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Maturation of the Locomotor Circuitry in Children With Cerebral Palsy

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The first years of life represent an important phase of maturation of the central nervous system, processing of sensory information, posture control and acquisition of the locomotor function. Cerebral palsy (CP) is the most common group of motor disorders in childhood attributed to disturbances in the fetal or infant brain, frequently resulting in impaired gait. Here we will consider various findings about functional maturation of the locomotor output in early infancy, and how much the dysfunction of gait in children with CP can be related to spinal neuronal networks vs. supraspinal dysfunction. A better knowledge about pattern generation circuitries in infancy may improve our understanding of developmental motor disorders, highlighting the necessity for regulating the functional properties of abnormally developed neuronal locomotor networks as a target for early sensorimotor rehabilitation. Various clinical approaches and advances in biotechnology are also considered that might promote acquisition of the locomotor function in infants at risk for locomotor delays.

Keywords: cerebral palsy, abnormal development, early development of locomotion, neuromuscular pattern generation, spinal locomotor output, rehabilitation

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INTRODUCTION

The first years of life represent an extremely important phase of maturation and learning and the acquisition of bipedal locomotion is a celebrated milestone in infant development. Early injuries to developing brain may significantly affect this period of maturation and evoke impairments in the locomotor function and its delay (Rosenbaum et al., 2014). Cerebral palsy (CP) is the most common form of motor disability in childhood. It is often characterized by muscle weakness, impaired coordination of muscles and spasticity characterized by hypertonia, hyperreflexia, clonus, spasms and co-contraction (Poon and Hui-Chan, 2009). People with CP have a diversity of symptoms and severity and CP is sometimes accompanied by other disorders such as cognitive dysfunction, epilepsy, deficits in vision, speech (Christensen et al., 2014; Rosenbaum et al., 2014). Gait abnormalities represent essential concern. Indeed, about seventy percent of children with CP are able to walk though they experience problems with walking (from minimal disability to the need of walking aids), while the others require a wheelchair (Hutton and Pharoah, 2002), and life

expectancy is related to the degree of impairments. This topic has broad appeal due to the general interest in the evolution of locomotion, interaction between developing spinal and supraspinal pattern generation circuitries, potential broad impact of early sensorimotor disorders, as well as its implications for understanding the basic physiological mechanisms involved.

Understanding mechanisms of early development and learning are also the basis for designing rehabilitation strategies and interventions for infants at risk for locomotor delays. We will not discuss here all aspects of impairments in the function due to CP. Instead, we will focus on motor disability in CP and gait dysfunction in particular. While the spinal pattern generation circuitry and stepping-like movements are present at birth, the locomotor behavior and the spatiotemporal structure of the motor patterns in infants undergo substantial maturation (Forssberg, 1985; Thelen and Cooke, 1987; Lacquaniti et al., 2012a; Yang et al., 2015). In the first sections, we will consider the functional and structural consequences of early injuries to developing motor regions of the brain, including pattern generation circuitry, forms of early locomotor behavior, the critical role of balance demands and sensorimotor integration, with a particular emphasis on the first years of life. We will also argue that interventions may be more efficacious if they promote quadrupedal locomotion and posture in the early months of life, and training to enhance stepping. Finally, we will consider physical therapy interventions, recent advances in biotechnology and neuromodulation of the locomotor circuitry that might promote early motor recovery in children with CP.

GAIT IMPAIRMENTS IN CP

Detailed descriptions of gait impairments in cerebral palsy have been reported in numerous studies (Rethlefsen et al., 2017). Despite heterogeneity of symptoms and brain damage, there are typical gait abnormalities and frequent clinical problems, such as foot drop and toe walking in children with cerebral palsy. They show difficulties in developing the major features of adult gait, ankle plantarflexion with hip extension at the end of stance, increased co-activation of the leg muscles, low activation of the calf muscles, impaired ability of tibialis anterior to dorsiflex the ankle, maturation of the spinal locomotor output, and enhanced short latency proprioceptive reflexes (Berger et al., 1982, 1984; Leonard et al., 1991; Berger and Adolph, 2007; Cappellini et al., 2016).

Some characteristic features of gait are illustrated in **Figure 1**. In line with the general hypothesis of delayed maturation (Forssberg, 1999), many idiosyncratic features of gait in older children with CP resemble those in typically developing (TD) children at the onset of independent walking (Cappellini et al., 2016), for instance, the prominent single-peak foot lift during swing and disordered vertical hip displacements. Indeed, in addition to gait instability and slower speeds (**Figure 1A**), the adult-like stereotyped, two-peaked trajectory of the foot with minimal toe clearance at mid-swing representing the result of a safe, accurate endpoint control (Bernstein, 1967; Winter, 1992; Ivanenko et al., 2002) is lacking in children with CP (**Figure 1B**). Instead, a single-peaked foot lift is observed across all sampled ages in children with bilateral CP and on the most affected (MA) side in children with unilateral CP, typical for TD toddlers (**Figure 1B**). The vertical ground reaction forces often showed a decreased second peak in late stance in CP (**Figure 1B**), consistent with weak plantarflexion at the end of stance (Williams et al., 2011; Cappellini et al., 2016). Disordered vertical hip displacements and a lack of the gravity-related pendulum mechanism of walking in both TD toddlers (Ivanenko et al., 2004) and children with CP (Cappellini et al., 2016; Zollinger et al., 2016) are consistent with a reduced capacity in absorbing and decelerating the speed of the center of mass and in decreasing the walking energy cost.

Children with CP may develop other motor dysfunctions due to impaired corticospinal interactions, including dystonia, muscle contractures, lack of coordination (Crenna, 1998; Gormley, 2001), weak and often atrophic muscles, increased passive musculotendinous stiffness, changes in the structure of muscle fibers and connective tissue (Willerslev-Olsen et al., 2013; Mathewson and Lieber, 2015; Lieber and Fridén, 2019), so that biomechanical and histopathological changes are also contributing factors to gait abnormalities in CP (Hanson and Jones, 1989; Sutherland and Davids, 1993).

Finally, in children with disorders of the central nervous system, upper limb function is often impaired, which affects interlimb coordination and coordinative stability of limb pairs during gait. Children with CP may rely on "guard" arm postures, especially on the least affected side, as a compensation strategy to maintain balance comparable to newly walking toddlers (Meyns et al., 2012, 2016). Both less affected and more affected sides demonstrate substantially altered arm postures and movements in children with unilateral CP, associated with spasticity, balance control and other contributing factors. Given that human bipedal walking shares many features with that in quadrupeds, including similar regulation and coordination of upper and lower limb movements by central pattern generators and sensory feedback (Zehr and Duysens, 2004; Sylos-Labini et al., 2014; Solopova et al., 2016), lost or compromised arm movements in children with CP support the idea of including appropriate arm activity as a component of gait training after neurotrauma (Zehr et al., 2016; Bleyenheuft et al., 2017; Sidiropoulos et al., 2019). Thus, assessing upper limb function comprehensively is also important for planning and evaluating neurorehabilitative interventions.

