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Development of human locomotion

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Neural control of locomotion in human adults involves the generation of a small set of basic patterned commands directed to the leg muscles. The commands are generated sequentially in time during each step by neural networks located in the spinal cord, called Central Pattern Generators. This review outlines recent advances in understanding how motor commands are expressed at different stages of human development. Similar commands are found in several other vertebrates, indicating that locomotion development follows common principles of organization of the control networks. Movements show a high degree of flexibility at all stages of development, which is instrumental for learning and exploration of variable interactions with the environment.

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Introduction

Human neonates exhibit transitory, primitive behaviors that develop *in utero* and disappear a few months after birth [1,2]. Some of these are critical for survival; for instance, rooting and sucking reflexes are essential for feeding. But the significance of other primitive behaviors and their relationship with more mature behaviors are a long-standing riddle [3,4,5•]. Traditionally, it is thought that primitive behaviors are suppressed as a result of brain maturation. However, there is now evidence that some basic control principles are conserved through development, so that the primitive patterns can be considered as precursors of the mature patterns.

Locomotor behavior is a case in point. Human newborns exhibit a stepping reflex that typically disappears at ∼2 months and reappears several months later when it evolves into intentional walking. It was once thought that the patterns of muscle control in newborn stepping are discarded during development, replaced by entirely new patterns of walking. Instead, it has recently been shown that the primitive stepping patterns are retained and tuned, while new patterns are added during development [6•]. Surprisingly similar patterns are observed also in several other animal species, suggesting that locomotion is built starting from common elements, perhaps related to ancestral neural networks [7].

Here we first review recent findings on the prenatal and postnatal development of motor patterns in human children, and on a comparative analysis with other animal species. Next we consider the role of learning and exploration in human locomotor development. In a final section, we deal with abnormalities of motor development as typified by cerebral palsy.

Prenatal movements

Spontaneous movements begin as soon as there are functioning muscles and nervous system in developing humans and animals. In humans, small, slow, cyclic bending of the head and/or trunk are detected with 4D-ultrasonography at 5 weeks post-conception [8]. Waxing and waning general movements can be observed slightly later, at 7 weeks, and persist throughout pregnancy and the first months after term birth [9–11]. They consist of complex, variable, flexion-extensions of the whole body and limbs, they are not triggered by external stimuli and lack distinctive sequencing of different body parts. In addition, human fetuses exhibit a rich repertoire of leg movements that includes single leg kicks, symmetrical double legs kicks, and symmetrical inter-limb alternation with variable phase [12,13]. Spontaneous movements of the limbs evolve toward an increased coordination between the arms and between the legs, at 2–4 months after birth [14•]. Abnormal movements lack complexity, variation, and fluency, and are associated with an increased probability of cerebral palsy [10,15].

While only kinematic analyses are currently available for human fetuses [16], direct recordings of electrical muscle activity (EMG) are possible in animals. EMG reflects the output of spinal α-motoneurons, and therefore the neural commands for movement. Detailed EMG recordings in chick embryos during the final week of incubation showed that the profiles of EMG activity during repetitive limb movements resemble those of locomotion at hatching [17]. However, in contrast with mature locomotor activity, EMG burst duration does not scale with movement cycle duration in chick embryos.

Optical imaging of spontaneous activity in ventral spinal neurons of the zebrafish embryo showed a rapid (few hours) transition from uncorrelated, sporadic slow activity to ipsilaterally correlated and contralaterally anticorrelated fast activity involving several adjacent somites [18]. The transition to correlated activity may depend on electrical connections initially coupling nearby neurons in local microcircuits and then merging to include the majority of active ipsilateral neurons into a single coupled network [18]. Recurrently connected excitatory networks within the spinal cord are transiently silenced by activity-dependent depression [19]. In these networks, motoneurons generate large, slow depolarizations crested by bursts of action potentials, resulting in the correlated discharge across a population of neurons with a periodicity in the order of minutes, a firing pattern that drives spontaneous embryonic movements [20,21]. Thus, the episodes of spontaneous activity are presumably triggered by motoneurons, but the periodicity of activity is set by recurrent excitatory interactions in the network [21]. Bursting activity occurs while motoneurons are still migrating and prolonging their axons toward the base of the limbs, so that correct motor axon path-finding is contingent on normal bursting activity [22]. In addition, spontaneous motor activity at an early developmental stage may facilitate the self-organization of neural circuits at both spinal and supra-spinal levels [21]. Thus, motor activity modulates the spinal circuits of central pattern generators (CPG) and those of nociceptive withdrawal reflexes [23], and it also modulates cortical somatosensory maps in a somatotopic manner [24]. Once established, spinal CPGs underlie fetal movements [22], but developing supra-spinal structures (such as the transient cortical subplate) presumably also play a role in more complex sequences of general movements, as demonstrated by the abnormality of general movements in human fetuses with brain disorders [10].

