A test of a dual central pattern generator hypothesis for subcortical control of locomotion

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Abstract

This study was designed to examine the nature of neural circuits involved in subcortical inter-limb coordination and reflex modulation mechanisms of locomotion. These circuits, called central pattern generators (CPGs), are believed to receive tonic input and generate rhythmically alternating sets of commands. Although CPGs have been theorized to exist in humans, their potential dual role in inter-limb coordination and reflex modulation is unclear. In the present study, nine participants walked on a treadmill, timing their heel-strikes to a metronome which varied the phase lag from 0.5 to 1.0 pi radians (0.1 pi intervals). A stimulus was delivered to the sural nerve and reflexes were measured in the ipsilateral and contralateral lower extremities through electromyography. The similarity between phase lag conditions for both temporal coordination (i.e., relative timing aspects between muscles and/or limbs) and reflex intensities suggested that they may be controlled by the same subcortical circuitry. Two plausible explanations exist: (1) a single CPG coordinates muscular contractions and phasically alters proprioceptive reflex modulation, as well as cutaneous input, using feed-forward control; (2) two separate circuits are strongly entrained, producing synchronous outputs for inter-limb coordination and reflex modulation. The out-of-phase task used in this study was limited in discerning such a difference, if it exists.

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1. Introduction

The study of the underlying mechanisms regulating locomotion is of importance because it is a fundamental component for activities of daily living. The hope for restoration of locomotion in those people who have lost the ability to walk due to a compromised neuromuscular system lies not only in the elucidation of the neural circuitry in coordination of the musculature involved, but also in the control of reflexes associated with normal locomotor function. The current study was designed to examine locomotion by analyzing the nature of the neural circuitry considered critical for human locomotion: the central pattern generator (CPG). More specifically, the current study was designed to assess the potential existence of separate CPGs for (1) subcortical coordination and (2) reflex modulation mechanisms of locomotion. Although the notion of separate CPGs has been theorized, it has not been observed empirically in humans. The current study attempted to quantify the potential for dual CPGs by using a previously unexplored methodology in humans.

It has been demonstrated that many animals possess spinal mechanisms for controlling locomotion. The precise neural circuitry responsible for this control has been demonstrated in some simple species as well as some mammalian systems [1–5]. For example, when a cat’s spine is transected, the cat can ambulate somewhat normally on a treadmill, with basic coordination and reflex activity like that found in normal cats. This “fictive locomotion” lends support to the notion of spinal circuitry for locomotion in mammals, as well as lower organisms [6]. An underlying assumption of fictive locomotion is that subcortical circuitry is responsible for coordinating the onset, duration, and magnitude of muscular contractions [3,7]. Because of the apparent central nervous system location of this type of circuitry and its function, it is termed as central pattern generator (CPG).
One hypothesis from studies of spinal cats was that the same circuit controlling inter-limb coordination also controlled reflex modulation. The observation of both behaviors (coordination and reflex modulation) without supraspinal influence certainly supported this assumption, because transections at different levels of the spinal cord either produced both behaviors or neither [8]. Likewise, it has been suggested that movement is produced by a central modulation of reflexes. This implies that inter-limb and intra-limb coordination is controlled by reflex modulation [9]. However, there are other possible explanations for these observations. Assuming the two tasks (coordination and reflex modulation) may operate without cortical control, there may be two separate circuits that function without supraspinal influence. The circuits may be linked, or synchronized, through parallel top–down commands [4]. If two separate circuits exist, then they may have different characteristics which produce a dissociation when a task is employed that strains one circuit but not the other. Presumably, the more adaptable of the two circuits will exhibit fewer errors than the more rigid circuit when a task is involved which includes complicated timing and reflex activity. The task must be similar enough to walking to utilize the same circuitry, but possess enough computational difficulty to strain each possible circuit.

