Modulating Locomotor Adaptation with Cerebellar Stimulation
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Abstract

Human locomotor adaptation is necessary to maintain flexibility of walking. Several lines of research suggest that the cerebellum plays a critical role in motor adaptation. In this paper we investigated the effects of non-invasive stimulation of the cerebellum to enhance locomotor adaptation. We found that anodal cerebellar tDCS applied during adaptation expedited the adaptive process while cathodal cerebellar tDCS slowed it down, without affecting the rate of de-adaptation of the new locomotor pattern. Interestingly cerebellar tDCS affected the adaptation rate of spatial but not temporal elements of walking. It may be that spatial and temporal control mechanisms are accessible through different neural circuits. Our results suggest that tDCS could be used as a tool to modulate locomotor training in neurological patients with gait impairments.
Introduction

The ability to learn a new motor pattern depends on multiple behavioral and neural processes. An important question is whether we can selectively enhance one process to compensate for a deficiency in another. As a step towards this goal, we studied whether non-invasive brain stimulation can alter sensorimotor adaptation, which is a well-characterized form of motor learning. Adaptation occurs on a time scale of minutes to hours, and is essential for flexibility of movement control (Bastian 2008). It is driven by errors that act to recalibrate motor commands for predictable demands or perturbations (Martin et al. 1996). This form of rapid error-based learning is essential because it increases movement accuracy. Importantly, once a movement has been adapted, the calibration must be actively unlearned or washed out in order for the movement to return to its baseline state.

Adaptive learning mechanisms are known to normally contribute to a broad range of behaviors, including reaching, walking, balance, and eye movements (Horak and Diener 1994; Reisman et al. 2005; Shadmehr and Mussa-Ivaldi 1994; Wallman and Fuchs 1998). The cerebellum is known to be essential for this learning process. For instance, prior work has shown that damage to the cerebellum compromises adaptive ability across all the above-mentioned actions (Horak and Diener 1994; Lang and Bastian 1999; Martin et al. 1996; Morton and Bastian 2006; Smith and Shadmehr 2005; Xu-Wilson et al. 2009; Yagi et al. 1981). In addition, cerebellar excitability changes, as measured with transcranial magnetic stimulation (TMS), are strongly correlated with the magnitude of behavioral adaptation during walking in healthy individuals (Jayaram et al. 2011). As such, the cerebellum is a clear target for non-invasive brain stimulation to enhance this process.

Importantly, adaptive learning is also known to benefit individuals with cerebral stroke, making a cerebellar target for brain stimulation clinically important. Prism adaptation can mitigate hemineglect in patients with right-sided cerebral (parietal) damage, producing benefits that last up to a week (Rossetti et al. 1998). Walking adaptation on a split-belt treadmill can result in after-effects that improve the walking symmetry of
individuals with chronic cerebral stroke in the short- (Reisman et al. 2007; 2009) and
long-term (Reisman et al. 2010).

Here we investigated the effects of cerebellar transcranial direct current stimulation
(tDCS) on locomotor adaptation using a well-studied split-belt walking task that is known
to be cerebellum dependent. During split-belt walking, one leg is set to move 3 times
faster than the other. This initially disrupts coordination between the legs such that the
fast and slow leg steps are asymmetric, over time subjects learn to predict and account for
the perturbation (Reisman et al., 2005b). We investigated the laterality of adaptive
changes by separately stimulating the cerebellar hemisphere ipsilateral to fast and slow
legs. Recent studies have shown that non-invasive cerebellar stimulation can affect motor
behavior. For instance, 1Hz repetitive transcranial magnetic stimulation (rTMS), an
inhibitory protocol, applied over the cerebellum can increase variability of finger tapping
(Theoret et al. 2001) and reduce essential tremor (Gironell et al. 2002). tDCS, an
intervention known to modulate primary motor cortex excitability (Nitsche and Paulus
2000b), can also elicit changes in cerebellar excitability in a polarity-specific manner
where anodal tDCS increases excitability and cathodal tDCS decreases excitability
(Galea et al. 2009). Indeed, we have also recently showed that cerebellar tDCS can
increase acquisition in a reaching adaptation paradigm (Galea et al. 2011). Here we
hypothesized that anodal tDCS over the cerebellar hemisphere ipsilateral to the fast leg
would increase the rate of locomotor adaptation on the split-belt treadmill and cathodal
tDCS would diminish the rate of adaptation. The results from this study open up an
exciting opportunity for cerebellar tDCS as a rehabilitation tool to augment learning in
patients with walking asymmetries.