Postnatal development of locomotion

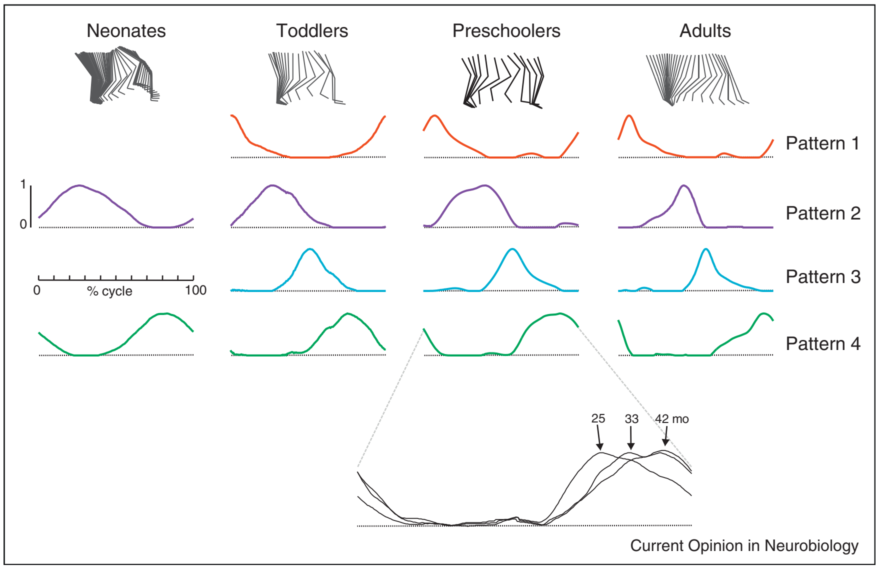
In addition to the spontaneous general movements, human newborns also exhibit stepping movements. These can be elicited in an infant supported under the arms in an upright, slightly tilted forward posture, after contacting ground with the feet soles [6•,25]. Reflex stepping has been reported also in premature infants at 30+ post-conception weeks [26] and anencephalic newborns [27]. This suggests a predominant role of spinal and brainstem mechanisms, owing to immature cerebral connections to the spinal cord [28]. While buoyancy of the amniotic fluid counteracts gravity effects in the human fetus (and other amniotes), newborns must deal with gravity to move their limbs and support their body weight. They can support ~30–40% of their weight, the remaining being supported from the outside. Infant stepping is irregular, variable, and lacks several features of more mature walking, most notably postural control [6•,25,29–31]. It looks like an exaggerated marching with flexed legs, high foot lift, and flat-foot touch-down (instead of heel-contact as in adults). Ground forces are not accurately controlled: newborns typically exert vertical forces supporting part of their weight, but only negligible horizontal (shear) forces. However, the angular motion of the lower limbs segments is already coordinated, resulting in a planar inter-segmental covariance roughly comparable to that seen in adults [6•].

Upright stepping often becomes very difficult to elicit in infants between ~2 and 7 months of age, while supine kicking (which shares some features of stepping) continues [29]. The disappearance of stepping presumably depends on both neural changes in the CNS (supraspinal inhibitory influences on spinal CPGs) and biomechanical factors (the legs may become too heavy for the muscle strength [29]). However, stepping can still be evoked during that period with daily practice [29,30,32] or supporting the legs' weight by means of water immersion [29]. Practice increases the incidence of alternating steps, but does not appreciably affect the muscle activity profiles [30]. Infant stepping shows sensory adaptation to imposed loading and perturbations [33]. Longitudinal studies carried out over the first year show a progressive reduction of muscle co-contraction and increasingly selective activation patterns [31,34•]. However, there is a persistently large inter-step variability of EMG activities compared with more repeatable kinematics. The latter finding is reminiscent of adult locomotion, and depends on a prominent role of passive biomechanics in locomotion in both infants and adults [35,36].

The neural patterns of muscle control can be revealed by factorization of EMG activity [36]. In human newborns, two patterns are sinusoidally modulated over the step cycle: one pattern (#2 in Figure 1) helps providing body support during stance, while the other one (#4) helps driving the limb during swing, but there is no specific activation pattern at either touch-down or lift-off [6•]. EMG factorization in toddlers (~1-year-old) at their first unsupported steps finds the same two patterns (#2 and #4 in Figure 1) of the newborn, plus two new patterns timed at touch-down (#1) and lift-off (#3) that contribute shear forces necessary to decelerate and accelerate the body, respectively [6•]. In preschoolers (2–4-years), all four patterns show transitional shapes. Thus, the waveform shifts in time relative to the step cycle progressively with age (see lower panel in Figure 1): the older the child, the closer the waveform to the adult. In sum, two basic control patterns are retained from the stage of newborn stepping, while two other patterns develop after that stage. Transitional patterns indicate a continuous development of the corresponding motor control modules.