IMPAIRED CORTICOSPINAL PATHWAYS IN CP

The control of human locomotion involves multiple neural networks including sensory, supraspinal (motor cortex, basal ganglia, thalamus, cerebellum), and spinal pattern generators signals (Grillner and El Manira, 2020). Furthermore, in contrast with many mammals, humans start to walk relatively late (Garwicz et al., 2009), and a prolonged developmental timescale can be related to postural challenges of bipedal gait, a large brain and its high rate of growth (Leigh, 2004; Kaas, 2005;

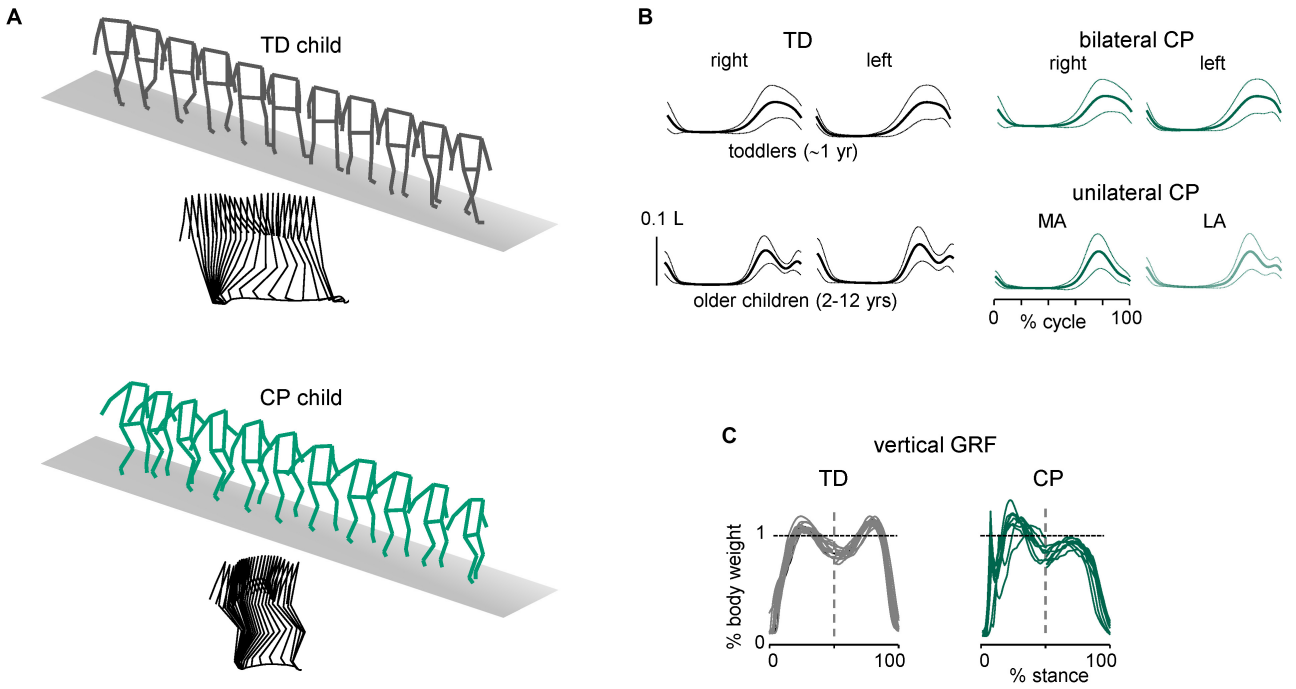

FIGURE 1 | Distinctive features of ground reaction forces and foot trajectory control during walking in children with cerebral palsy. **(A)** Stick diagrams (both 3D and sagittal) of 1 stride in one TD child (5.7 years) and one child with bilateral CP (5.4 years). Note typical two peaked profile of vertical hip position during one stride in TD child (pendulum mechanism of walking) and variable pattern in child with CP. **(B)** Ensemble-averaged (across subjects, ±SD) vertical foot movements (normalized by the limb length L). MA, most affected; LA, least affected side. **(C)** Examples of vertical ground reaction forces in one TD (11.8 years) child and one representative child with bilateral CP (6.1 years). The data from several strides were superimposed (adapted from Cappellini et al., 2016).

Dehorter et al., 2012), and more intensive cortical participation in human locomotion than in animals (Capaday, 2002; Yang and Gorassini, 2006). Biomechanical factors, such as very slow muscle fibers at birth and even in older children (Denny-Brown, 1929; Buller et al., 1960; Dayanidhi et al., 2013), shape and soft tissues of the child's foot sole (Maier, 1961; Gould et al., 1989; Bertsch et al., 2004), lack of extensor strength due to immature muscle cells, etc., also play a role in locomotor development and the reasons human infants do not walk sooner and do not express mature patterns (Thelen, 1995; Adolph et al., 2018; Dewolf et al., 2020). Motor problems in CP are associated with damage to motor pathways from the brain, including the corticospinal tract (CST). Importantly, the formation of specific circuits or the excitatory-inhibitory balance within them are more susceptible to damage at certain times in development in both humans and animal models of developmental motor disorders (Cavarsan et al., 2019). In particular, while reticulospinal projections from the brainstem are the first to arrive in the spinal cord followed by other tracts (Kudo et al., 1993; Sundström et al., 1993; Perreault and Glover, 2013), the CST is the last to arrive in the spinal cord (at ∼30 post-gestational week) and estimated critical period for its maturation is between few months and 2 years based on a period of CST myelination (Yakovlev and Lecours, 1967; Martin, 2005; Yeo et al., 2014). Neuroimaging methods can confirm and quantify impairments in the CST (Nemanich et al., 2019; Papadelis et al., 2019). Given that CST projection activities significantly shape the spinal cord motor function (Eyre et al., 2001), neuronal activity appear to be essential during the critical period for the normal development of the motor circuits (Yang et al., 2013).

One way to probe the development of functional corticospinal connectivity is to estimate the oscillatory drive of the motor cortex to the spinal cord using coherence analysis of MEG/EEG and EMG signals (Ritterband-Rosenbaum et al., 2017). For instance, beta and gamma frequency drive to the motor pool can be accessed through the surface EMG by evaluating coherence and synchronization of motor units within and between muscles. Beta frequency oscillations (15–35 Hz), which are coherent with similar frequencies in corticomuscular coherence in healthy adults (Salenius et al., 1996; Mima and Hallett, 1999), have been shown to be impaired in CNS lesions (Hansen et al., 2005; Nielsen et al., 2008). Thus, coherence and synchrony between EMGs are dependent on intact central motor pathways and these features may serve as physiological markers of impaired supraspinal control of gait (Hansen et al., 2005).

This method has also been used to evaluate developmental changes of functional corticospinal connectivity. For instance, recent data suggest that the corticospinal drive to muscles shows significant developmental changes with an increase in functional coupling in infants aged 9–25 weeks (**Figure 2A**; Ritterband-Rosenbaum et al., 2017), a sensitive period which coincides with the developmental period of normal fidgety movements in TD infants, noticeable manifestation of muscle reactions and self-organization of neural circuits (Blankenship and Feller, 2010; Hadders-Algra, 2018; Solopova et al., 2019). The coherence and