Materials and Methods
Forty naïve healthy subjects (15 female, 25 male; mean age 27, range 20 to 33) with no
known neurological disorder participated in the main experiment (5 groups of 8).
Additionally, eight healthy subjects participated in the first control experiment (3 female,
5 male; mean age 26, range 22 to 31) and five healthy, naive subjects (3 female, 2 male;
mean age 25, range 23 to 30) participated in the second control experiment. This
investigation was approved by the Johns Hopkins University Institutional Review Board. All methods conformed to the Declaration of Helsinki and all participants provided written informed consent.

Main Experiment

**Split-belt treadmill walking**

Split-belt walking was studied using a custom-built treadmill (Woodway, WI, USA). Speed commands for each belt were sent to the treadmill through a custom MATLAB (MathWorks) program. Subjects wore a safety harness and were oriented with one leg on each belt. Split-belt walking consisted of a 2 minutes baseline period of tied-belt walking at both slow (0.5 m/s) speeds (Figure 1). After this, participants were exposed to a 15min adaptation period where one belt moved at 1.5 m/s and the other at 0.5 m/s (Figure 1b). Split-belt walking initially disrupts coordination between the legs such that the fast and slow leg steps are asymmetric and the fast leg’s motion is phase advanced relative to that of the slow leg. In other words, subjects walk with a ‘limp’. We refer to the limb on the slow belt in the split-belt period as the slow limb and the limb on the fast belt as the fast limb. The split-belt perturbation is predictable, so adaptive mechanisms act to eliminate the limp in about ten minutes (Reisman et al., 2005b). Finally, when participants are re-exposed to tied-belt walking in the post-adaptation period they limp in the opposite way. This occurs because the newly adapted split-belt pattern is now being used for tied belt walking, and demonstrates storage of the new locomotor pattern.

During walking, kinematic data were collected at 100 Hz using Optotrak (Northern Digital, Waterloo, ON). We placed bilateral infrared-emitting markers over the following joints: foot (fifth metatarsal head), ankle (lateral malleolus), knee (lateral femoral epicondyle), hip (greater trochanter), pelvis (iliac crest) and shoulder (acromion process).

**tDCS**

Using a factorial design, subjects were randomized to receive either anodal tDCS (n = 8) over the cerebellar hemisphere ipsilateral to the fast leg, cathodal tDCS (n = 8) over the cerebellar hemisphere ipsilateral to the fast leg, anodal tDCS (n = 8) over the cerebellar hemisphere ipsilateral to the fast leg, and cathodal tDCS (n = 8) over the cerebellar hemisphere ipsilateral to the slow leg.
hemisphere ipsilateral to the slow leg, cathodal tDCS (n = 8) over the cerebellar hemisphere ipsilateral to the slow leg, or sham tDCS (n = 8). tDCS was delivered (only during the adaptation period) through two sponge electrodes (surface area 25 cm²) embedded in a saline solution. One electrode was applied over the cerebellum 3 cm lateral to the inion (Galea et al. 2009). The second electrode was positioned on the ipsilateral buccinator muscle. The intensity of stimulation was set at 2 mA (calculated current density of 0.08 mA/cm²), which is well below the threshold for tissue damage (Boggio et al. 2006). Unbeknownst to the subject, anodal, cathodal or sham stimulation was delivered for 15 minutes using a Phoresor II Auto (model PM850, IOMED). In the sham session, anodal tDCS was applied for 30 s and then shut off. In all conditions current was ramped up as adaptation began and ramped down just prior to post-adaptation.

