How deletions in a model could help explain deletions in the laboratory

To the Editor: In the recent article by Lafreniere-Roula and McCrea an impressive account is given of so-called “deletions” of rhythmic motoneuron activity periods in fictive locomotion and scratching (August issue, p. 1120–1132). These deletions are of great interest since they provide insight in the central organization of locomotion. The deletions typically represent threshold behavior. In most of the cases shown, both here and in previous work, the deletions have an “all or none” character. For the authors mentioned, the data were primarily taken to support a model of the central pattern generator for locomotion and scratch that functions as a single rhythm generator with separate and multiple pattern formation modules for the generation of bursts of activity in subsets of motoneurons within the limb. The model is fine but not fully appropriate since it fails to explain some important observations.

First, according to the fully symmetrical model one might expect just as many flexor than extensor deletions. However, this is not what is observed. Deletions of extensor activity are the only deletions found in fictive scratching. Furthermore, for locomotion the paper presents more and better examples of extensor than of flexor deletions. Similarly, in work on walking premammillary cats, published earlier in Journal of Neurophysiology, spontaneous deletions occurred exclusively in extensors (Duysens 1977). Why this dominance of extensor deletions? There may be two basic reasons, namely first that the flexor part of the generator is much less affected by absence of afferent feedback and second that the flexor part is most directly controlled by the rhythm generator.

Consider first the issue ofafferent asymmetry. In terms of sensory feedback the organization of gait is basically asymmetrical since interaction with the environment is much more intense during the stance phase. This is because during stance one has to act against gravity and the input of load receptors is crucial (for review see Dietz and Duysens 2000; Duysens et al. 2000). In fact, in the past the McCrea group has provided evidence in support of an excitatory feedback system, reinforcing on-going extensor activity during the stance phase of the step cycle (McCrea et al. 1995). Deletions typically occur under circumstances when sensory input is reduced. In fictive scratching or locomotion there is no movement at all (Burke et al. 2001; Lafreniere-Roula and McCrea 2005). In premammillary or mesencephalic locomotion the cats walk but the limb investigated is kept immobile and/or is partially or fully denervated (Duysens 1977; Duysens and Pearson 1980; Grillner and Zanger 1979). Since the main source of feedback is of the extensor reinforcing type it is no surprise to find that spontaneous burst failures in such deafferented animals mostly occur in extensor motoneuron pools. To be complete, it therefore would have been nice that the model included the strong reinforcing afferent drive to the extensor center.

Furthermore, flexor and extensor centers differ in another aspect, namely in their input from the rhythm generator. A feature, which is not explained by the current model, is that extensor deletions can easily occur despite the presence of concomitant flexor relaxations (Fig. 4C in Lafreniere-Roula and McCrea 2005; Fig. 9 in Duysens 1977). In contrast, inverse examples are absent as far as I can judge. When flexor bursts disappear this is accompanied by an absence of extensor relaxations. This asymmetry is also present in the case of induced deletions. Flexor burst deletions do occur in premammillary preparations but not spontaneously. They have to be induced artificially. As mentioned above, during stance the feedback from load receptors reinforces extensor activity and suppresses flexor bursts. By augmenting this type of feedback it is possible to introduce flexor burst deletions (Conway et al. 1987; Duysens and Pearson 1980). In such cases one does not observe extensor relaxations however (see Figs. 2 and 3 in Duysens and Pearson 1980).

In contrast, when extensor deletions are induced a concomitant flexor relaxation is commonly observed, although it is shorter than normal (Fig. 8, Duysens 1977). Taken together, these observations support the notion that the periodic inactivation of the extensor bursts requires the presence of a flexor burst while the inverse is not true. In other words, flexor bursts do not need the presence of an extensor burst to be inactivated. The reason for this asymmetry must be that there is another mechanism available to suppress the flexor center which is not available to the extensor center.

Current knowledge makes it likely that this other mechanism is related to inhibitory input from the contralateral rhythm generator. Kjaerulff and Kiehn (1997) studied crossed rhythmic synaptic input during locomotion of the in vitro neonatal rat. It was found that output from the contralateral extensor burst generator is weak or absent, while the input from the contralateral flexor burst generator is strong. This was taken as support for a model whereby the coupling between the CPGs on the 2 sides occurs primarily through inhibitory connections between the flexor burst generators on the 2 sides. These connections make that the flexor burst generator plays a more central role in the coordination of the various locomotor circuits. In fact, this comes close to an earlier model, proposed by Pearson and Duysens (1976). In this “swing generator model” (later renamed as “flexor burst generator model”) there is indeed a basic asymmetry present in that the flexor part of the CPG is taken as the dominant center, closest to the “central command”. Unfortunately, such asymmetrical models are not discussed in the paper by Lafreniere-Roula and McCrea (although they refer to “more robust activity of flexors” to explain the absence of flexor failures in scratch). Instead the authors suggest in their model that both flexor and extensor centers have equally strong connections to the CRP (Central Rhythm Generator). Possibly by accident however, in their figure of the model the authors have positioned their CRG closer to the flexor than to the extensor centers (their Fig. 10). This is a very fortuitous accident and it is suggested here that a further improvement would be the deletion of the arrow from the CRF to the extensor generator modules. Such a deletion in the model could help to better explain deletions in the laboratory.