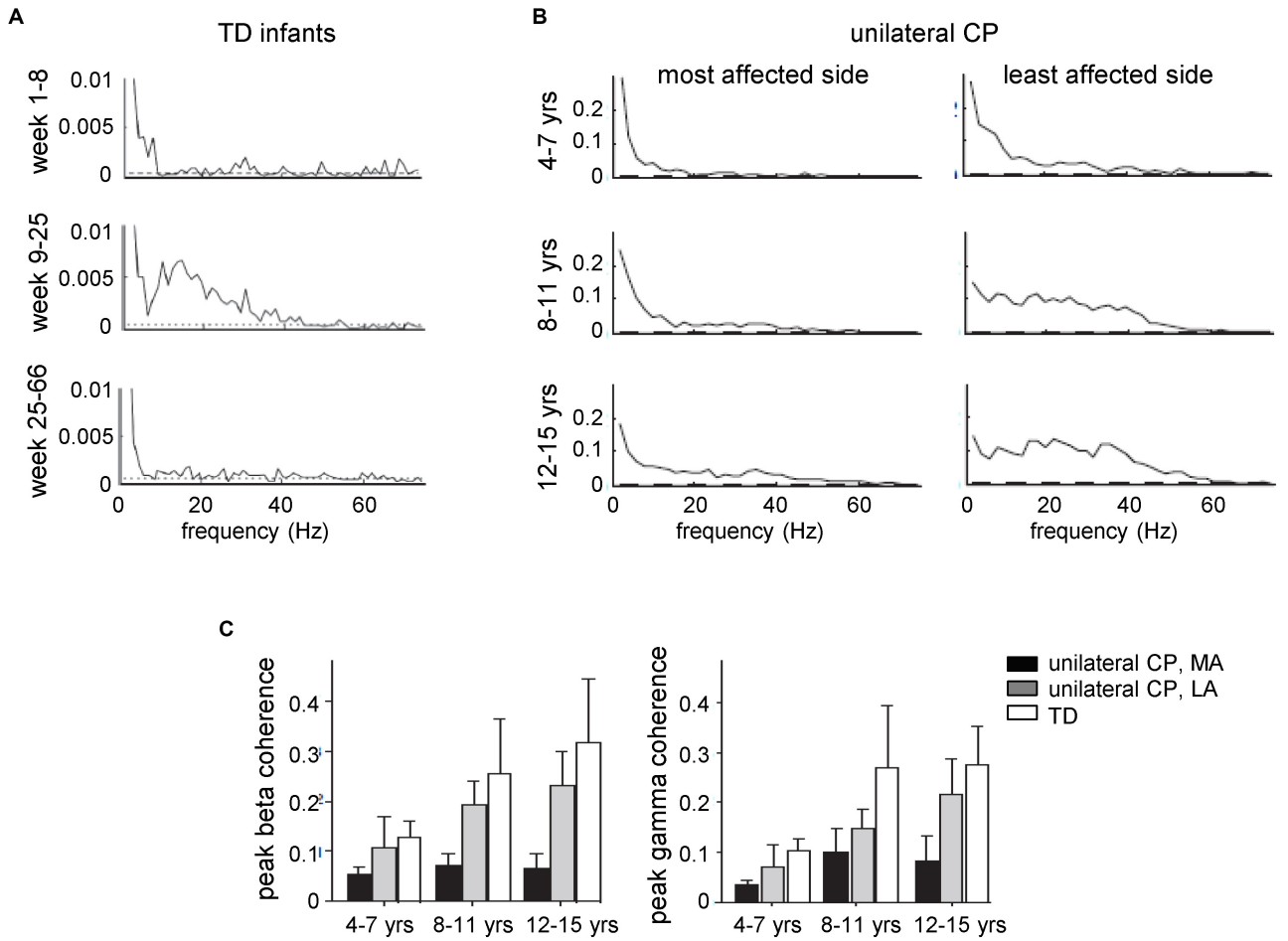

FIGURE 2 | Development of central common drive to a leg muscle. EMG traces were obtained from electrodes placed at the proximal and distal part of the tibialis anterior muscle. Coherence estimates provide a measure of the fraction of the activity in one surface EMG signal at any given frequency that can be predicted by the activity in the second surface EMG signal, reflecting the strength of common rhythmic synaptic inputs distributed across the motoneuron pool. **(A)** EMG–EMG pooled coherence at different frequencies for the three age groups given by the corrected age: 1–8, 9–25, and 25–66 weeks. The dashed lines indicate the 95% confidence levels for the pooled data (adapted from Ritterband-Rosenbaum et al., 2017 with permission). **(B)** Pooled estimates of coherence from all subjects with unilateral CP for the most and least affected sides for three different age groups: 4–7, 8–11, and 12–15 years. **(C)** Peak beta-band and gamma-band coherences in CP (MA, most affected; LA, least affected side) and TD children across the three different age groups. Error bars denote 95% confidence intervals [panels **(B,C)** adapted from Petersen et al., 2013 with permission].

synchrony between EMGs undergo developmental increases in late childhood (**Figure 2B**, TD children). In children with CP, there is a frequent problem of foot drop during gait associated with impaired control of the ankle dorsiflexors and reflected also in impaired tibialis anterior EMG-EMG coherence in the beta and gamma frequency bands on the most affected side, as well as lack of age-related increase of coherence (**Figure 2**; Petersen et al., 2013). Furthermore, toe walking in children with CP appears to be controlled differently from voluntary toe walking in typically developing children and is accompanied by differences in motor unit synchronization and coherence between antagonist EMGs (Lorentzen et al., 2019). Interestingly, 4 weeks of daily intensive treadmill training with an incline in children with CP may improve the control of the ankle joint (number and amplitude of toe lifts in the swing phase) and evoke plastic changes in the corticospinal tract associated with increased beta and gamma oscillatory drive to motoneurons (Willerslev-Olsen et al., 2015).

NEUROMUSCULAR GENERATION AND MATURATION OF LOCOMOTOR CIRCUITRY IN EARLY INFANCY

While the above-mentioned assessments of the functional corticospinal connectivity provide important information about output of the motor cortex and its transmission to the spinal cord, one should keep in mind that these measurements are nevertheless limited in their ability to assess the actual state of the spinal locomotor circuitry and its impairment in CP. Indeed, whereas subcortical and cortical structures coordinate locomotor responses, especially when gait is made

more difficult by demanding external conditions or postural instability, the basic neural control mechanism is largely governed by spinal pattern generators (Kiehn, 2016; Minassian et al., 2017; Gill et al., 2018; Grillner and El Manira, 2020). Using electrophysiological, pharmacological, or neuroanatomical approaches in invertebrates and vertebrates, the identification of the spinal interneurons and investigation of the locomotor circuitry provided important insights into how these functional circuits are formed during development. In particular, such studies showed considerable reorganization of spinal circuitry and the involvement of new circuitry during early development of locomotion (Vinay et al., 2002; Rauscent et al., 2006; Chakrabarty et al., 2009; Fetcho and McLean, 2010; Currie and Sillar, 2018). Therefore, even though the primary deficit in children with CP originates from the damage to the brain, a large part of the locomotor dysfunction might be attributable to the impaired state of the developing spinal circuitry, which has been somewhat overlooked.

An essential aspect of damage to developing brain is a risk of substantial or even irreversible changes in the state of the locomotor network during early development and critical developmental windows in particular. Moreover, if the state of the spinal circuitry is impaired, it should be controlled differently by descending motor pathways, which in turn would enhance the reorganization and involvement of the supraspinal structures to compensate for these abnormalities. These reciprocal spinal-supraspinal compensatory mechanisms create a risk of irreversible changes in the state of locomotor circuitry during early development, especially during critical developmental windows (Hadders-Algra, 2004; Yang et al., 2013; Friel et al., 2014; Cappellini et al., 2016).