The gradual development of adult gait from infant stepping is generally believed to stem from a growing integration of supraspinal, intraspinal and sensory control [3,30]. The lack of activation patterns corresponding to

Figure 1



Basic patterns of muscle control at different ages. Top. Stick diagrams depicting one step cycle starting with stance onset in neonates (2–7-days-old), toddlers (11–14-months-old), preschoolers (24–48-months), and adults. Middle. Basic activation patterns obtained by non-negative matrix factorization of averaged EMG profiles of 24 bilateral leg muscles in each age group. Patterns are plotted versus normalized gait cycle (aligned with stance onset in the right leg). Bottom. Pattern # 4 was averaged separately in 3 different subgroups of preschoolers with the indicated mean age. Notice the shift of the waveform with increasing age.

foot contact in the neonate could depend on immature sensory and/or descending modulation of stepping. Indeed, in the absence of sensory modulation (e.g. during fictive motor tasks), the spinal circuitry of animals tends to produce sinusoidal-like patterns [37,38], similar to those observed in the human neonate. The addition of basic patterns in the first months of life implies a functional reorganization of inter-neuronal connectivity, the appearance of additional functional layers in the CPGs, and/or more powerful descending and sensory influences on CPGs. In particular, there is increasing consensus that motor centers in the brain play an important and greater role in human adult walking than in quadrupeds [39]. Indeed, there is evidence for maturation of cortico-spinal drive on leg muscles during locomotor development [40•].

Comparative aspects

In postembryonic tadpoles, motoneurons initially innervate most of the dorso-ventral extent of the swimming muscles, but during early larval life the innervation fields become restricted to a limited sector of each muscle block [41•]. This developmental trend leads to more selective and flexible control of the muscles. Just as humans, rats do not have a mature neural control of locomotion at birth, and they walk only several days later. The CPGs of neonatal rat spinal cord are intrinsically flexible, inasmuch as different patterns of hindlimb muscle activation are evoked depending on whether pharmacological (serotonin and N-methyl-D-aspartic acid) modulation or sensory afferent stimulation is applied [42•,43]. Locomotor-like oscillatory activity can be recorded from the lumbar and sacral ventral roots of the isolated spinal cord of neonatal rats, bathed with dopamine plus NMDA or serotonin [37]. Factorization of the electroneurograms associated with this fictive walking reveals two patterns essentially identical to those of human newborns [6•]. Factorization of the EMG of adult rats, cats, macaques, and guinea fowls shows four patterns, closely resembling those found in human toddlers [6•].

These results are consistent with comparative studies in vertebrates based on genetic and electrophysiological approaches which demonstrate that, despite the existence of species-specific features, there are several common principles in the organization and regulation of CPGs [44,45]. In particular, the core premotor components of locomotor circuitry mainly derive from a set of embryonic interneurons that are remarkably conserved across different species [46]. Grillner [7] hypothesizes that the neural control system for locomotion can be traced back to the oldest known vertebrate, the lamprey, which appeared more than 500 million years ago, before any legged animal had evolved yet. Evolutionary conservation of developmental patterns [6•] and neural core control networks [44–46,47•] points to the comparative approach as a most fruitful one for the study of locomotor development [47•,48].

Human development shows commonalities with other animal species, but also important idiosyncratic features, as demonstrated by the distinct motor patterns of the adults [6•]. Thus, we are the only animals to use habitually an erect bipedal locomotion with a heel-strike well ahead of the body. The long time required to develop independent locomotion in humans is probably related to the overall complexity of neural wiring in our species. Consistent with this view, it has been shown [49] that the time from conception to independent locomotion is linearly related to the adult brain mass across 24 different mammalian species: the bigger the brain, the longer the time to start walking. This suggests that the development of independent locomotion depends on the duration of overall neural development, presumably because of the need to develop stance, balance and orientation control in parallel with locomotor control; these diverse functions require maturation of large parts of the CNS.

Learning and exploration

Motor patterns of locomotion are not fixed but highly flexible. Variability and versatility of behavior may be instrumental for learning and exploration of different solutions in different environmental contexts [3,5•,50].

Infant movements display a high degree of variability at all stages of development, starting from fetal stages. After birth, stepping remains non-functional until a stable erect posture can be maintained, and infants adopt a variety of different crawling styles to move around, although a significant proportion (~30%) never crawls and walks upright directly [5•,51]. Infants can crawl on hands-and-knees, hands-and-feet, hands-and-buttocks, or on the belly. Inter-limb coupling may involve diagonal trot-like gait, or ipsilateral pace-like gait. This versatility reflects a flexible coupling between cervical and lumbosacral CPGs (controlling upper and lower limbs respectively) that persists till adulthood [52].