In cats, fictive locomotion mimics, but is not as smooth as normal locomotion [6]. This observation weakens the hypothesis that a purely subcortical CPG may have considerable control of locomotion. This point has far reaching implications because many behaviors observed in cats (especially those involving reflexes) can also be observed in humans, allowing some legitimate extrapolation to humans [10,11]. However, humans possess a much more complicated central nervous system than cats [8,12]. Fortunately, it is exactly this complexity of the human nervous system that may help exhibit the internal control mechanisms involved in locomotion.

If two (or more) circuits exist for coordinating the musculature during walking and modulation reflexes, then they may act as one through entrainment. When neural circuits are entrained, their phases become locked together. The relationship that results from this phase locking is constrained to certain ratios that are determined by the strength of the linking between the two circuits [13]. An entrained system with rigid links would be constrained to a small number of ratios whereas a more flexible system would allow many ratios between the two systems [14,15]. The examination of temporal coordination and reflex modulation in a task with various phase lags may strain the proposed two circuits to varying degrees depending on the amount of supraspinal control and the degree of entrainment between them. Circuits with a great deal of supraspinal control will be more flexible than those which are hard-wired into the spinal cord circuitry. Because inter-limb coordination in an out-of-phase task appears to be supraspinal in humans [16], it is likely that temporal error would remain constant during movements such as limping.

Reflex modulation exhibit characteristics that strongly suggest it is under spinal control, whereas inter-limb coordination exhibits characteristics that are less tenable in regard to its spinal control. Therefore it is logical that the strength of reflex responses may vary across phase lag conditions in a weakly entrained system, particularly with contralateral responses. The lack of rigidity between the coordinating and reflex modulation circuitry would allow these variations to occur in selecting a response, by modulation circuitry which would operate under the standard phase lag options of 0 or pi radians, resulting in an inappropriate reflex for the true phase of the contralateral leg. If the modulation circuitry does not share the same temporal information available to the coordinating circuitry, then it is forced to operate as it usually does, rather than adapt to the requirements of a new task.

By contrast, a strong entrainment between coordination and modulation circuitry would likely yield reflex responses with a constant latency across various phase lags in the ipsilateral and contralateral leg. Because the reflex modulation circuit is locked in phase with the temporal coordination circuit, it may be pulled from a natural tendency for phase lags of pi or 0 radians. If the coordination circuit itself is flexible enough to allow various phase lags, then accurate coordination of temporal parameters should be observed.

Similar outcomes may be observed for both strongly entrained dual circuits and a single CPG that controls both inter-limb coordination and reflex modulation. It may be difficult to dissociate two strongly entrained circuits, resulting in the appearance of similar patterns of errors. The same result could be expected of a single CPG. Coordination and reflex modulation could vary together under both scenarios, irrespective of the system’s ability as a whole to adapt to a novel task. However, one task that may independently strain the computational demands of inter-limb coordination and modulation is limping. In quadrupeds, a number of phase relationships have been identified, yielding different types of locomotion (e.g., canter, gallop, trot, etc.) [13]. In humans, temporal constancy of phase was confirmed in infants, toddlers, and adults in a walking task [17]. Biomechanical similarity has also been observed between hemiplegic and normal gait [18]. However, Boylls et al., [16] found out-of-phase cycling to be under supraspinal control and free of neurological constraints like those seen in cats in out-of-phase walking. This would implicate higher mechanisms as primarily controlling out-of-phase tasks like limping in humans.

Reflex modulation has also been examined in tasks with varying phase lags like running, walking, cycling (all with phase lags of 0.5 cycles or pi radians), and
hopping (with a phase lag of 0.0 cycles or 0 radians) [19–21]. Different patterns of reflexes were observed with these different phase lag tasks, suggesting either separate circuits responsible for modulation in each task or, more plausibly, complex circuitry that controls many tasks. Although the patterns of reflex responses differed, their sub-cortical nature was evident by the adaptability of the reflexes.

The purpose of the present study was to determine whether separate circuitry exists for coordination of movement and modulation of reflexes and if such circuits act independently of each other. This was accomplished through the observation of temporal error (as a measure of coordination) and reflex intensity (as a measure of reflex modulation) across varying phase lag conditions in an out-of-phase walking task.