What are indicators of the spinal cord involvement in CP? First, although it has been argued that the proximity of the spinal circuitry to the outer world may demand a more rigid organization compared to the highly flexible cortical circuits (Christiansen et al., 2017), this statement is valid only to some extent and unlikely for the developing spinal cord. Definitely, the spinal cord is not a simple relay structure for communication between central structures and skeletal musculature but is flexible (Heng and de Leon, 2007), capable of performing coordinate transformations (Fukson et al., 1980; Windhorst, 1996a; Poppele and Bosco, 2003), synapse daily turnover, cell death and atrophy after a spinal cord injury (Dietz and Müller, 2004; Gazula et al., 2004) or after brain damage (Drobyshevsky and Quinlan, 2017). In humans, examination of spinal neuronal circuitries is difficult to perform by non-invasive methods though some structural changes were documented. For instance, postmortem examination of children with CP showed abnormalities in the rostral segments of the spinal cord (Levchenkova and Semenova, 2012), while magnetic resonance imaging of the spinal cord in the subjects with spastic bilateral CP showed a reduced white matter crosssectional area at C6/C7 and T10/T11 segments (Noble, 2014). Early corticospinal lesion at the spinal level in humans also affects the immature spinal cord and gait maturation (Dan et al., 2004). As far as it concerns the mechanisms of early motor dysfunctions in CP, animal studies convincingly show that injury to the supraspinal systems or removing descending input severely disrupts spinal cord neuromodulation and the postnatal development of spinal circuits (Clowry, 2007; Friel et al., 2014; Smith et al., 2017; Jiang et al., 2018). The spinal interneurons mature in common with the CST connections (Chakrabarty et al., 2009) and extensively in the early period (possibly equivalent to ages 3–5 months in human infants), suggesting that if that window closes, full recovery is not possible (Friel et al., 2014). Furthermore, unilateral CST inactivation produces not only contralateral but also ipsilateral effects on the developing spinal circuitry, due to both sparse ipsilateral terminations and indirect ipsilateral influences at multiple levels of the CNS, reflecting the balanced contributions from the motor cortex on each side, rather than overwhelmingly from the contralateral side (Friel and Martin, 2007). Descending pathways also regulate spontaneous activity, which is likely a major trigger for early maturation of lumbar locomotor networks (Vinay et al., 2002).

Second, most synapses in the spinal cord are inhibitory (Levine et al., 2014) and contribute to network stability, preparation of an appropriate state of spinal circuitries to accommodate a specific supraspinal command (since the same interneurons and motoneurons participate in a wide range of movements and synergistic actions) and avoiding an excessive motor reaction (Windhorst, 1996b). However, in individuals with CP, damaging cortico-, rubro-, reticulo-, and vestibulo-spinal glutamatergic projections to the spinal cord through spinal inhibitory interneurons (Jankowska et al., 1976) can reduce inhibitory tone in the spinal cord and contribute to hypertonia (Sanger, 2003; Deon and Gaebler-Spira, 2010). The excitatory-inhibitory misbalance in the spinal circuitry in persons with CP is manifested by enhanced segmental reflexes with abnormal radiation of stretch reflexes to other muscles including the lack of the development of reciprocal inhibition of antagonist muscles (Berger et al., 1982, 1984; Myklebust et al., 1982; Myklebust, 1990), and the greater the imbalance the more severe the motor disorders (Condliffe et al., 2016).

Third, neuromodulation of the physiological state of the spinal cord is known to affect locomotor performance (Ivanenko et al., 2017; Gill et al., 2018). For instance, the locomotor function can be improved in children with CP using transcutaneous spinal cord stimulation during gait training (Solopova et al., 2017). It is also worth mentioning that these promising findings have been obtained in relatively older children (7–11 years), when substantial spinal abnormality induced by perinatal brain damage was already developed, and they need to be explored further to assess more comprehensively the more responsive neuromechanical characteristics and age-effect of such locomotor improvements. In addition to influences on locomotor function (Solopova et al., 2017), high-frequency spinal cord stimulation may reduce spasticity in children with CP (Shabalov et al., 2006; Dekopov et al., 2015).

To end with, the final neural output of spinal locomotor circuitry is represented by the spatiotemporal modulation of alpha-motoneuron (MN) activity, which can be assessed by mapping the activity patterns from a large number of simultaneously recorded muscles onto the anatomical rostrocaudal location of the MN pools in the spinal cord (Yakovenko et al., 2002; Ivanenko et al., 2013;

Wenger et al., 2016), and by decomposing the coordinated muscle activation profiles into a small set of common factors as a means to look backward from the periphery to the CNS (Davis and Vaughan, 1993; Lacquaniti et al., 2012b). There are now several studies that evaluated the spatiotemporal organization of the spinal locomotor output in CP (Steele et al., 2015, 2019; Tang et al., 2015; Cappellini et al., 2016; Shuman et al., 2016, 2017, 2018, 2019a,b; Hashiguchi et al., 2018; Kim et al., 2018; Booth et al., 2019; Yu et al., 2019; Falisse et al., 2020; Pitto et al., 2020; Short et al., 2020).

Figures 3, **4** illustrate typical features of spinal locomotor output impairments in CP. TD children show a progressive reduction of EMG burst durations with increasing age (**Figure 3A**) likely reflecting an essential developmental aspect of muscular control optimization. This might be important for coordination of locomotion with voluntary movements, which requires a precise coordination of activation timings of the locomotor and voluntary motor programs (Ivanenko et al., 2005), and for optimization of the energetic cost of walking. For the assessment of motor coordination, one may test a modular approach for neuromuscular control providing information about temporal patterns of muscle activation shared by different muscles along with corresponding muscle synergies (Davis and Vaughan, 1993; Lacquaniti et al., 2012b). Such factorization of the EMG signals revealed a comparable structure of the motor output in children with CP and TD children, but significantly wider temporal activation patterns in children with CP, resembling the patterns of much younger TD infants (**Figure 3B**; Cappellini et al., 2016). Reduction of dimensionality (the smaller number of muscle synergies) found in some previous studies (e.g., Steele et al., 2015; Tang et al., 2015; Shuman et al., 2016) may depend on the criterion used to define the minimum number of synergies (Hug et al., 2012; Russo et al., 2014) and/or the limited number of recorded muscles (Steele et al., 2013; Zelik et al., 2014; Damiano, 2015). Nevertheless, the observed phenomenon of widening (**Figure 3B**) does not depend on the exact number of modules retained by the specific non-negative matrix factorization procedure (Martino et al., 2015), was confirmed in other studies as well, and seems to be a characteristic feature of CP gait. Furthermore, wider basic muscle activity patterns in CP were observed independent of the GMFCS level (**Figure 3C**; Yu et al., 2019). Thus, locomotor patterns of older children with cerebral palsy show lack of maturation and similarity of the early stages of gait development in healthy children.

A similar picture emerges when considering the spatiotemporal maps of alpha-motoneuron activation (**Figure 4**). The spinal maps of motor pool activation can be estimated by mapping EMG activity of a large number of simultaneously recorded muscles onto the anatomical rostrocaudal location of the MN pools under the assumption that the rectified EMG provides an indirect measure of the net firing of MNs of that muscle in the spinal cord (Yakovenko et al., 2002; Ivanenko et al., 2013). TD children show a gradual reorganization of the spatiotemporal MN output with increasing age (Ivanenko et al., 2013; Dewolf et al., 2020), consisting in more narrow loci of MN activity and a progressive shift of the timing of maximum activation of sacral segments toward later stance (**Figure 4B**, right panel). By contrast, this developmental trend in children with CP is lacking (on both sides for children with bilateral CP and the affected side for children with unilateral CP). Therefore, children with CP show very limited age-related changes of muscle activity pattern durations and motoneuron output (Cappellini et al., 2016), consistent with the idea that early injuries to developing brain substantially affect the maturation of the spinal locomotor output.