Also upright walking before independent walking shows great flexibility. Infants may first cruise sideways while grasping furniture with both hands for support, then turn their body to face forwards holding furniture with one hand only [5•,53•]. Different developmental stages (for instance, crawling and cruising) may be concurrent rather than serial, and there may even be a reversal of order (cruising before crawling). Moreover, often there is no transfer of learning environmental risks from one locomotor mode to the next: experienced crawlers or cruisers discriminate very precisely affordable versus unaffordable support surfaces, but when they start walking independently they may fall because they do not discriminate anymore [53•].

Infants start walking independently around 12-months (median, 9–18 months range), but cultural child-rearing habits may anticipate or delay this time [5•]. Unsupported walking is jerky and variable, with poor balance over the single support leg (while swinging the contralateral leg), the arms raised above the waist (as balance poles), legs splayed wide apart, and short variable steps [5•,25,54–59]. Double support is relatively prolonged, while swing is brief. Touch-down is with flat-foot or toes-first. Some idiosyncratic features of toddlers gait may be useful to cope with initial unstable conditions of unsupported walking, such as the increased base of support and the flailing arms [58]. Also, non-plantigrade gait with a high foot lift represents a simple strategy to avoid stumbling and falling, while reducing foot drag owing to limited dorsiflexor activity. However, energy recovery by exchanging forward kinetic energy and gravitational potential energy of the center of body mass is very limited [55].

It is often assumed that infants cannot walk independently until they achieve balance control, but it has been shown that step variability and several other gait parameters of toddlers remain unchanged even when balance is augmented with the help of a parent or experimenter hand [56]. Moreover, walking experience rather than chronological age explains improvement in performance [5•]. Indeed, onset of unsupported locomotion triggers the improvement of several gait parameters (speed, inter-step repeatability, trunk oscillations, tuning of planar covariance, energy recovery) relative to the previous supported locomotion [55,58]. These changes occur rapidly over the first 6 months after the onset of independent walking. Afterwards, gait continues to develop more slowly until 8–10 years of age, as shown by changes in several parameters, such as stride length, cadence, coordination timing, and energy recovery [5•,54,59].

When toddlers must step across an obstacle or walk on a staircase, they do not adapt the inter-segmental coordination to the surface inclination and height as adults do, but they keep constant phase relationships [60•]. This is consistent with the hypothesis proposed decades ago by Nikolai Bernstein that, when humans start learning a skill, they restrict the number of controlled degrees of freedom to reduce the size of the search space and simplify the coordination. Toddlers often place a foot on the obstacle or on the edges of the stairs, presumably as part of an exploratory strategy of the environment [5•,60•,61]. Naturalistic observations at the infants' home show that most toddlers spontaneously carry objects while walking, combining locomotor and manual skills. Despite the additional biomechanical constraints, carrying an object is actually associated with improved upright balance, as demonstrated by smaller probabilities of falling with the object than without [62].

Split-belts treadmills can impose a different direction and/or speed to the motion under each leg during locomotion. They are especially suited for studying sensorimotor adaptation and learning mechanisms. Young infants (7–12 months of age) show the ability to adapt to asynchronous split-belt motion [63]. However, the mechanisms controlling temporal and spatial adaptation to these conditions are different and mature at different times, with spatial parameters adapting more slowly than temporal ones [64•,65•].

Body size and proportions change dramatically during development. Locomotor commands must take these changes into account to keep limb segment motion calibrated with body size. The importance of a body scheme incorporating limb and body parameters is demonstrated by the observation that an 11-years-old child, who underwent surgical elongation of the shanks by >50%, walked as if on the pre-surgery shorter legs, just as do adults walking on stilts [66].

Cerebral palsy

Cerebral palsy (CP) is one of the most common developmental motor disorders. It is a non-progressive syndrome involving poor motor control, spasticity, paralysis, and other neurological problems resulting from perinatal brain injury [67]. It may be hypothesized that neural control patterns in CP children are closer to those of younger, normally developing children, and this would reflect relative immaturity of the locomotor networks. Many CP children start walking much later than normal. Till adulthood, they continue walking on their toes with knee hyper-flexion during stance and ankle dorsiflexion during swing [68]. The foot trajectory is undulating owing to poor control of ankle torque. Muscle co-activation is greater than in healthy children of the same age. Hip flexors lack phasic activity, hip extensors and adductors are hyper-active, while gastrocnemius is hypoactive at push-off [68]. The normal tonic depression of soleus H-reflex during gait is absent in CP, reflecting a lack of maturation of the corticospinal tract [69]. Reflex behavior and walking speed improves with treadmill training [68], although the long-term effectiveness of this protocol remains to be validated [70] also using energy expenditure monitoring [71].