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REPLY

To the Editor: We thank Dr. Duysens for taking the time to comment on our article. In our opinion, the important theoretical aspects argued for in the paper are the organization of the locomotor central pattern generator (CPG) into separate rhythm-generation (RG) and pattern-formation (PF) networks and the existence of multiple PF networks. Neither idea is novel, but we think that our study of spontaneously occurring “errors” of CPG operation (deletions) provides strong support for the CPG organization that we present in the cartoon in Fig. 10 (Lafreniere-Roula and McCrea 2005). It is important to clarify that this figure is not yet a model of the CPG because it lacks details of the internal structure, descending and sensory control, and interactions with rhythm generation in the other limbs. These and other additions to a large scale computational model are currently being pursued in the laboratory (McCrea et al. 2004; Rybak and McCrea 2005). One critical element of our schematic is that the RG network can maintain cycle timing during deletions of motoneuron activity caused by failures occurring at the level of the PF networks. Our data show that in the absence of rhythmic sensory feedback during fictive locomotion, rhythm maintenance can occur during complete omissions of motoneuron activity. Because of the potential for rhythmic sensory feedback to reinforce the ongoing cycle period, our review of the literature concentrated on studies discussing CPG organization in preparations without strong sensory feedback. Duysens (1977) also noted the absence of large fluctuations in cycle period (maintenance of timing) during extensor deletions in decerebrate cats during treadmill walking and provides other examples of deletions in walking cats in his letter. Deletions are not necessarily “all or none.” The observation of reductions in activity in select motoneuron pools (our Fig. 4A) and the uneven recovery from deletions (Fig. 4B) suggested the need to postulate multiple PF modules in our Fig. 10.

Dr. Duysens argues that the flexor and extensor portions of the CPG may be asymmetrically organized. Although it is obvious that CPG operation can be asymmetrical between the flexion and extension phases, we believe that there is no solid evidence that the intrinsic organization of rhythm-generation circuitry is asymmetrical. The absence of proprioceptive feedback in the fictive-locomotion preparation offers particular advantages toward understanding the fundamental organization of the locomotor CPG. Fictive locomotion in decerebrate cats can show either a dominance of flexor or extensor phase duration with about 2/3 of the preparations in our laboratory being flexor dominated (Yakovenko et al. 2005). In all cases examined, the shorter duration (weaker, nondominant) phase is subject to more frequent deletions and, therefore there is a predominance of extensor deletions in our data. Across fictive locomotion preparations, however, both extensor and flexor deletions can and do occur spontaneously and without artificial induction (e.g., Fig. 1). We believe that the frequency of particular types of deletions is an issue of neuronal excitability not organization. The existence of both full and partial deletions and in both flexors and extensors is consistent with a symmetrical CPG organization. Deletions during fictive scratch, on the other hand, involve only the very brief bursts of extensor activity and not the longer duration flexion phase.

Dr. Duysens also suggests that the flexor portion of the CPG is directly controlled by the rhythm generator and that we should remove similar control (the arrow) from the RG to the extensor PF networks in Fig. 10. If extensor rhythm is collaterally to flexor rhythm, how would extensor activity be initiated and maintained during flexor deletions? Not only is there a maintenance of antagonist activity during deletions, but in the majority of deletions, there is also some degree of rhythmic modulation (relaxations) in the antagonists. This includes flexor deletions (note the rhythmic fluctuations in the quasitonic extensor discharges in Fig. 1A). Figure 3 of Duysens and Pearson (1980) provides an example in which flexor deletions also can occur in the presence of partial extensor relaxations (the inverse of the example referred to in the letter). It shows rhythmic fluctuations in ipsilateral extensor force during complete flexor deletions. We suggest that the source of these force fluctuations is rhythmic excitation from the RG network directly to the extensor PF network. The failure to completely silence extensor activity is due to the failure of the flexors to be activated by the RG and hence provide strong rhythmic inhibition to the extensors. The example in Fig. 4 is our solitary example of fully developed flexor rhythm in the absence of extensor activity. We would need to examine many more preparations than the eight included in the paper before concluding that the converse (fully rhythmic extension without flexion) cannot occur. As mentioned in the preceding text, the extensor phase dominates in 1/3 of our fictive locomotion preparations all of which are devoid of rhythmic sensory feedback. Thus we believe that the flexor and extensor portions of the CPG both have rhythmic potential and that if the postulated separation of RG and PF networks exists, the RG network directly controls both extensor and flexor PF networks.  