In sum, how intrinsic spinal locomotor circuits are remodeled after a perinatal brain injury needs to be better understood since they play a key role in locomotor dysfunction in CP and in developing locomotor neuromuscular pattern generation in general, taking into consideration a substantial ongoing reorganization of the locomotor output in TD infants during the first year of life (Dominici et al., 2011; Ivanenko et al., 2013; Sylos-Labini et al., 2020). Also, the efficacy to repair supraspinal (CST) connections to the spinal cord is strongly reduced after the critical period and is insufficient to restore significant function unless promoted (Friel et al., 2014). This suggests the necessity for early central pattern generator-modulating therapies and early gait rehabilitation in children with CP to assist in the normal development of the spinal motor circuits and enhancing walking (Yang et al., 2013; Cappellini et al., 2016; Hurd et al., 2017).

ADAPTIVE GAIT CONTROL IN CP

Locomotor movements must be accommodated to different environments and directions of progression. The ability to adapt is of particular interest in the context of cerebral dysfunction, since the control of adaptive locomotion may involve accurate foot placements, their visual guidance, changes in the coordination, greater balance control, anticipatory locomotor adjustments, and thus require larger cortical involvement. Whereas the impairments of standard forward 'steady state' gait on a flat surface have been extensively investigated in children with CP, the neural mechanisms of the adaptive locomotor behavior have been studied to a lesser extent, even though difficulties in performing complex locomotor movements (walking on inclines, uneven terrain, in crowded area, climbing stairs) are included in the GMFM (Gross Motor Function Measure) assessment in persons with CP. Below we consider some examples of such movements supporting the idea that complex locomotor movements can be used for more comprehensive diagnosis of CP as well as for gait rehabilitation.

Locomotion rarely occurs on a flat surface and we often encounter obstacles in our pathway. In general, children with CP have difficulties in clearing an obstacle, being slower in approach and crossing speed along with unsteadiness of gait and balance adaptations of the trunk control (Law and Webb, 2005; Malone et al., 2016). For instance, in a recent study (Cappellini et al., 2020) we showed that about 30% of children with bilateral CP failed to perform the task (they stopped before the obstacle, performed lateral obstacle avoidance, stumbled or stepped onto the obstacle). Interestingly, they had mostly posterior lesions of the brain (Cappellini et al., 2020), in relation to their deficits in the anticipatory visuomotor control and important role of

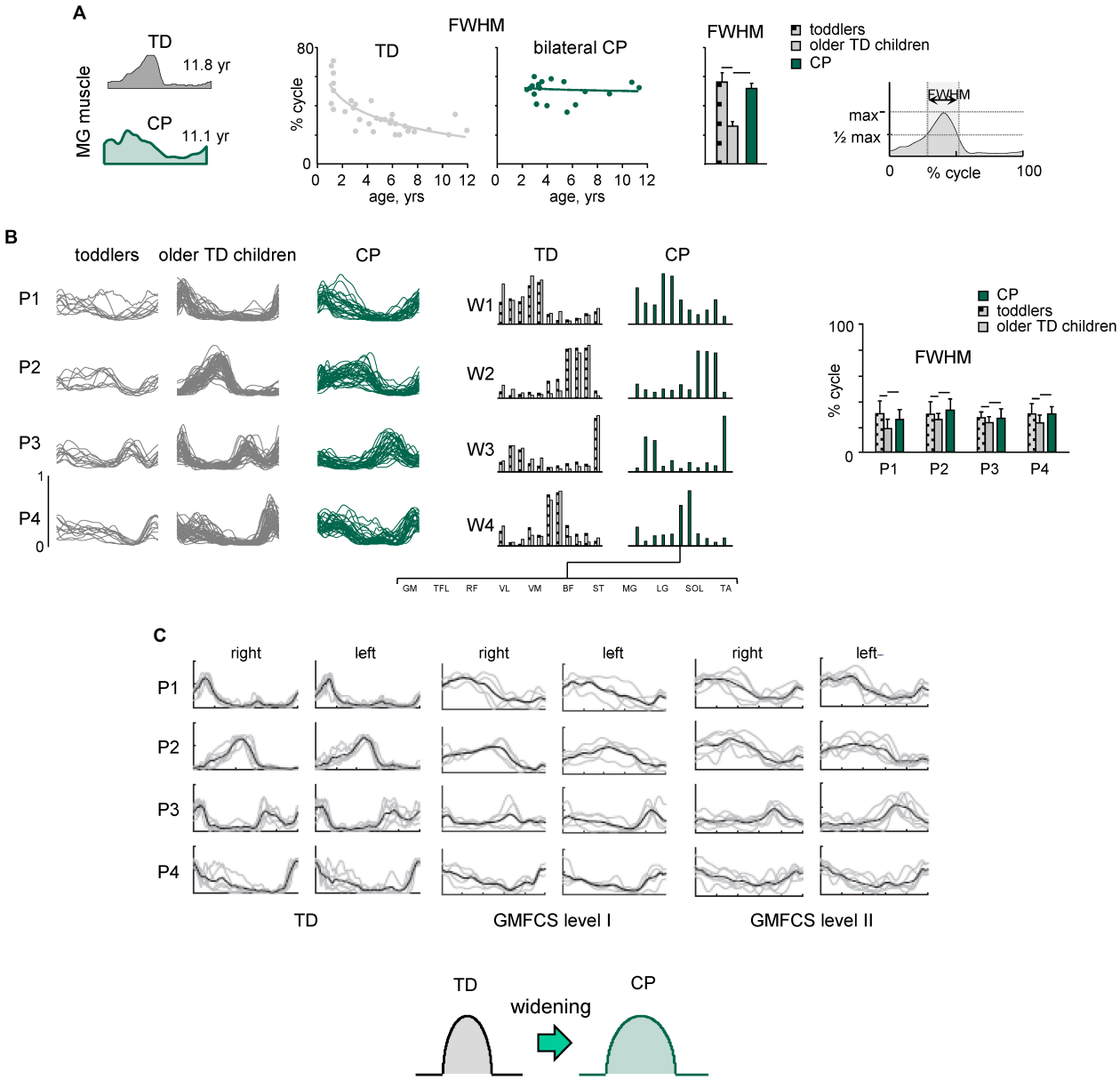

FIGURE 3 | Spatiotemporal organization of muscle activity patterns during walking. **(A)** Developmental trend for the duration of muscle (MG, medial gastrocnemius) activity. From left to right: examples of MG activity in one TD child and one child with bilateral CP, duration of MG activity (FWHM, full width at half maximum, see right panel) as a function of age (continuous lines represent exponential fittings), and averaged across children [horizontal lines denote significant differences compared with older TD children (2–12 years)]. **(B)** Statistical analysis of EMG patterns: basic activation patterns P1–P4 (each curve represents the pattern for an individual child) and corresponding weights W1–W4 (muscle synergies). Right panel – mean (+SD) FWHM of consistent basic activation patterns (P1–P4). Adapted from Cappellini et al. (2016). **(C)** Basic activation patterns (for the right and left sides) in TD children and children with bilateral CP at Gross Motor Function Classification System (GMFCS) levels I and II (adapted from Yu et al., 2019 with permission). Note significantly wider patterns in CP, independent of GMFCS level.

parietal lobe activity in visually planning gait adaptations (Drew et al., 2008; Lajoie et al., 2010; Drew and Marigold, 2015). Remaining children with CP (∼70%), who succeeded with obstacle clearance, performed the task significantly slower than age-matched TD children, demonstrating a high foot lift of the trailing (unseen) limb, smaller range of motion and muscle moments of the distal (ankle) joint (**Figure 5A**, left panels), and limited adaptation of task-relevant activity of hamstring muscles timed to the voluntary task of foot lift over the obstacle (Cappellini et al., 2020). Thus, impaired task performance in children with CP may reflect basic developmental deficits in the adaptable control of gait when the locomotor task is superimposed with the voluntary movement, suggesting that gait rehabilitation strategies should involve tasks performed in challenging environments to enhance the functional capacity of gait controllers.