Conclusions

We argued that the neural control patterns underlying mature locomotion are tightly related to those involved in primitive movements. In addition, development of motor patterns shows variability and versatility of behavior presumably as a means to learn and explore different solutions. Notice that this holds true not only for locomotion, but even for behaviors – such as vocalization in birds – where mature neural substrates are definitely distinct from the immature ones [50]. We also highlighted the remarkable similarities in motor patterns across different animal species, despite gross morpho-functional differences in the musculo-skeletal architecture. These similarities probably reflect common principles in the underlying control mechanisms, as well as common biomechanical constraints related to stability, kinematics, kinetics, and energy-efficiency [72,73]. An emerging view is that the co-ordination of limb and body segments in mature locomotion arises from the coupling of neural oscillators between each other and with limb mechanical oscillators [35,36]. Muscle activations intervene at discrete times to re-excite the intrinsic oscillations of the system when energy is lost. Development of motor patterns, then, requires progressively tuning the timing and amplitude of muscle activity to the intrinsic modes of mechanical behavior resulting from the interaction of the limbs/body parts between each other and with the environment, also taking into account the growing body of the child.

The current coarse picture of the development of human locomotor patterns needs now to be refined in order to understand how the locomotor networks are configured precisely at different developmental stages. Moreover, the functional abnormalities associated with perinatal motor disorders such as CP need to be understood, also taking advantage of the application of modern quantitative analyses of the motor patterns.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Milani-Comparetti A, Gidoni EA: **Routine developmental examination in normal and retarded children**. *Dev Med Child Neurol* 1967, **9**:631-638.

2. Zafeiriou DI: **Primitive reflexes and postural reactions in the neurodevelopmental examination**. *Pediatr Neurol* 2004, **31**:1-8.

3. Forssberg H: **Neural control of human motor development**. *Curr Opin Neurobiol* 1999, **9**:676-682.

4. Konczak J: **On the notion of motor primitives in humans and robots**. In In *Proceedings of the Fifth International Workshop on Epigenetic Robotics: Modeling Cognitive Development in Robotic Systems.* Edited by Berthouze L *et al.*: *Proceedings of the Fifth International Workshop on Epigenetic Robotics: Modeling Cognitive Development in Robotic Systems* Lund University Cognitive Studies; 2005:47-53.

5. • Adolph KE, Robinson SR: **The road to walking: What learning to walk tells us about development**. In *Oxford handbook of developmental psychology*. Edited by Zelazo P. NY: Oxford University Press; 2012, in press.

In this enjoyable review, the authors argue for flexibility and versatility as common developmental threads providing plenty insightful observations from developmental psychology.

6. • Dominici N, Ivanenko YP, Cappellini G, d'Avella A, Mondì V, Cicchese M, Fabiano A, Silei T, Di Paolo A, Giannini C *et al.*: **Locomotor primitives in newborn babies and their development**. *Science* 2011, **334**:997-999.

This paper compares the neural patterns of muscle control in human neonates, toddlers, preschoolers, adults, and several animal species. It shows that both human and rat newborns have two phases of activation, out-of-phase between each other. Human toddlers and adult rats, cats, macaques and guinea fowls have the same activation patterns as neonates, and in addition two other shorter activations at touch down and liftoff. The four activation patterns in human adults become pulsatile. These findings suggest that locomotion in humans and other species is built starting from common elements, and adding few new elements during development.

7. Grillner S: **Neuroscience. Human locomotor circuits conform**. *Science* 2011, **334**:912-913.

8. Felt RH, Mulder EJ, Lüchinger AB, van Kan CM, Taverne MA, de Vries JI: **Spontaneous cyclic embryonic movements in humans and guinea pigs**. *Dev Neurobiol* 2011 http://dx.doi.org/10.1002/dneu.20945.

9. de Vries JI, Visser GH, Prechtl HF: **The emergence of fetal behaviour. I. Qualitative aspects**. *Early Hum Dev* 1982, **7**:301-322.

10. Hadders-Algra M: **Putative neural substrate of normal and abnormal general movements**. *Neurosci Biobehav Rev* 2007, **31**:1181-1190.

11. Lüchinger AB, Hadders-Algra M, van Kan CM, de Vries JI: **Fetal onset of general movements**. *Pediatr Res* 2008, **63**:191-195.

12. Piontelli A: *Development of Normal Fetal Movements: The First 25 Weeks of Gestation*. Italy: Springer-Verlag; 2010.

13. Stanojevic M, Kurjak A, Salihagić-Kadić A, Vasilj O, Miskovic B, Shaddad AN, Ahmed B, Tomasović S: **Neurobehavioral continuity from fetus to neonate**. *J Perinat Med* 2011, **39**:171-177.

14. • Kanemaru N, Watanabe H, Taga G: **Increasing selectivity of interlimb coordination during spontaneous movements in 2- to 4-month-old infants**. *Exp Brain Res* 2012, **218**:49-61.

Longitudinal examination of spontaneous movements in 2–4-months infants showed an age-related increase in the velocity and position correlation between the arms and between the legs. This corresponds to a progression from a general activity involving all the limbs to an activity involving more selective interlimb coordination.

15. Hamer EG, Bos AF, Hadders-Algra M: **Assessment of specific characteristics of abnormal general movements: does it enhance the prediction of cerebral palsy?** *Dev Med Child Neurol* 2011, **53**:751-756.