Optotrack motion analysis data

Custom software in MATLAB (Mathworks) was used for all analyses. Infrared emitting markers were placed on the fifth metatarsal head (toe), lateral malleolus (ankle), lateral femoral epicondyle (knee), greater trochanter (hip), iliac crest (pelvis), and acromion process (shoulder). Limb angle was defined as the angle between a vertical line and the vector from hip to the toe on an x-y plane (Figure 1b and c). Limb angle is positive during flexion when the foot is in front of the hip and negative when the foot is behind the hip. Based on our previous work, we calculated measures of interlimb coordination that are adapted during split-belt walking, as previously demonstrated by Reisman and colleagues (Reisman et al. 2005). Typically, during overground walking, step length is calculated as the distance between the point of initial contact of one foot and the point of initial contact of the opposite foot. Since the feet are constantly in motion on the treadmill, the conventional calculation is not possible. Instead, we calculated a modified version of step length for the treadmill, where each step length was the anterior-posterior distance between the ankle marker of each leg at heel strike (HS) of the leading leg; fast step length refers to the step length measured at fast leg heel strike and slow step length refers to the step length at slow leg heel-strike (Figure 1b and c). Step symmetry (SS) was calculated (Malone and Bastian 2010) as the difference in fast (SLf) and slow (SLs) step lengths, normalized to their sum to allow for comparisons across subjects who might take
different sized steps and have different leg lengths (Equation 1). A value of 0 indicates
symmetry and a positive value means that the fast step is larger than the slow step. We
then calculated the magnitude of step symmetry for each pair of steps occurring during
adaptation, and post adaptation (Reisman et al. 2005). Step symmetry is typically plotted
for each stride, which consists of two steps.

Equation 1: 

$$\text{Step Symmetry} = \frac{\text{Step Length}_{\text{fast}} - \text{Step Length}_{\text{slow}}}{\text{Step Length}_{\text{fast}} + \text{Step Length}_{\text{slow}}}$$

There are two common ways that subjects can alter their step lengths: by shifting the
center of oscillation for each leg and by changing the phasing between the legs (Figure
1c) (Malone and Bastian 2010). Each subject’s center of oscillation was calculated as the
midpoint of the limb angle between heel strike and toe off for each leg. When the limb
was oscillating symmetrically around a vertical axis at the top of the pelvis, the center of
oscillation value was defined as zero. The center of oscillation of the slow leg was
subtracted from that of the fast leg to obtain the center of oscillation difference, where
zero indicates symmetry in the spatial realm. Subjects can also alter their step lengths by
shifting the timing between the two legs. We captured the temporal element of walking
by calculating phasing which was determined using the time series of limb angles for
each leg (Choi and Bastian 2007). It was calculated as the lag time at the peak cross-
correlation (Signal Processing Toolbox, MATLAB) of the limb angle trajectories over
one stride cycle, with reference to the slow leg (Choi and Bastian 2007). Phasing values
range from 0 to 1, where symmetry is indicated by 0.5. We have previously shown that
these two parameters can adapt at different rates, have different sensitivities for day-to-
day consolidation, and have different developmental time courses in children. (Malone
and Bastian 2010; Vasudevan et al. 2011; Malone et al. 2011). Thus we have speculated
that adaptation of the center of oscillation and phase may be under somewhat
independent neural control.
We used a single exponential function \(y = ae^{-\frac{x}{b}} + c\) to fit our group Step Symmetry and our group individual step length data. We only considered time constants from fits with \(R^2 > 0.8\). To ensure that all groups experienced the same perturbation, we used a one-way ANOVA to compare the first three steps of adaptation across stimulation groups. Rates of adaptation and post adaptation for each parameter were quantified by taking the average of the first 150 steps. To better visualize differences between groups, individual curves were smoothed with a moving average and binned by three strides. Statistics were performed on the unsmoothed data.