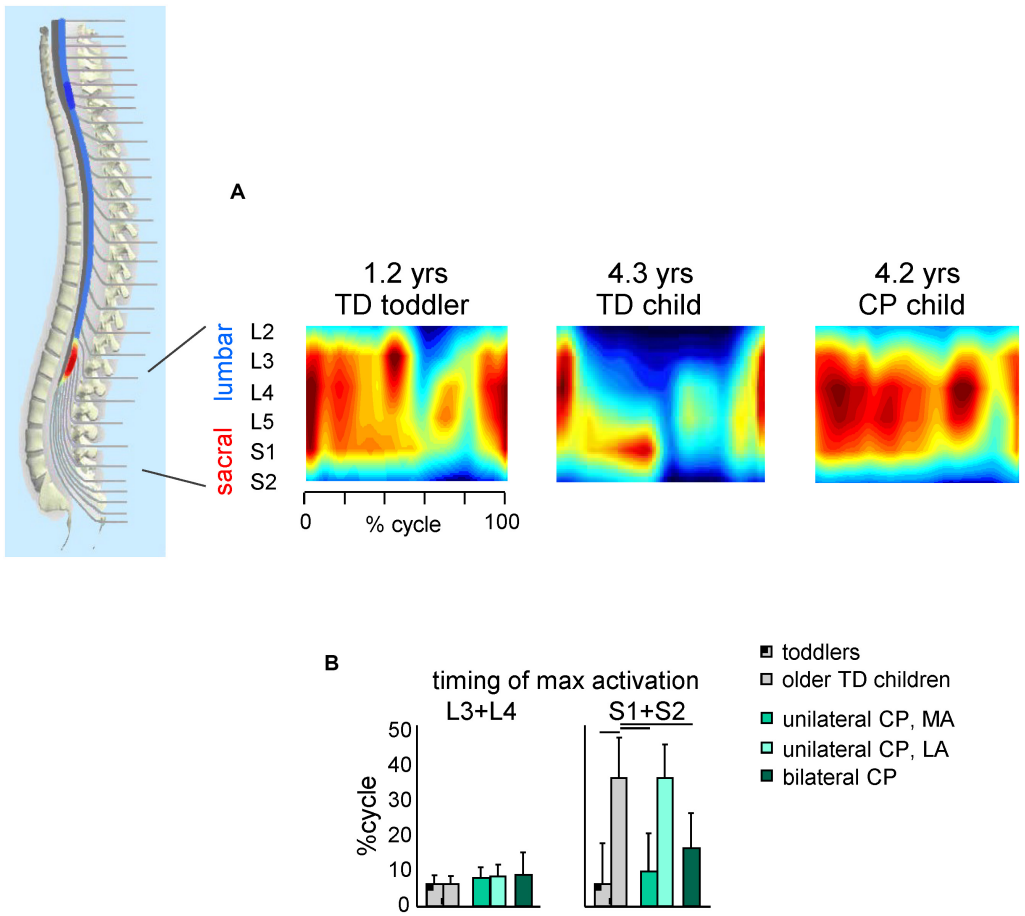

FIGURE 4 | Spatiotemporal maps of motoneuron activity of the lumbosacral enlargement in TD children and children with CP. **(A)** Examples of segmental output in one TD toddler (1.2 years), one TD older child (4.3 years) and one child with CP (4.2 years) (adapted from Cappellini et al., 2016). **(B)** Timing (+SD) of maximum activation of lumbar (L3 + L4) and sacral (S1 + S2) segments. Lines over bars denote significant differences compared with older TD children.

Backward walking (BW) is another example of adaptive locomotor behavior. It has been argued that BW uses the same rhythm circuitry as forward walking (FW) but involves additional specialized control circuits (Hoogkamer et al., 2014). BW is also a beneficial physical activity used in the rehabilitation of children with CP to improve walking abilities, strengthen RF and TA muscles, as well as augmenting hip extension and knee flexion with ankle dorsiflexion (Kim et al., 2016; Abdel-Aziem and El-Basatiny, 2017; Hösl et al., 2018; Elnahhas et al., 2019). Furthermore, BW highlights prominent gait asymmetries in children with CP and thus may give a more comprehensive assessment of the gait pathology (Cappellini et al., 2018). In particular, gait asymmetries, which were not evident during FW in children with bilateral CP, became evident during BW (**Figure 5B**). Accordingly, the most affected side in bilateral cerebral palsy can be defined based on the limb that show shorter stance duration during BW. The definition of unilateral cerebral palsy is usually not etiologic but functional (Bax et al., 2005; Rosenbaum et al., 2014), as a neuromuscular disorder that involves one half of the body (most affected side). The reason for the lack of asymmetry during FW in children with bilateral CP might be explained by the fact that the diagnosis of asymmetry is determined by clinical observation (e.g., the side on which the leg has the highest spasticity measure), and to our knowledge there is no valid criterion based on instrumented gait analysis to distinguish between asymmetric and symmetric children with bilateral CP. BW may also be more asymmetric because it is a less practiced form of gait than FW. Walking asymmetry can be problematic for many reasons and is increasingly measured and used as an important marker of gait recovery after stroke (Patterson et al., 2010; Wonsetler and Bowden, 2017). Spatiotemporal asymmetry assessments during BW in CP might reflect an impaired state and/or descending control of the spinal locomotor circuitry and can be used to help the diagnosis of the most affected side and as complementary markers of gait recovery.

To sum up, early injuries to developing brain affect both normal walking and other forms of locomotor behavior: complex locomotor movements (Law and Webb, 2005; Dixon et al., 2016; Mawase et al., 2016; Lewerenz et al., 2019; Cappellini et al., 2020), running (Böhm and Döderlein, 2012), weighting of legs (Bulea et al., 2017), backward walking (Cappellini et al., 2018), and even