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Drugs that block spinal inhibition (e.g., bicuculline and strychnine) convert an alternating rhythm into synchronized bursts of activity between the sides in the lamprey (e.g., Cohen and Harris-Warrick 1984) and in flexor and extensor within a limb as well as between the limbs in neonatal rat (Cowley and Schmidt 1995) and adult cat (Noga et al. 1993; J. Quevedo, K. Stecina, and D. A. McCrea, unpublished observations). These observations are easily accommodated by a symmetrical CPG in which rhythm generation controls both flexor and extensor motoneuron activity from the “top down” in a half-center type of organization. It is more difficult to imagine how the synchronous activity in flexors and extensors is achieved under these conditions in an organization in which one side of the CPG drives the other.

Regarding the issue of apparent asymmetrical control of the CPG by afferent feedback, we agree that extensor-related feedback during locomotion is critical to the control of cycle phase transitions and contributes substantially to motoneuron recruitment during locomotion (see McCrea 2001). Our recent identification of a population of interneurons likely responsible for feedback-evoked disynaptic excitation of extensor motoneurons (Angel et al. 2005) shows that our interest in this topic has not waned. We feel strongly, however, that the demonstration of a dominance of extensor feedback control of the CPG under particular conditions does not indicate an asymmetry in CPG organization.

Studies during fictive locomotion show that sensory feedback from flexor afferents can exert as powerful a control over CPG operation as that from extensor afferents. Thus in a manner similar to extensor group I muscle spindle afferents, flexor group I afferents can control the duration of the flexor phase as well as cycle period (Perreault et al. 1995; Stecina et al. 2005). In addition, flexor group I afferents evoke a disynaptic excitation of flexor motoneurons (Degtyarenko et al. 1998; Quevedo et al. 2000) similar to that evoked in extensor motoneurons by extensor afferents (Angel et al. 1996; McCrea et al. 1995). Flexor group II muscle spindle afferents evoke a very strong resetting of the step cycle (Perreault et al. 1995; Stecina et al. 2005), a feature not shared by extensor group II afferents. The importance of hip flexor muscle length in controlling swing to stance transitions is also well documented in the cat (e.g., Lam and Pearson 2001) and in human infants (Pang and Yang 2000). Thus there is the potential for sensory feedback to control both the extensor and flexor phase durations, the overall cycle period, and the recruitment of flexor and extensor motoneurons. An organization in which there is a symmetrical organization of rhythm generation to flexors and extensors on which afferent feedback can produce a dominant control of one phase or the other provides for great flexibility in regulating locomotion under different circumstances (see Yakovenko et al. 2005).

We appreciate the need for precise control of rhythm and phase generation between the limbs and the frequent need to inhibit the initiation of bilateral flexion and prevent instability. However, the notion raised by Dr. Duysens that the contralateral limb exerts only an inhibitory control of ipsilateral flexor activity is hard to justify in the case of symmetrical gaits such as gallop. Again we urge strong caution in extrapolating from observations of commonly observed behaviors to inferences about constraints in the intrinsic structure of the CPG. In the case of the PF networks, we think that there is a great deal of asymmetry between flexion and extension portions of the CPG. Observations in intact and reduced preparations show a remarkable flexibility in the patterns of flexor motoneuron activity as well as in motoneurons innervating the bifunctional muscles (e.g., Chakrabarty et al. 2004). We remain unconvinced by arguments raised by Dr. Duysens that we should abandon our current concept about symmetry within the RG portions of the CPG. This “symmetrical organization” does not mean that all parameters, such as weights of synaptic connections within the circuitry and from supraspinal and peripheral afferents, are identical for the flexor and extensor sides. We believe that specific control of these circuits can result in asymmetrical CPG operation under the appropriate circumstances. Our Fig. 10 does not have a fortuitous juxtaposition of the RG circuitry closer to the flexor side; it is from all viewpoints symmetrical. Available data indicate that the arrow from the RG to the extensor PF networks should stay.

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