Control Experiments

Control Experiment 1

To determine whether tDCS changes baseline (i.e. tied belt) walking on the treadmill we performed a control experiment in 8 healthy, naive subjects (2 female, 3 male; mean age 27, range 22 to 30). Here, participants walked on the split belt treadmill with the belts tied at a slow speed (0.5m/s) for 5 minutes without tDCS and then for 5 minutes while receiving either anodal, cathodal or sham cerebellar tDCS as applied in the main experiment. We compared their variance in step symmetry with and without tDCS.

Control Experiment 2

Applying galvanic vestibular stimulation in blindfolded individuals causes subjects to deviate from their planned walking trajectory and shift their center of position in the direction of anodal stimulation (Fitzpatrick et al. 1999; Inglis et al. 1995). Therefore, it is possible that the effects of cerebellar tDCS on locomotor adaptation could result from vestibular stimulation, which may cause alteration of step lengths consistent with turning or shifts in center of position. Thus, we investigated whether tDCS applied over the cerebellum can affect walking trajectory. Five subjects participated in one session where we assessed walking trajectories by determining subjects’ lateral deviation when asked to walk 10 feet straight ahead (3x) with their eyes closed and their head tilted down as though they were looking at the floor. Subjects received anodal tDCS over the cerebellum for 20 minutes and walking trajectories were assessed before, during and after stimulation.
Statistical analysis

Separate one-way ANOVAs with the factor Stimulation (anodal, cathodal and sham) were used to compare the average step symmetry, phase and center of oscillation of the first 3 steps of adaptation, the first 150 and last 150 steps for each stimulation group. Post hoc pair-wise comparisons were done using a Fisher LSD test. For the control experiment, a two-way ANOVA with factors Stimulation (anodal, cathodal and sham) and Time (pre-stimulation, mid-stimulation, post-stimulation) was used to compare walking trajectories for the control experiments. Data are expressed as mean ± SEM, and effects were considered significant if p < 0.05.

Results

Main Experiment

All subjects were able to complete the walking task without difficulty, regardless of group assignment. The average mean step symmetry during the last minute of the baseline periods were not statistically different between stimulation groups (F[2,23] = 0.54, P = 0.94), or from zero (i.e. symmetry; P > 0.7). Therefore, we subtracted the average values of symmetry during baseline (tied-belt) walking from all data.

In general, we saw walking adaptation proceed as has been previously described, albeit at different rates. Generally, we found that during early adaptation there was a large asymmetry in step lengths (negative values) that rapidly return to baseline symmetry (zero). After adaptation, the belts were tied at the slow baseline speed (post-adaptation phase), which resulted in subjects having an after effect consisting of an asymmetric gait in the opposite direction to the early adaptation.

Anodal tDCS over the ‘fast-leg’ cerebellum improves adaptation

We found that adaptation rate of step symmetry changed when we stimulated the cerebellum ipsilateral to the fast leg. We first compared the initial three strides during adaptation to determine whether subjects experienced the same initial perturbations. There was no significant difference in the size of the initial asymmetry during early
adaptation (F[2,23] = 0.67, P = 0.52), indicating that all groups were similarly perturbed when the belts were first split. To assess the speed of adaptation, we fit the group adaptation learning curves for step symmetry using a single exponential function (Figure 3). The time constant of the exponential, which can be thought of as the number of strides to reach 2/3 of the total adaptation curve, was considerably smaller for the anodal group (8.7 strides) and larger for the cathodal group (31.1 strides) relative to sham (12.6 strides). Note that there are two steps in each stride to calculate step symmetry. To quantify the amount of learning early in adaptation, we averaged the first 150 strides of adaptation. We found that early in the adaptation period there was a main effect with regard to the amount of adaptation to the split belt perturbation across the three groups (F[2,23] = 5.17, P = 0.017; Figure 2i). Post-hoc tests revealed that anodal stimulation increased the amount of adaptation (t = 2.3, p = 0.04, df = 14) and cathodal stimulation tended to decrease it (t = -1.8, p = 0.06 , df = 14) relative to sham.