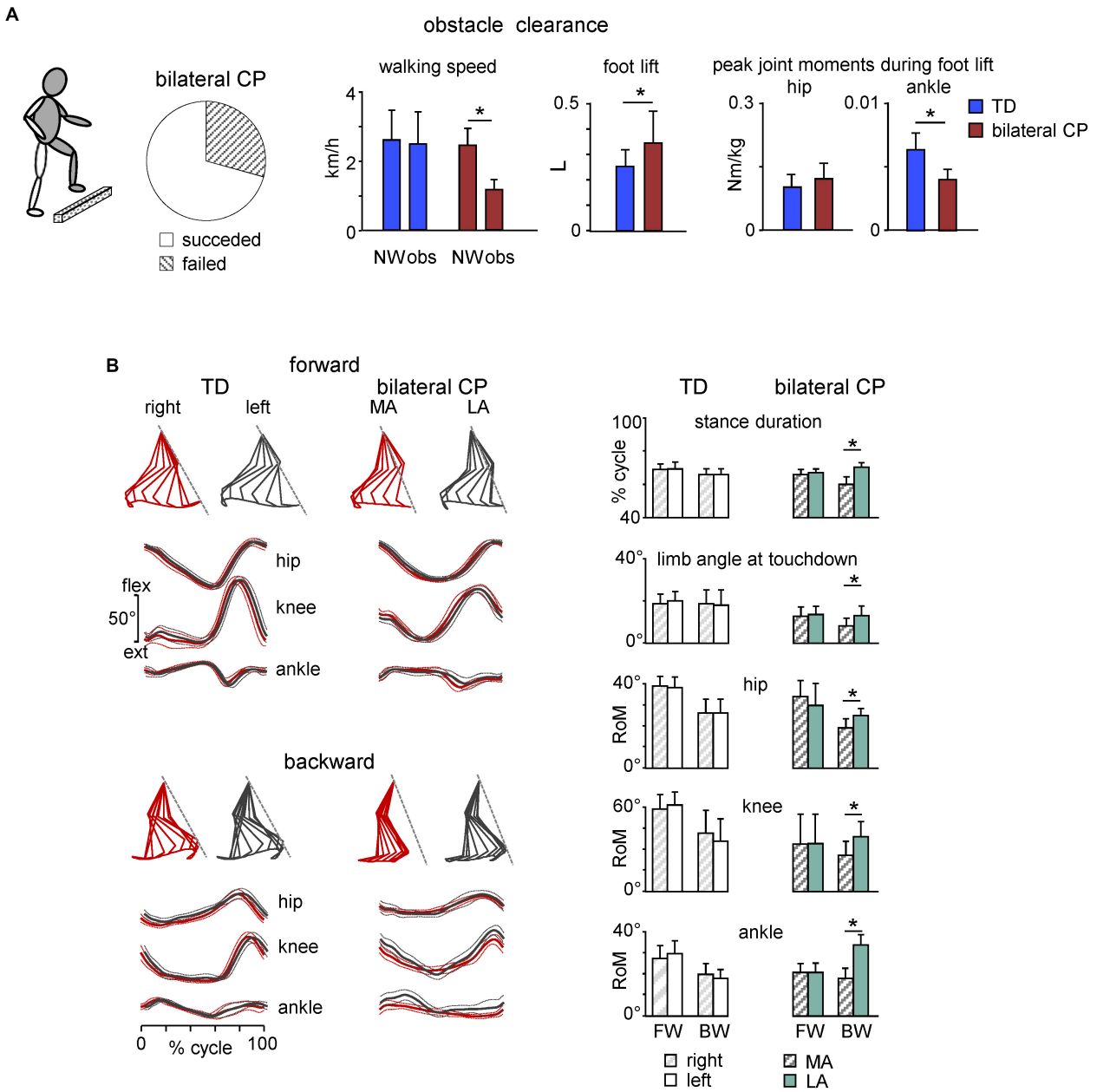

FIGURE 5 | Adaptive locomotion in children with CP. **(A)** Obstacle task performance in children with bilateral CP. From left to right: pie chart showing the percentage of trials for children with succeeded and failed obstacle clearance, mean (+SD) walking speed for successful trials, foot lift and flexor peak hip and ankle muscle moments during trailing limb elevation. Asterisks denote significant side differences. Adapted from Cappellini et al. (2020). **(B)** Kinematics of forward and backward walking in TD and children with bilateral CP. Left panels: examples of forward gait kinematics in one TD child (5.7 years) and one child with CP (6.1 years) during forward and backward walking. From top to bottom: stick diagrams of the swing phase of a single step for both legs (relative to the instantaneous hip position), and ensemble-averaged (across all strides, ±SD) hip, knee, and ankle joint angles (red corresponds to the most affected side in CP). Dashed lines in stick diagrams correspond to the orientation of the left (in TD) and least affected (in CP) limb during touchdown. Right panels: comparison of gait parameters and ranges of angular motion (+SD) for both legs in TD and children with bilateral CP during forward (FW) and backward (BW) walking. MA, most affected; LA, least affected side. Adapted from Cappellini et al. (2018).

earlier locomotor movements such as crawling in infants with developmental delay (Xiong et al., 2018; Li et al., 2019). Current interventions are being developed that emphasize including more complex and voluntary locomotion in gait rehabilitation of children with CP. For instance, intensive training of walking on the inclined surface represents a promising protocol aimed at improving the control of the ankle joint and foot drop in CP (Willerslev-Olsen et al., 2015), while the standardized walking obstacle course was included as a part of movement therapy (Malone et al., 2016). Given that the support surface and external

objects are included in the locomotor body scheme and its development (Dominici et al., 2010; Pearson and Gramlich, 2010; Ivanenko et al., 2011), navigating complex terrain, e.g., using the "magic carpet," can further enhance spatial representation and generation of locomotor trajectories in CP (Berthoz and Zaoui, 2015; Belmonti et al., 2016). Thus, the best possible understanding of the impaired control of compound locomotor movements and their development is relevant for the ongoing work on improvement of the locomotor function in early childhood in persons with CP.

EARLY INTERVENTIONS TO PROMOTE THE LOCOMOTOR FUNCTION IN INFANTS WITH CP

The development of efficient and independent walking is an important therapeutic goal for children with CP (Willoughby et al., 2009; Smania et al., 2011; Degelean et al., 2012; Drużbicki et al., 2013; Willerslev-Olsen et al., 2015; Graham et al., 2016; Lerner et al., 2017). This may include advances in biotechnology to unveil new information about the impaired locomotor output or infant general movements for the early diagnosis of CP (Zhu et al., 2015; Redd et al., 2019; Airaksinen et al., 2020; Sylos-Labini et al., 2020), to develop central pattern generator-modulating therapies (Solopova et al., 2017) and to enhance walking. For example, initially shown to be effective for mammalian gait retraining (e.g., Barbeau and Rossignol, 1987; van den Brand et al., 2015; von Zitzewitz et al., 2016), a therapeutic intervention for gait retraining with partial body weight support using a harness system (McNevin et al., 2000) or water immersion (Oliveira et al., 2014) may improve walking capacity in children with CP (Day et al., 2004; Azizi et al., 2017). Given a positive effect of repetitive locomotor exercise on gait characteristics in CP (Smania et al., 2011; Willerslev-Olsen et al., 2015), also with the use of wearable exoskeleton (Lerner et al., 2017), the rehabilitative protocol may further focus on improving the locomotor output, e.g., by providing a feedback on specific features of the spinal locomotor output (**Figures 3**, **4**) or implementing gait training program with real-time feedback of the body's center-of-mass vertical displacement to restore the pendulum mechanism and decrease the walking energy cost (Massaad et al., 2010). Such approaches may be complementary to current concepts in rehabilitation of gait in children with CP. In addition, combining gait training with spinal cord neuromodulation may also improve locomotor function (Solopova et al., 2017). In addition, given that the muscles are weak and often quite atrophic in children with CP, resulting in

