ltd: [Spinal Cord] (Wang N, Zhang S, Zhang AF, Yang ZY, Li XG. Sodium hyaluronate-CNTF gelatinous particles promote axonal growth, neurogenesis and functional recovery after spinal cord injury. Spinal Cord. 52(7):517-523, copyright 2014.

particles directly into the site of SCI in rats. These implants were created by dissolving CNTF and sodium hyaluronate gelatinous particles in phosphate-buffered saline.

In their experiments, rats were anesthetized and underwent T8-9 laminectomies, followed by direct injury to the spinal cord. The rats were divided into 4 groups based on the type of implant: sodium hyaluronate-CNTF particles, sodium hyaluronate alone, CNTF alone, and controls. They were then subjected to locomotive testing, electrophysiological assessment, and eventually sacrificed to perform immunohistochemistry and tissue analysis. The sodium hyaluronate–CNTF group demonstrated significantly better results on locomotive testing compared with the other 3 groups. Additionally, electrophysiological improvement in the sodium hyaluronate–CNTF group, as measured with cortical motor evoked potentials and sensory evoked potentials, was greater than in the other 3 groups. On immunohistochemistry analysis, the authors found that expression of neuron-specific intermediate filaments and β-tubulin III was significantly higher in the sodium hyaluronate-CNTF group, suggesting increased axonal growth and neurogenesis (Figure). Subsequently, they demonstrated that this result was related to the promotion of proliferation and differentiation of endogenous neural progenitor cells in response to the sodium hyaluronate–CNTF particles.

The authors' novel method of introducing an effective exogenous neurotrophic factor into the site of SCI holds great promise as a useful means of translating important basic science research in SCI to the clinical setting. The concept behind this research highlights the importance of closing the gap between successful bench therapies and realistic applications in the treatment of human disease. Translating bench science to the bedside is often limited by the challenge of establishing an effective and safe vehicle for drug administration. From a neurosurgical standpoint, the potential usefulness of this technique extends well beyond the realm of SCI, providing an important means of bypassing the blood-brain barrier, avoiding systemic side effects, and delivering high concentrations of therapeutic agents for sustained periods of time directly to the targeted area. This conceptual design has given rise to implantable carmustine-impregnated biodegradable copolymers for the treatment of gliomas.

As a result in large part of advances in genetics, proteomics, and molecular biology, scientists and physicians have enhanced understanding of the pathophysiological mechanisms of SCI. Disease processes are rapidly being broken down to the molecular level, and understanding the critical steps in a disease process permits the development of targeted therapies. Surgical intervention is only a minor part of the comprehensive care required in patients with severe or complete SCI. This work by Wang et al sheds new light on an old problem. In the future, development of biodegradable vehicles for the delivery of effective pharmaceuticals directly to

site of injury could improve the long-term outlooks for patients with SCI.

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Therapeutic Cortical-Cortical Coupling in Parkinson Disease

Closed-loop deep brain stimulation, in which neural signals collected from implanted electrodes control the timing and mode of therapeutic stimulation, has been proposed as a potential treatment for a number of brain disorders. The fundamental basis of the closed-loop approach is the identification of electrophysiological biomarkers that will successfully guide stimulation. In Parkinson disease (PD), there is a growing body of work describing candidate biomarkers. In particular, deep brain stimulation disrupts hypersynchronous activity in the beta band within the subthalamic nucleus and motor cortex[1] and disrupts pathological modulation of gamma activity in primary motor cortex (M1) by beta activity in the subthalamic nucleus.[2]

In a recent study, Herz and colleagues[3] investigated the neural dynamics of motor pathways in patients with PD, providing an additional potential electrophysiological biomarker of the disease. Using high-density electroencephalography, coupled with multiple-source beam-former analysis and dynamic causal modeling, the authors recorded cortical activity from a group of patients with PD while they performed a simple task of repetitive finger movements while both on and off levodopa. They compared these data with brain activity recorded in healthy, elderly control subjects. On the basis of their findings, the authors propose that PD pathology involves a functional disconnection of mesial premotor cortex, manifested primarily as reduced gamma-gamma coupling from the lateral premotor cortex (LPM) to the supplementary motor area, whereas a functional connection between the LPM and primary motor cortex (M1) remains intact. Levodopa treatment restored gamma-gamma coupling between the LPM and supplementary motor area in patients with PD but did not restore the beta-beta coupling that was observed in healthy subjects. However, an additional effect of dopamine replacement was the emergence of a feedback connection between M1 and the LPM (Figure). A strong inverse correlation between cross-frequency theta-beta coupling from M1 to the LPM and individual motor improvement occurred after levodopa intake: The more beta activity in the LPM was suppressed by theta activity in M1, the stronger the individual benefit in motor function was.

As the authors point out, these findings are limited by the low spatial resolution of electroencephalography, such that the oscillatory activity recorded over M1 is likely to contain activity from adjacent parts of dorsal premotor and somatosensory cortex. In this regard, they suggest that their data may indicate a dopamine-dependent mechanism that improves integration of afferent sensory feedback, leading to suppression of antikinetic beta oscillations in the premotor cortex. Further work is needed with higher-resolution recording modalities such as electrocorticography or magnetoencephalography to better localize the sources of these coupling relationships and to explore the potential role of sensory cortex–basal ganglia interactions in control of movement gain.

The coupling described by Herz et al may provide a viable biomarker of therapeutic stimulation for monitoring by a closed-loop neuromodulation system, albeit one that requires implantation of cortical surface electrodes. A primary goal in advancing neuromodulation technology remains to develop the ability to adapt stimulation to the patient's fluctuating conditions, which are dynamically modulated by variations in medication levels and physical demands. In this way, it may be possible to provide better symptom control during times of high demand and to dial down stimulation

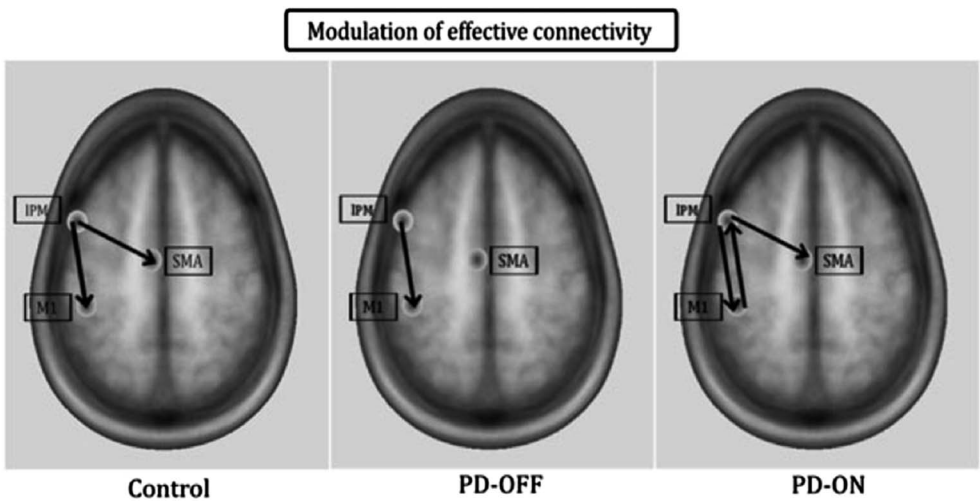

Figure. Spatial distribution of task-induced effective connectivity. LPM, lateral premotor cortex; PD, Parkinson disease; SMA, supplementary motor area. Reprinted with permission from Herz et al.[3]