16. Castiello U, Becchio C, Zoia S, Nelini C, Sartori L, Blason L, D'Ottavio G, Bulgheroni M, Gallese V: **Wired to be social: the ontogeny of human interaction**. *PLoS ONE* 2010, **5**:e13199.

17. Ryu YU, Bradley NS: **Precocious locomotor behavior begins in the egg: development of leg muscle patterns for stepping in the chick**. *PLoS ONE* 2009, **4**:e6111.

18. Warp E, Agarwal G, Wyart C, Friedmann D, Oldfield CS, Conner A, Del Bene F, Arrenberg AB, Baier H, Isacoff EY: **Emergence of patterned activity in the developing zebrafish spinal cord**. *Curr Biol* 2012, **22**:93-102.

19. O'Donovan MJ: **The origin of spontaneous activity in developing networks of the vertebrate nervous system**. *Curr Opin Neurobiol* 1999, **9**:94-104.

20. Feller MB: **Spontaneous correlated activity in developing neural circuits**. *Neuron* 1999, **22**:653-656.

21. Blankenship AG, Feller MB: **Mechanisms underlying spontaneous patterned activity in developing neural circuits**. *Nat Rev Neurosci* 2010, **11**:18-29.

22. Hanson MG, Milner LD, Landmesser LT: **Spontaneous rhythmic activity in early chick spinal cord influences distinct motor axon pathfinding decisions**. *Brain Res Rev* 2008, **57**:77-85.

23. Petersson P, Waldenström A, Fåhraeus C, Schouenborg J: **Spontaneous muscle twitches during sleep guide spinal self-organization**. *Nature* 2003, **424**:72-75.

24. Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsáki G: **Early motor activity drives spindle bursts in the developing somatosensory cortex**. *Nature* 2004, **432**:758-761.

25. Forssberg H: **Ontogeny of human locomotor control. I. Infant stepping, supported locomotion and transition to independent locomotion**. *Exp Brain Res* 1985, **57**:480-493.

26. Allen MC, Capute AJ: **The evolution of primitive reflexes in extremely premature infants**. *Pediatr Res* 1986, **20**:1284-1289.

27. Peiper A: *Cerebral Function in Infancy and Childhood*. New York: Consultants Bureau; 1961.

28. Martin JH: **The corticospinal system: from development to motor control**. *Neuroscientist* 2005, **11**:161-173.

29. Thelen E, Cooke DW: **Relationship between newborn stepping and later walking: a new interpretation**. *Dev Med Child Neurol* 1987, **29**:380-393.

30. Yang JF, Stephens MJ, Vishram R: **Infant stepping: a method to study the sensory control of human walking**. *J Physiol* 1998, **507**:927-937.

31. Okamoto T, Okamoto K: *Development of Gait by Electromyography. Walking Development Group*. 2007.

32. Zelazo PR, Zelazo NA, Kolb S: **"Walking" in the newborn**. *Science* 1972, **176**:314-315.

33. Pang MYC, Lam T, Yang JF: **Infants adapt their stepping to repeated trip-inducing stimuli**. *J Neurophysiol* 2003, **90**:2731-2740.

34. • Teulier C, Sansom JK, Muraszko K, Ulrich BD: **Longitudinal changes in muscle activity during infants' treadmill stepping**. *J Neurophysiol* 2012, in press.

This paper presents a longitudinal comparison of muscle activation profiles in children stepping on a treadmill at 1, 6 and 12 months of age. Although agonist-antagonist muscle co-activation decreased with age, inter-step variability remained high throughout the follow-up study.

35. Lacquaniti F, Grasso R, Zago M: **Motor patterns in walking**. *News Physiol Sci* 1999, **14**:168-174.

36. Lacquaniti F, Ivanenko YP, Zago M: **Patterned control of human locomotion**. *J Physiol* 2012, http://dx.doi.org/10.1113/jphysiol.2011.215137.

37. Falgairolle M, Cazalets JR: **Metachronal coupling between spinal neuronal networks during locomotor activity in newborn rat**. *J Physiol* 2007, **580**:87-102.

38. Cuellar CA, Tapia JA, Juárez V, Quevedo J, Linares P, Martínez L, Manjarrez E: **Propagation of sinusoidal electrical waves along the spinal cord during a fictive motor task**. *J Neurosci* 2009, **29**:798-810.

39. Nielsen JB: **How we walk: central control of muscle activity during human walking**. *Neuroscientist* 2003, **9**:195-204.

40. • Petersen TH, Kliim-Due M, Farmer SF, Nielsen JB: **Childhood development of common drive to a human leg muscle during ankle dorsiflexion and gait**. *J Physiol* 2010, **588**:4387-4400.