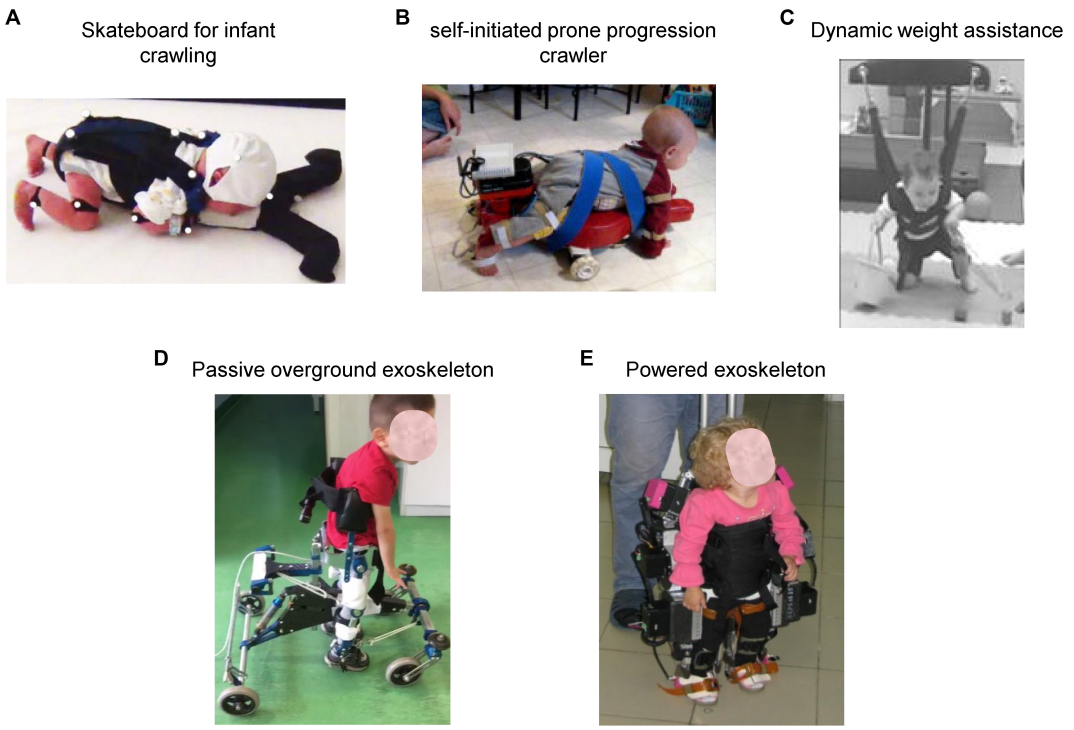

FIGURE 6 | Physical therapy interventions that may promote early locomotor movements and enhance stepping for infants at risk for locomotor delays. **(A)** Pediatric skateboard for entraining quadrupedal locomotion (crawling) in infants in early months of life [reproduced from Forma et al. (2019) with permission]. **(B)** Self-initiated prone progression crawler containing active components enabling the infant to push harder to produce the intended movement [reproduced from Kolobe and Fagg (2019) with permission]. **(C)** Dynamic weight assistance system allowing practice of motor skills that infants are not yet able to perform on their own (crawling, knee walking, walking, climbing, attempts to jump and falling) [reproduced from Prosser et al. (2012) with permission]. **(D)** Passive non-actuated exoskeleton ("Moonwalker" used to facilitate upright posture and stepping in young children with cerebral palsy (courtesy of Hilenia Catania). **(E)** Powered exoskeleton ("ExoAtlet Bambini") for assisting stepping in children suffering from early neurological gait impairment (courtesy of Elena Pismennaya).

significantly reduced volumes in leg muscles and in bone changes (Barrett and Lichtwark, 2010; Moreau et al., 2010; Oberhofer et al., 2010; Willerslev-Olsen et al., 2013; Noble et al., 2014; Handsfield et al., 2016), interventions increasing muscle length or strength can also improve gait. Early recognition of progressive deformity in the muscles and joints of the lower extremity and the spine in children with CP may allow timely treatment and prevention of irreversible changes (Morrell et al., 2002; Barber et al., 2011; Handsfield et al., 2016). Nevertheless, the reported gait recovery or power to find significant results still remains often limited (Valentín-Gudiol et al., 2017). Furthermore, in the great majority of studies, the CP participants benefited from locomotor training after the age of 3–5 years, keeping also in mind the delayed onset of independent walking in many infants with CP.

Frequent treatment for the lower limbs in young children with CP is more passive, typically including stretching, an ankle-foot orthosis for the affected leg (Wingstrand et al., 2014), and botulinum toxin A injections to reduce the abnormal muscle tone (Koman et al., 2003). Given critical developmental periods for maturation of the locomotor networks and corticospinal connectivity (see above section "*Neuromuscular Generation and Maturation of Locomotor Circuitry in Early Infancy*"), the key missing element in the majority of studies focusing on neurodevelopmental treatment - intensive child-initiated motor activity (Hurd et al., 2017). However, investigations focusing on early therapy of the lower limbs and the locomotor function are sparse (Richards et al., 1997; Campbell et al., 2012; Prosser et al., 2012; Hurd et al., 2017; Kolobe and Fagg, 2019).

Based on knowledge of neuroplasticity and the idea of critical developmental windows (Yang et al., 2013; Friel et al., 2014; Hadders-Algra, 2014; Reid et al., 2015; Cappellini et al., 2016; Hurd et al., 2017; Williams et al., 2017), the potential impact of initiating training at an earlier age is also an important consideration for clinicians working with children with CP. It is also worth noting available evidence for early accurate diagnosis of cerebral palsy that now can be made before 6 months' corrected age (Novak et al., 2017). Taking advantage of newly available biotechnology for pediatric rehabilitation, training in the sensitive period for maturation would help to optimize infant motor and cognitive plasticity and enhance more effectively their locomotor function, that we briefly consider below.

Figure 6 illustrates some recent technological assistive solutions for implementing early locomotor behavior therapy in children with CP younger than 2 years of age. For instance, Forma et al. (2019) argued that a quadrupedal organization underlying locomotor movements in humans is manifested rather early (see also La Scaleia et al., 2018), particularly apparent on the skateboard (**Figure 6A**), and thus early quadrupedal training may enhance interventions designed to hasten the onset of independent walking in infants with cerebral palsy and developmental delays. In the same vein, the SIPPC (self-initiated prone progression crawler) system represents an integration of robotics and sensor technologies designed to capture (recognize one of 20 different crawling-like gestures of the arms and feet) and influence movement effort as infants learn prone locomotion (Kolobe and Fagg, 2019). With this idea of early crawling, it is worth stressing the fact that upper limb retraining may induce modification of locomotor function (Delabastita et al., 2016; Meyns et al., 2017).

The potential for infants to learn new behaviors and the acquisition of early locomotor function is also important for shaping and normal maturation of sensorimotor integration and psychological development (Anderson et al., 2013, 2016, 2019). Therapy utilizing novel dynamic weight assistance technology (Prosser et al., 2012; **Figure 6C**) may allow practice of motor skills that children are not yet able to perform on their own (crawling, knee walking, walking, climbing, attempts to jump and falling). A passive non-actuated exoskeleton provides further opportunity to develop the child's potential for independent movement ("Moonwalker" and "NF-Walker®" available in the market, **Figure 6D**). It can also be modified using the actuated robotic aid by means of artificial muscles (Smania et al., 2012) and represents an individually adjustable device with a high amount of postural control, which assists children with severe gait impairment to attain independent mobility in standing position (Kuenzle and Brunner, 2009). Finally, a recently developed powered exoskeleton ("ExoAtlet Bambini," **Figure 6E**)[1] is able to provide assistance for stepping and help young children (∼2 years) to learn how to walk. Stimulation or early training of the locomotor function may have a greater impact on the onset of independent walking for children with development disorders and have the potential to alter the trajectory of motor development in CP (Prosser et al., 2012).

Research is also required to explore neural changes in response to training, especially given the capacity for change in developing nervous systems. In this respect, better understanding of early remodeling of intrinsic locomotor circuits after a perinatal brain injury is warranted to evaluate and develop successful strategies for early interventions in infants at risk of developmental delays. Studies using animal models of cerebral palsy could further advance our ability to treat and cure a variety of conditions (e.g., using medication and neuromodulation of neuronal circuits, Cavarsan et al., 2019), ameliorate motor symptoms, facilitate a more basic mechanistic understanding of the neurobiological underpinnings of neuroplasticity of cerebral palsy and develop early central pattern generator-modulating therapies.

AUTHOR CONTRIBUTIONS

All the authors made contributions in drafting the manuscript and have approved the final version.

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[1] https://exoatlet.lu/bambini/

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