Despite differences in the early adaptation period, all groups reached similar levels of adaptation as indicated by no statistical main effect when comparing the last 150 strides of step symmetry during the split-belt period (F[2,23] = 0.2, P = 0.82). Finally, we found no statistical significant difference in the after-effect size across groups when assessing either the first 3 steps of post-adaptation (F[2,23]=0.16, P=0.80); or the rate of post adaptation in the first 150 steps (F[2,23] = 0.13, P = 0.87; Figure 2ii).

We then considered whether there were any differences in the adaptation amount or rate for each leg’s step length individually (rather than step symmetry). We found that the fast leg generally adapts its step length more than the slow leg (e.g. sham condition, fast leg adapts 176 mm; slow leg 81 mm). The extent of adaptation in the fast and slow legs did not differ across groups, as they all adapted the same amount. What was different was the effect of ‘fast-leg’ cerebellar stimulation on the adaptation rate (time constant) in the fast leg: anodal (14 steps), cathodal (74 steps), and sham (19 steps). The rate of
adaptation in the slow leg was rapid and not strongly affected by stimulation (5, 5, and 9 steps respectively) for the three groups.

Anodal cerebellar tDCS improves adaptation via a spatial strategy

There are two strategies that subjects could use to adapt their step sizes: they could alter the phasing of the motion between the limbs (a temporal strategy) and/or they could shift where the legs oscillate relative to the trunk (a spatial strategy) (Malone and Bastian 2010).

When assessing the first 150 steps of center of oscillation early during adaptation we found a strong trend towards significance (F[2,23] = 3.3, P = 0.06; Figure 4Ai), where anodal tDCS shifted the center of oscillation at a faster rate and cathodal tDCS at a slower rate relative to sham (Figure 4A). Note here that a positive value means that the fast leg is oscillating in front of the slow leg and vice versa. There were no group differences in center of oscillation for post adaptation [F[2,23] = 0.20, P = 0.82; Figure 4Aii]. Interestingly, the directionality of the changes were consistent with those observed in step symmetry.

We found that there was no difference in phasing between the three groups in first 150 steps of the adaptation period (F[2,23] = 0.15, P = 0.86; Figure 4Bi). Not surprisingly, there was also no difference in phasing during the post adaptation phase [F[2,23] = 0.28, P = 0.76; Figure 4Bii].

Anodal tDCS over the ‘slow-leg’ cerebellum does not affect adaptation

16 subjects received anodal or cathodal tDCS over the cerebellum ipsilateral to the slow leg (Figure 5). Surprisingly, when looking at the first 150 steps, we found no clear group differences in adaptation (F[2,23] = 0.68, P = 0.51; Figure 5i) or post adaptation (F[2,23] = 1.16, P = 0.33 Figure 5ii).
Control Experiments

**Experiment 1: Cerebellar tDCS does not affect normal walking**

Walking on the treadmill with tied-belts did not affect step symmetry variance when anodal, cathodal or sham cerebellar tDCS was applied \(F(2,23) < 0.001, P > 0.99\). Additionally, the average step symmetry did not differ from 0 (i.e. perfect symmetry) in any condition \(P > 0.4\).

**Experiment 2: Cerebellar tDCS does not affect walking trajectory**

Following anodal stimulation, subjects had an average deviation to the right of 0.08±0.04m during baseline, 0.09 ± 0.04m during stimulation and 0.09 ± 0.04m after stimulation. Thus, there was no effect of stimulation \(F(1,4) = 0.46, P = 0.50\) on walking trajectories.