2. Methods

In the present study participants were asked to walk on a treadmill in concert with a metronome. The metronome varied the gait cycle from normal walking (1.0 pi radians) to something more akin to a limp (0.5 pi radians). During the walking task participants were stimulated by an electrical pulse and reflex and timing measures were taken.

2.1. Participants

Nine individuals (5 males and 4 females) volunteered to participate in the study. All participants were university students ranging in age from 20 to 34 years, with a mean age of 24 years. Additionally, all participants were free from any pathology that would adversely impact their performance. Each participant read and signed an institutionally approved informed consent form prior to participation in the study.

2.2. Design

The experimental design was a 2 (stimulus delay)×3 (trial)×6 (phase lag condition) mixed design. Stimulus Delay was a between-subjects factor with two levels, early and late stimulus delay, corresponding to points approximately 15% and 80% of the swing phase for the left (ipsilateral) leg. Trial and Condition variables were within-subjects factors. Each participant completed three trials, each separated by approximately 15–20 step cycles for each of the phase lag conditions ranging from 0.5 pi radians to 1.0 pi radian, at 0.1 pi radian increments. A phase lag of 1.0 pi radians equated to 180 degrees out of phase, or normal walking. A phase lag of 0.5 pi radians equated to 90 degrees out of phase, which is essentially one leg taking half the stride as the other. The dependent variables of interest were left (ipsilateral) timing error, and electromyographical (EMG) recording from the ipsilateral tibialis anterior, contralateral tibialis anterior, and contralateral gastrocnemius.

2.3. Apparatus and procedure

Participants were asked to walk normally on a treadmill (International Medical Corporation) which was set at a 0 degree incline and a 0.83 Hz cadence (Fig. 1). A metronome using alternating high and low tones corresponding to the left and right heel-strikes, respectively, maintained cadence. EMG recordings of the medial head of the gastrocnemius (right, or contralateral leg) and tibialis anterior (both legs) were collected using surface electrodes (Norotrode 2.0 silver/silver chloride bipolar electrodes).

Participant preparation and EMG data collection were adhered to according to those established by the International Society for Electromyographical Kinesiology (ISEK). Electrode sites were prepared by shaving the site and rigorously cleansing the skin. Conductive gel was included in the pre-packaged electrode. Electrodes were placed over the muscle belly of each muscle. Impedance of each site was noted prior to testing and site preparation was repeated if the impedance was greater than 10 kiloohms. Custom-made electronic switches (approximately 15 mm diameter and 4 mm thick, spring steel and externally padded) measured the timing error of the left heel-strike and toe-off. All EMG and timing data were recorded on a Gateway 2000 computer using Noraxon Myosoft software.

In addition to the recording measures described above, an electrical stimulus was applied over the sural nerve of the left leg. The purpose of this stimulus was to elicit a reflexive response in the muscles being monitored as established in previous research [9] using procedures similar to those of the present study. A bar electrode (Lafayette Instruments) was used to transmit the stimulus to the sural nerve. This stimulus was delivered transcutaneously, and posterior to the lateral maleolus. The source of the stimulus was an operating-room grade electrical stimulator (Grass Instrument Company, Model S44). A stimulus isolation/constant current unit (Grass Instrument Company, Model SIU7) was used to accommodate any changes in impedance that may have occurred during the experiment. The unit was also used to protect the participants from accidental discharges of current. The stimulation itself consisted of a train of six rectangular pulses of 1 ms, given over a period of 20 ms. The amplitude of these pulses was 2.5 times detection threshold (as determined by the method of limits prior to testing). The effect of this stimulation was a sensation of a touch on the lateral side of the foot. Thus, the perception would be similar to contact with “most likely . . . an obstructing object” [10]. For each participant, relative
stimulus strength was maintained throughout the experiment.