This paper assesses the cortico-spinal drive in 4–15-years-old children using EMG coherence and synchrony. A significant increase of coherence with increasing age was found in the 30–45 Hz frequency band (gamma) during walking and during static ankle dorsiflexion. The changes continued till adolescence, presumably indicating that maturation of cortico-spinal control is not complete till that age.

41. • Zhang HY, Issberner J, Sillar KT: **Development of a spinal locomotor rheostat**. *Proc Natl Acad Sci USA* 2011, **108**:11674-11679.

The authors show that swim motorneurons of frog tadpoles initially form a homogenous pool discharging isolated action potentials and innervating diffusely the dorsoventral extent of the swimming muscles. Subsequently, the innervation fields become restricted to a limited sector of each muscle block.

42. • Klein DA, Patino A, Tresch MC: **Flexibility of motor pattern generation across stimulation conditions by the neonatal rat spinal cord**. *J Neurophysiol* 2010, **103**:1580-1590.

This study uses the *in vitro* neonatal rat spinal cord with attached hindlimb to examine the muscle activation patterns evoked by different types of stimulation. They found that the rectus femoris and semitendinosus muscles were activated differentially depending on whether 5-HT and NMDA or electrical stimulation of the cauda equina were applied.

43. Klein DA, Tresch MC: **Specificity of intramuscular activation during rhythms produced by spinal patterning systems in the in vitro neonatal rat with hindlimb attached preparation**. *J Neurophysiol* 2010, **104**:2158-2168.

44. Garcia-Campmany L, Stam FJ, Goulding M: **From circuits to behaviour: motor networks in vertebrates**. *Curr Opin Neurobiol* 2010, **20**:116-125.

45. Kiehn O: **Development and functional organization of spinal locomotor circuits**. *Curr Opin Neurobiol* 2011, **21**:100-109.

46. Goulding M: **Circuits controlling vertebrate locomotion: moving in a new direction**. *Nat Rev Neurosci* 2009, **10**:507-518.

47. • Stephenson-Jones M, Samuelsson E, Ericsson J, Robertson B, Grillner S: **Evolutionary conservation of the basal ganglia as a common vertebrate mechanism for action selection**. *Curr Biol* 2011, **21**:1081-1091.

This paper shows that the basal ganglia circuitry is present in the lamprey, the phylogenetically oldest vertebrate, and has been conserved as a mechanism for action selection used by all vertebrates for >560 million years. All sectors of the mammalian basal ganglia (striatum, globus pallidus, and subthalamic nucleus) are present in the lamprey forebrain. Moreover, the circuit features, molecular markers, and physiological activity patterns are conserved.

48. Clancy B, Finlay BL, Darlington RB, Anand KJ: **Extrapolating brain development from experimental species to humans**. *Neurotoxicology* 2007, **28**:931-937.

49. Garwicz M, Christensson M, Psouni E: **A unifying model for timing of walking onset in humans and other mammals**. *Proc Natl Acad Sci USA* 2009, **106**:21889-21893.

50. Aronov D, Andalman AS, Fee MS: **A specialized forebrain circuit for vocal babbling in the juvenile songbird**. *Science* 2008, **320**:630-634.

51. Patrick SK, Noah JA, Yang JF: **Interlimb coordination in human crawling reveals similarities in development and neural control with quadrupeds**. *J Neurophysiol* 2009, **101**:603-613.

52. Maclellan MJ, Ivanenko YP, Cappellini G, Sylos Labini F, Lacquaniti F: **Features of hand-foot crawling behavior in human adults**. *J Neurophysiol* 2012, **107**:114-125.

53. • Adolph KE, Berger SE, Leo AJ: **Developmental continuity? Crawling, cruising, and walking**. *Dev Sci* 2011, **14**:306-318.

Before walking, most infants cruise by grasping stable objects such as furniture. Cruising infants perceive affordances for locomotion over an adjustable gap in a handrail used for manual support. However, when they start walking independently, despite weeks of cruising experience, they are surprisingly oblivious to the dangers of gaps in the handrail.

54. Cheron G, Bouillot E, Dan B, Bengoetxea A, Draye JP, Lacquaniti F: **Development of a kinematic coordination pattern in toddler locomotion: planar covariation**. *Exp Brain Res* 2001, **137**:455-466.

55. Ivanenko YP, Dominici N, Cappellini G, Dan B, Cheron G, Lacquaniti F: **Development of pendulum mechanism and kinematic coordination from the first unsupported steps in toddlers**. *J Exp Biol* 2004, **207**:3797-3810.

56. Ivanenko YP, Dominici N, Cappellini G, Lacquaniti F: **Kinematics in newly walking toddlers does not depend upon postural stability**. *J Neurophysiol* 2005, **94**:754-763.

57. Dominici N, Ivanenko YP, Lacquaniti F: **Control of foot trajectory in walking toddlers: adaptation to load changes**. *J Neurophysiol* 2007, **97**:2790-2801.