**Discussion**

Our results show that cerebellar tDCS can enhance cerebellum-dependent locomotor learning. Importantly, we show that we can increase or decrease the rate of walking adaptation through anodal or cathodal tDCS (respectively) over the cerebellum. Galea et al. (2011) previously showed that anodal cerebellar tDCS can increase adaptation rate during a visuomotor task. Here we demonstrate behavioral effects that are specific to the polarity of stimulation, which argues that these findings are not merely a general modulation of the system. This work also extends other work that has used tDCS to influence motor skill learning by stimulating the primary motor cortex (Reis et al. 2009).

This study follows on our previous work using TMS to investigate the neurophysiological correlates of split-belt walking adaptation. In that work, we demonstrated that the cerebellar-brain inhibition (CBI), normally seen using paired pulse TMS (Pinto and Chen 2001; Ugawa et al. 1995), was reduced in the leg on the fast belt following 15 min of locomotor adaptation on the split-belt treadmill (Jayaram et al. 2009). CBI reflects the
connectivity between the cerebellum and M1. Specifically, it is thought that activation of Purkinje cells by a conditioning TMS pulse over the cerebellum elicits inhibition of the excitatory dentate-thalamo cortical pathway resulting in reduced facilitation of M1. This is evident by reduced motor evoked potentials amplitudes (MEP) when M1 is stimulated 5 ms after the conditioning stimulation of the cerebellum (Daskalakis et al. 2004; Pinto and Chen 2001; Ugawa et al. 1995). In this manner, the magnitude of CBI depends on the excitability of the Purkinje cells in the cerebellar cortex and the excitability of cells in M1. We previously found that CBI is reduced after learning in the absence of excitability changes in M1, and thus interpreted that Purkinje cells were less excitable after learning. This reduced excitability in Purkinje cells after adaptation could be explained by long-term depression (LTD) changes. This idea is supported by animal studies that indicate that development of LTD in Purkinje cells is associated with adaptive learning (Gilbert and Thach 1977; Medina and Lisberger 2008). LTD in Purkinje cells occurs when parallel fibers are activated in conjunction with climbing fibers. It is believed that the inhibitory output of Purkinje cells is partially modulated by climbing fiber inputs that transmit error signals (Ito 1998; Wolpert and Miall 1996). Cerebellar excitability can also be modulated by tDCS applied over the cerebellum. We previously showed that anodal tDCS effects were consistent with an increased excitability of Purkinje cells, since we were able to elicit CBI at very low conditioning stimulation intensity. On the other hand, cathodal tDCS resulted in decreased CBI, which was interpreted as inhibition of Purkinje cells (Galea et al. 2009).

Why would anodal tDCS improve learning rate, when learning is associated with decreased CBI (Jayaram et al. 2011)? We speculate that anodal tDCS acts in different ways. First, it is possible that anodal tDCS over the cerebellum broaden the population of Purkinje cells that are available for learning. Thus, pairing anodal stimulation with a behavioral learning paradigm might allow greater engagement of cerebellar cortex in learning. A second possibility, is that anodal tDCS increases the dynamic range available to Purkinje cells. In contrast, cathodal tDCS likely reduces the population of Purkinje cells available by reducing their excitability. Though cathodal stimulation on its own reduces CBI, it is likely to be non-specific and therefore not equivalent to a reduction in
CBI from learning, a pattern that was sculpted by the natural behavior. A third possibility that can explain the behavioral effects found here with anodal tDCS is related to its mechanism of action. In mice slice preparations from M1, anodal tDCS enhances secretion of brain derived neurotrophic factor (BDNF) and increases activation of the high affinity tyrosine kinase receptors (TrkB) (Fritsch et al. 2010). However, at this point it is unknown whether such mechanisms also occur in the cerebellum.