Fig. 1 is a graphic of the experimental protocol. Participants were asked to walk on the treadmill at the predetermined speed and tempo timed with the metronome sounds. Phase lag was varied by changing the delay between the high and low tones, with a delay of 0.5 cycle duration corresponding to a phase lag of π radians. Participants were tested in each phase lag condition (0.5 to 1.0 π radians at 0.1 π increments). The order of the phase lag was randomly assigned for each participant. During a selected cycle (approximately 15–20 cycles apart), the stimulus was delivered at a point in time during the stimulated leg’s swing phase. This point at which the stimulus was delivered was unexpected by the participant. Two stimulus delays were used. Participants 1, 2, 4, 7, and 9 received the stimulus approximately 80% through the swing phase (late), while participants 3, 5, 6, and 8 received the stimulus approximately 15% through the swing phase (early). This between-subjects design was used to avoid the effects of repeated testing/learning.

2.4. Outcome measures

Data were prepared by identifying onset of the left tone, left heel-strike and toe-off, right tone, right heel-strike and toe-off, and stimulus onset, as well as the latency and amplitude of the muscles sampled (i.e., ipsilateral tibialis anterior, contralateral tibialis anterior, and contralateral gastrocnemius). The absolute time (in ms), excitability levels (in mV), and area between events (in mV×ms) was determined using Noraxon Myosoft’s multiple marker analysis. From this data, the timing error, phase lag, stimulus delay, and reflex intensities were derived.

Timing error was determined by calculating the difference between the onset of the left tone and the corresponding left heel-strike. Phase lag was determined by dividing the duration of the left leg cycle by the inter-tone delay. Stimulus delay was calculated by dividing the stimulus onset relative to toe-off by the duration of the swing phase. Reflex intensity was derived by subtracting the area under the stimulated contraction curve (20–120 ms following stimulus onset) from the average area of the two preceding contractions at the corresponding point in the swing phase. The first 20 ms were eliminated from reflex intensity to eliminate widespread subcutaneous activation, which has been shown to contaminate recordings in similar protocols [10,11,22].

2.5. Analysis

Separate analysis of variance (ANOVA) procedures were performed on each of the four dependent variables. Again, the dependent variables of interest were left timing error and ipsilateral tibialis anterior, contralateral tibialis anterior, and contralateral gastrocnemius electromyography (EMG) latency. In each case, data were analyzed using a 2 (stimulus delay)×3 (trial)×6 (phase lag condition) ANOVA with repeated measures on the last two factors. When appropriate, follow-up analyses were used to further analyze the data (Tukey’s post hoc test). An α of 0.05 level was used for all comparisons.

3. Results

3.1. Left timing error and tibialis anterior reflex

The analysis revealed no significant main effects for condition, trial, or stimulus delay. There were no significant interactions between these variables for left timing error and tibialis anterior reflex.
3.2. Contralateral tibialis anterior (EMG)

There was a main effect of stimulus delay \[ F(1,5)=10.11, p=0.02 \]. All other main effects and interactions were not significant.

3.3. Contralateral gastrocnemius (EMG)

There were no main effects, but there was a significant condition\(\times\)stimulus delay interaction \[ F(5,10)=2.69, p<0.05 \]. All other interactions for contralateral gastrocnemius EMG were not significant. Simple main effects of the independent variables condition and stimulus delay yielded a significant difference between stimulus delays at condition 0.6 pi radians phase lag \[ F(1,5)=4.19, p<0.05 \]. All other differences were not significant (Fig. 2).

Because stimulus delay had only two levels, post hoc analyses were not needed for the dependent variable, contralateral tibialis anterior EMG, and the independent variable stimulus delay. The reflex intensity of the contralateral tibialis anterior varied from inhibition in early swing (mean=−1.63 mV) to nearly non-existent in the late swing (mean=−0.35 mV). As stated earlier, the excitability levels (e.g., −1.63 mV) represent the reflex intensity as derived by subtracting the area under thestimulated contraction (20–120 ms following stimulus onset) from the average area of the two preceding contractions at the corresponding point in the swing phase. Therefore, a negative number represented a greater reflex intensity when stimulated than when not stimulated.

