Targeted exercises to increase cortical influence over spinal reflexes
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Background: Spinal contusions tend to spare a portion of neural circuitry. Spared circuits consist predominantly of reflexive brainstem- and spinal-origin tracts rather than volitional corticospinal fibers. To improve volitional control of muscles below spinal injuries, cortical connections to spared brainstem circuits must be strengthened above spinal injuries. We hypothesize that through Hebbian mechanisms, repetitive co-activation of cortical and brainstem circuits will strengthen detour pathways for cortical signals to travel around spinal lesions.

Objective: To use targeted exercises to demonstrate the utility of strengthening cortical influence over spinal reflexes.

Methods: Proof-of-concept studies were performed in two different models of mouse central nervous system injury. In a human pilot study, uninjured volunteers underwent one session each of three different types of exercise: (1) treadmill walking, (2) balance platform exercise, or (3) balance exercise combined with skilled hand activities (multimodal exercise). Electrophysiological outcome measures were recorded immediately before and after each exercise session. The primary outcome is the magnitude of soleus H-reflex facilitation by subthreshold transcranial magnetic stimulation (TMS). H-reflex facilitation occurs during two peak time windows relative to TMS – an “early” (<20 ms) window thought to represent direct corticospinal facilitation, and a “late” (60-80 ms) window thought to represent indirect facilitation, partly through corticobulbar connections. Other outcomes include soleus H/M ratio (an electrophysiological proxy for spasticity), central motor conduction time (a marker for speed of transmission between the cortex and spinal cord), and motor evoked potential amplitudes.

Results: Results in models of mouse CNS injury showed a consistent trend toward improved functional recovery in mice undergoing multimodal ‘Hebbian’ training. Preliminary results of the human pilot study, based on enrollment of 18 out of 24 planned participants, show post-exercise H-reflex facilitation in the late time window of 136.1±9.0%, 129.8±7.8%, and 117.7±4.5% after balance training, multimodal training, and treadmill training, respectively. In the early time window, post-exercise H-reflex facilitation is 128.3±9.2%, 121.5±5.6%, and 109.2±2.0% after balance, multimodal, and treadmill training, respectively. The ratio of maximal H/M amplitude decreased by 17.2±6.1%, 14.3±7.1%, and 6.2±10.3% after multimodal, balance, and treadmill training, respectively. Furthermore, central motor conduction time decreased by 0.83±0.44 ms and 0.63±0.32 ms after multimodal and balance training, respectively, whereas it increased 0.18±0.36 ms after treadmill training.

Conclusions: Balance training may increase supraspinal influence over spinal reflexes in the legs. While this pilot study in uninjured individuals continues, we have begun to incorporate a similar training and measurement approach into a clinical trial to test the effects of treadmill versus multimodal exercise in individuals with chronic spinal injury (clinicaltrials.gov/ct2/show/NCT01740128).
Figure 1 – Recovery through rerouting, not regeneration. Schematic of corticospinal (red) and brainstem tracts (green). In many cases of spinal cord injury (SCI), brainstem fibers make up the only surviving descending supraspinal fibers to cross the lesion. Any treatment that strengthens corticobulbar synaptic strength may establish a detour route for cortical signals to travel across the injury along spared brainstem pathways.

Pilot study in uninjured humans
1 session (30 min) each of 3 different exercises:

- Treadmill (CPG)
- Balance (BS)
- Balance + Hand Exercises (BS+CST)

Measure electrophysiological outcomes before & after each session

Figure 3 – Design of pilot study in uninjured human volunteers. The major CNS circuits targeted by each exercise modality are highlighted in yellow. CPG, spinal locomotor central pattern generator.

Figure 2 – Multimodal training in mouse CNS injury. A) To stimulate brainstem and corticospinal circuits in mice, wire platforms supported by elastic bands were designed to sway unpredictably. The swaying motion triggers postural responses mediated by brainstem circuits. The wire grating simultaneously stimulates CST circuits involved in distal limb grasp (BS+CST). The smooth surface limits stimulation to brainstem circuits (BS Only). The stationary wire grating stimulates CST circuits only. B) BS+CST-trained mice (yellow) tend to show the most improvement in impaired limb placement errors on a ladder-climbing task. C) Mice in both the CST-trained and BS+CST-trained groups showed a trend toward increased use of the impaired forelimb to explore a glass cylinder. *p per group shown in parentheses. NT = non-trained. Error bars = SEM. From Harel et al., 2013 (in press).

Soleus H-reflex facilitation

Figure 4 – Soleus H-reflex facilitation indicates magnitude of direct and indirect supraspinal influence. A) Electrical stimulation of the tibial nerve sends a descending impulse to the soleus muscle, resulting in an early M-wave, and an ascending sensory impulse to the spinal cord, synapsing on a soleus motor neuron, resulting in a late H-reflex. Transcranial magnetic stimulation (TMS) can influence the spinal synapse mediating the H-reflex, thereby resulting in H-reflex facilitation. B) If TMS is given at 0-20 ms prior to tibial nerve stimulation (Tib), this leads to H-reflex facilitation presumably through direct corticospinal pathways. If TMS is applied 60-80 ms prior to tibial nerve stimulation, this leads to H-reflex facilitation presumably through indirect pathways (adapted from Wolfa et al., 1995).

Figure 5 – Soleus H-reflex facilitation in uninjured volunteers. These are preliminary data derived from the first 18 of a planned 24 volunteers. The ratio of maximal tibial nerve-mediated H-reflex to M-wave amplitude serves as a proxy for spasticity. H/M ratio is expressed as percentage change following one session of either treadmill walking (black), balance exercise (green), or balance plus hand exercises (yellow). Balance and multimodal exercises trend toward increasing H-reflex facilitation more than treadmill exercise.

Figure 6 – Soleus H/M ratio and tibialis anterior central motor conduction time (CMCT) in uninjured volunteers. These are preliminary data derived from the first 18 of a planned 24 enrolled volunteers. A) The ratio of maximal tibial nerve-mediated H-reflex to M-wave amplitude serves as a proxy for spasticity. H/M ratio is expressed as percentage change following one session of either treadmill walking (black), balance exercise (green), or balance plus hand exercises (yellow). All three exercises trend toward decreasing H/M ratio. B) Change in central motor conduction time between motor cortex and tibialis anterior motor neurons. CMCT serves as an indicator of speed of direct corticospinal transmission. Both balance and multimodal exercise appear to increase transmission speed (decrease conduction time). Baseline average CMCT = 13.48 ms.