We do not think that residual stimulation of other brain structures is responsible for our results. We applied tDCS at a current density of 0.08 mA/cm². Due to the resistivity of the skull, a large proportion of the currently delivered is shunted through the scalp (Miranda et al. 2006), with the current density rapidly decaying with distance from the electrodes (Nathan et al. 1993) making it unlikely that residual stimulation of the brainstem occurred. Additionally, we know from a previous study that cerebellar tDCS applied as was done here did not alter any measures of brainstem excitability (Galea et al. 2009).

Though walking is a bilateral act, we found significant effects of tDCS only over the cerebellum ipsilateral to the fast leg during adaptation. Since our previous work only tested the neurophysiological changes in the fast leg following split-belt adaptation, we can only speculate why stimulation of the cerebellum ipsilateral to the fast leg is more effective. Typically, the ‘fast’ leg undergoes a much larger perturbation as the fast treadmill belt drives the leg far into extension. It is possible that this large perturbation results in larger error signals relative to the ‘slow’ limb. The ‘fast leg’ also adapts more than the ‘slow leg’ and only the adaptation rate of the ‘fast leg’ was influenced by tDCS. Therefore, it might be that there is more dynamic range in the ‘fast limb’ during this task for tDCS to induce a difference in adaptation. Further studies comparing neurophysiological changes in the fast and slow cerebellum following split belt adaptation might help us understand the laterality of the cerebellar stimulation effects on adaptive changes demonstrated here.
Interestingly, we found that tDCS changed the speed of adaptation of step lengths primarily by altering adaptation of spatial coordination (center of oscillation), but not temporal coordination (phasing). We have previously speculated that spatial and temporal coordination could be controlled by different neural structures (Malone and Bastian 2010). For example, tonic stimulation of the mesencephalic locomotor region can adjust the timing of gait (Shik et al. 1969), and descending drive from vestibular systems in decerebrate cats can change the balance of flexor and extensor muscle activity (Gottschall and Nichols 2007; Honeycutt et al. 2009), which could alter spatial elements of gait (i.e. center of oscillation). In healthy humans, conscious correction processes preferentially modified spatial, but not temporal control of the limbs, suggesting that spatial control of locomotion might be supraspinal (Malone and Bastian 2010). On the other hand, studies in patients with cerebellar degeneration performing the split belt treadmill task found compromised adaptation in both the spatial and temporal domain, but predominantly in spatial adaptation (Morton and Bastian 2006). It is possible that the pontocerebellum, which projects to cortical regions, plays a stronger role in the spatial control of locomotion and thus was more susceptible to being altered by tDCS preferentially applied to the lateral cerebellar hemispheres. Additionally, it is possible that the spinocerebellum, which projects to vestibulospinal and reticulospinal tracts, plays a stronger role in temporal control of locomotion but this warrants further investigation.

Cerebellar tDCS modulated the speed of adaptation but not the size of the after-effect or the speed of post-adaptation. This finding is consistent with reports of cerebellar tDCS modulating the rate of visuomotor adaptation without affecting the post-adaptation period (Galea et al. 2011). Importantly, all groups adapted to the same extent by the end of adaptation, thus it makes sense that the size of the after-effect was not different between groups. It is interesting to note that cerebellar tDCS effects on behavior were only present when it was on (i.e during adaptation). Neurophysiological changes from tDCS over M1 can outlast the stimulation period up to 90 min (Nitsche and Paulus 2000a), an effect believed to be dependent on NMDA receptor activity (Liebetanz et al. 2002). Interestingly, cerebellar Purkinje cells do not have NMDA receptors. There is currently no literature that reported the longevity of anodal cerebellar tDCS, and thus, it is possible
that the post stimulation effects of anodal cerebellar tDCS are different than M1 tDCS. In upper limb tasks, reduction of errors during adaptation is a strongly cerebellum-dependent process (Martin et al. 1996; Morton and Bastian 2006; Weiner et al. 1983), and M1 might play a stronger role in retention (Galea et al. 2011; Hadipour-Niktarash et al. 2007). It is not known whether this extends to walking, though our current data are consistent with this interpretation.