Considering the relatively small sample size, it is interesting to ponder that the lack of significant results were affected by low power. To this end, two non-significant effects did approach significance. The contralateral gastrocnemius approached significance for stimulus delay, \[ F(1,5)=4.46, p=0.073 \], as did the left timing error over phase lags \[ F(1,5)=2.13, p=0.088 \]. Fig. 3 is a graphic of the left timing error over phase lags. This figure demonstrates two points. First, a lack of a main effect in this case is likely due to a lack of power. Second, there is clearly no interaction present. This demonstrates the remarkable commonality of the timing error over phase lags, regardless of the actual timing of the stimulation.

4. Discussion

The purpose of this study was to determine whether separate circuitry exists for inter-limb coordination of movement and modulation of reflexes and if such circuits act independently of each other. If different patterns of errors occurred in temporal error and reflex intensities, then it would support the concept of two separate circuits. Conversely, an absence of a dissociation would lend support to either a single circuit or two highly entrained circuits. These hypotheses were investigated by comparing the patterns of timing and reflex errors in a novel walking task. The results showed a gait phase dependent difference in reflex intensity for the contralateral tibialis anterior EMG and a difference between stimulus delay conditions at phase lag 0.6 pi radians. There was no difference in temporal error or reflex intensity between different phase lag conditions.

Phase lag condition had no significant effect on timing error, nor any of the three reflexes examined. This supported the notion of either a single circuit or two entrained circuits for controlling temporal coordination and reflex modulation in normal walking. This finding could perhaps be generalized to similar tasks as well. A high degree of adaptability is known to be present in the central nervous system to accommodate the demands of a difficult walking task. The similarity of means over
The significant effect of stimulus delay on the contralateral tibialis anterior response is similar to previous studies that examined the nature of crossed spinal reflexes during walking. In the early part of the swing phase, this reflex is typically less excitatory than at later points in the swing phase [22]. The exact intensity of the responses varied between participants, but the relative intensities were consistent. The observation of a lesser inhibitory response of the contralateral tibialis anterior between early and late swing was congruent with other investigations [10,11]. Stimulus delay had no significant effect on the ipsilateral tibialis anterior or the contralateral gastrocnemius response. Both of these responses have been shown to be relatively constant throughout the swing phase [22]. There was an interaction between stimulus delay and phase lag condition for the contralateral gastrocnemius EMG. The observation of a dissociation between stimulus delay conditions at the 0.6 pi phase lag condition may have been the result of the position of the contralateral leg at that time of stimulation. Stimulation during early swing (15% of the swing phase) typically showed greater contralateral gastrocnemius response compared with the normal response as reported in a previous study [10]. A small late swing response (80% of the swing phase) in the contralateral gastrocnemius was typically inhibitory when compared with normal conditions. However, for the 0.6 pi phase lag condition, the contralateral leg was closer to the toe-off position than it was in normal walking. The presence of the significant inhibitory response in this condition was in agreement with previous research [10,11] (see Fig. 2).

The present study demonstrated similar patterns of errors for timing and reflex intensity across phase lag conditions. This supported either a single central pattern generator which is capable of controlling both coordinative and modulation tasks, or dual entrained central pattern generators which function as a single coordinated unit. It is also suggested that these tasks experienced some level of supraspinal control. When normal walking is compromised by neuromuscular pathology, the capacity may eventually exist to restore locomotor ability through reconstruction or artificial stimulation of the circuits as discussed in this study and elsewhere [23]. The findings of this study may be used to narrow the search for such circuits by demonstrating the similarities between the two functions. If the anatomy (i.e., location) of these circuits is also parallel, then one may expect to find either the individual circuits very near each other or it may be possible to locate a single circuit that can accommodate most of the needs for restored locomotion. If two circuits can be identified as individual circuits, then their functional link may indicate an anatomical link as well, making the discovery of the second much easier. In the current study gait adapted to perform normally with a perturbation, the most logical explanation is there is plasticity in the CNS. Therefore, the current study reinforced the plasticity of the human locomotor system.

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References


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