58. Ivanenko YP, Dominici N, Lacquaniti F: **Development of independent walking in toddlers**. *Exerc Sport Sci Rev* 2007, **35**:67-73.

59. Sutherland DH, Olshen R, Cooper L, Woo SL: **The development of mature gait**. *J Bone Joint Surg Am* 1980, **62**:336-353.

60. • Dominici N, Ivanenko YP, Cappellini G, Zampagni ML, Lacquaniti F: **Kinematic strategies in newly walking toddlers stepping over different support surfaces**. *J Neurophysiol* 2010, **103**:1673-1684.

This paper describes the strategies used by toddlers stepping over an obstacle, walking on an inclined surface or a staircase. In adults, the covariance plane describing the inter-segmental coordination rotates systematically across tasks, whereas its orientation remains constant in toddlers. This behavior restricts the number of degrees of freedom and simplifies the coordination. Moreover, the toddlers often place the foot onto the obstacle or across the edges of the stairs, as part of a haptic exploratory strategy.

61. Galloway JC, Thelen E: **Feet first: object exploration in young infants**. *Infant Behav Dev* 2004, **27**:107-112.

62. Karasik LB, Adolph KE, Tamis-Lemonda CS, Zuckerman AL: **Carry on: spontaneous object carrying in 13-month-old crawling and walking infants**. *Dev Psychol* 2011 http://dx.doi.org/10.1037/a0026040.

63. Yang JF, Lamont EV, Pang MY: **Split-belt treadmill stepping in infants suggests autonomous pattern generators for the left and right leg in humans**. *J Neurosci* 2005, **25**:6869-6876.

64. • Musselman KE, Patrick SK, Vasudevan EV, Bastian AJ, Yang JF: **Unique characteristics of motor adaptation during walking in young children**. *J Neurophysiol* 2011, **105**:2195-2203.

This and the following study use split-belt treadmill walking as a means to probe motor adaptation and learning in children. In this paper, 8–36-months children were studied. Most learnt the novel condition as shown by the slow, progressive reduction of asymmetries in temporal coordination with practice, and by the presence of aftereffects in the early post-split period. Instead, asymmetries in spatial coordination persisted during split-belt walking and no aftereffect was seen. These results are consistent with the hypothesis that the mechanisms controlling temporal and spatial adaptation are different and mature at different times.

65. • Vasudevan EV, Torres-Oviedo G, Morton SM, Yang JF, Bastian AJ: **Younger is not always better: development of locomotor adaptation from childhood to adulthood**. *J Neurosci* 2011, **31**:3055-3065.

Here 3–18-years children and adults with cerebellar damage were studied. All healthy children and adults learnt the new timing at the same rate and showed significant aftereffects. However, children younger than 6-years did not learn the new spatial coordination. Young children showed patterns similar to cerebellar patients, with greater deficits in spatial versus temporal adaptation. Taken together, this and the previous paper show that the maturation of locomotor adaptation follows at least two time courses, one for temporal and the other for spatial coordination, and this may depend on the developmental state of the cerebellum.

66. Dominici N, Daprati E, Nico D, Cappellini G, Ivanenko YP, Lacquaniti F: **Changes in the limb kinematics and walking distance estimation after shank elongation. Evidence for a locomotor body schema?** *J Neurophysiol* 2009, **101**:1419-1429.

67. Aisen ML, Kerkovich D, Mast J, Mulroy S, Wren TA, Kay RM, Rethlefsen SA: **Cerebral palsy: clinical care and neurological rehabilitation**. *Lancet Neurol* 2011, **10**:844-852.

68. Berger W: **Characteristics of locomotor control in children with cerebral palsy**. *Neurosci Biobehav Rev* 1998, **22**:579-582.

69. Hodapp M, Vry J, Mall V, Faist M: **Changes in soleus H-reflex modulation after treadmill training in children with cerebral palsy**. *Brain* 2009, **132**:37-44.

70. Valentin-Gudiol M, Mattern-Baxter K, Girabent-Farrés M, Bagur-Calafat C, Hadders-Algra M, Angulo-Barroso RM: **Treadmill interventions with partial body weight support in children under six years of age at risk of neuromotor delay**. *Cochrane Database Syst Rev* 2011, **12**:CD009242.

71. Van de Walle P, Hallemans A, Schwartz M, Truijen S, Gosselink R, Desloovere K: **Mechanical energy estimation during walking: validity and sensitivity in typical gait and in children with cerebral palsy**. *Gait Posture* 2012, **35**:231-237.

72. Dickinson MH, Farley CT, Full RJ, Koehl MAR, Kram R, Lehman S: **How animals move: an integrative view**. *Science* 2000, **288**:100-106.

73. Maus HM, Lipfert SW, Gross M, Rummel J, Seyfarth A: **Upright human gait did not provide a major mechanical challenge for our ancestors**. *Nat Commun* 2010 http://dx.doi.org/10.1038/ncomms1073.