This study provides evidence of how tDCS can be used as an experimental tool to assess and understand motor learning. Our results also open up an exciting opportunity to test in future studies the possibility of using cerebellar tDCS as a rehabilitation tool. We have previously shown that adults who have a hemiparesis post-stroke show improvements in walking symmetry when they have been trained on a split-belt treadmill (Reisman et al. 2007). If anodal tDCS allows subjects to adapt faster, this may reduce the amount of time needed to train these patients. Moreover, it may be possible to use cathodal tDCS to slow the speed of de-adaptation, if we apply tDCS during post-adaptation, so that these subjects can retain and practice this improved walking pattern for a longer period of time following each training session. Future work should address the effectiveness of tDCS in stroke subjects and evaluate whether this could be used to augment split-belt treadmill training effects.
Figure Captions

Figure 1

A) Experimental paradigm showing the periods of split-belt walking and conditions. B) Illustration of the fast (gray) and slow (black) step lengths, which are used to calculate step symmetry. C) Step lengths can return to symmetry by a spatial strategy, shifting the center of oscillation, or a temporal strategy, by changing the phasing between the limbs. The dots refer to heel strike of the fast (black) and slow (grey) leg.

Figure 2

Step symmetry plotted stride by stride for the three stimulation groups where we stimulated the cerebellar hemisphere ipsilateral to the fast leg with SE indicated by the shaded area. Baseline values are subtracted out from the curves (i.e., symmetry is indicated by a value of 0). i) Average step symmetry for the first 150 steps of adaptation. ii) Average step symmetry from the first 150 steps of de-adaptation. (* p<0.05).

Figure 3

Step symmetry plotted stride by stride for the three stimulation groups where we stimulated the cerebellar hemisphere ipsilateral to the fast leg. Each group has been fitted with a single exponential function. The decay constant (95% CI) in steps for the anodal group was 8.7 (7.55, 9.86), 31.12 (26.91, 35.33) for the cathodal group and 12.16 (10.96, 13.36).

Figure 4

A) Center of oscillation plotted stride by stride for the three stimulation groups where we stimulated the cerebellar hemisphere ipsilateral to the fast leg with SE indicated by the shaded area. Baseline values are subtracted out from the curves (i.e., symmetry is indicated by a value of 0). i) Average center of oscillation for the first 150 steps of adaptation. ii) Average center of oscillation from the first 150 steps of de-adaptation.
B) Phasing plotted stride by stride for the three stimulation groups where we stimulated
the cerebellar hemisphere ipsilateral to the fast leg with SE indicated by the shaded area.
Baseline values are subtracted out from the curves (i.e., symmetry is indicated by a value
of 0). i) Average phasing for the first 150 steps of adaptation. ii) Average phasing from
the first 150 steps of de-adaptation.

Figure 5
Step symmetry plotted stride by stride for the three stimulation groups where we
stimulated the cerebellar hemisphere ipsilateral to the slow leg with SE indicated by the
shaded area. Baseline values are subtracted out from the curves (i.e., symmetry is
indicated by a value of 0). i) Average step symmetry for the first 150 steps of adaptation.
ii) Average step symmetry from the first 150 steps of de-adaptation.

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**A**

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<tr>
<th>baseline</th>
<th>tied</th>
<th>0.5 m/s</th>
<th>2min</th>
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<tr>
<td>tDCS</td>
<td>(anodal/cathodal/sham)</td>
<td>adaptation</td>
<td>split</td>
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<tr>
<td>post-adapt</td>
<td>tied</td>
<td>0.5 m/s</td>
<td>10min</td>
</tr>
</tbody>
</table>

**B**

- Fast Step Length
- Slow Step Length

**C**

- Early adaptation
  - Slow HS
  - Fast HS
  - Center of oscillation shift
  - Phase shift
  - Fast Step Length
  - Slow Step Length