Can the period of postnatal co-development of the rubrospinal and corticospinal systems provide new insights into refinement of limb movement?

Article reviewed:

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Abstract

The corticospinal and the rubrospinal tracts are thought to synergistically contribute to the limb control during motor development. Williams et al. (2014) demonstrate that the postnatal maturation of red nucleus motor map and the rubrospinal tract develops earlier than the corticospinal tract, to support early forelimb control. They have two distinct phases of maturation; a “precorticospinal” phase characterized by development of the rubrospinal system, and a “cocorticospinal” phase where they overlap with corticospinal development.
In mammalian species, including humans and other primates, neural control of distal limbs is thought to be due to a concerted effort of the dominant lateral motor systems; primarily the corticospinal tract (CST) and the rubrospinal tract (RST), a phylogenetically older pathway (Lemon 2008). Substantial research in the last fifty years starting with work in primates initially by Hans Kuypers (Lawrence and Kuypers 1968a, 1968b), later by Roger Lemon (Lemon 2008) and recently in cats by Martin and colleagues (Chakrabarty and Martin 2000; Li and Martin 2001, 2002) has shown that the CST and its postnatal development is critical for improvements in fine motor skills of distal limbs. Particularly, in both primates and cats, it has been shown that this period of developmental neuroplasticity extends into adolescence and is amiable to experience-dependent training (Bengtsson et al. 2005). However it is still unclear what the exact timelines of postnatal development of the other lateral motor pathway RST are and what are their interactions, if any with CST development, which could be of significance in case of a perinatal corticospinal injury, such as cerebral palsy (CP).

In a recent paper published in The Journal of Neuroscience, Williams et al. (2014) test the hypothesis that the rubrospinal system develops earlier than the corticospinal system, such that it provides the rudiments for distal limb movements. They examine the relationship between the red nucleus (RN) motor map development and the rubrospinal tract (RST) projections to the forelimb motor pools, from early postnatal development (3 weeks) through late postnatal development (16 weeks) to adulthood in cats. In particular, they investigate the maturation of both the RN motor map with microstimulation and the RST cervical enlargement projections using anterograde tracers.
Firstly, Williams et al. (2014) meticulously ensure that the microstimulation and tracer injection sites are correctly located in the RN in three ways: 1) they identify the depth profile of antidromic field potentials of RST neurons in response to surface stimulation of the spinal cord at C2; 2) they electrically stimulate the RN to evoke responses from the extensor carpi radialis muscle, to confirm that the amplitude of evoked EMG and the largest antidromic fields correspond to the same depths; 3) finally, by using marking lesions and confirming histologically (post-experiments) that the electrode placements are within the magnocellular part of the RN.

Williams et al. (2014) use microstimulation over RN to determine the efficacy of rubrospinal projections, and evoke contralateral wrist, elbow and shoulder forelimb movements throughout the postnatal development period. They report that the RN map from week 5 onward is characterized by a dorsal-to-ventral and distal-to-proximal somatotopic organization similar to mature RN. However, there is an age-dependent increase in the percentage of sites where stimulation evokes a movement in the forelimb, termed “effective sites” by the authors. Importantly, the RN motor map development found by Williams et al. (2014) starts 3 weeks earlier than the motor map in M1 found by a previous study (Chakrabarty and Martin 2000). In that study they found corresponding age-dependent proximal-to-distal somatotopic organization that does not start to develop until postnatal 7-8 weeks. Nevertheless, from the age of 7-8 weeks onward M1 motor map has a faster rate of development than that of the RN map (Chakrabarty and Martin 2000; Williams et al. 2014), although importantly there is a period of parallel development until adolescence in both of them.
Moreover, Williams et al. (2014) find that the motor representations in RN show a developmental change in the percent of microstimulation sites evoking shoulder, elbow and wrist forelimb joints. Such representation has a dramatic overrepresentation of the wrist (~82%) at postnatal 5-6 weeks compared to the later ages. After 7 weeks, the contribution of each joints in the forelimb map become relatively more homogeneous but interestingly, overall the RN map appears to have a greater representation of the wrist (adult ~50%) compared to the other joints. The authors suggest that the overrepresentation of the wrist at week 5 could assist early forelimb distal control during the precorticospinal phase, i.e. the period before the M1 motor map related to forelimb begins to develop. The change of joint’s contribution after 7 weeks might reflect an interaction with corticospinal use-dependent forelimb motor representation. Indeed, Martin et al. (2005) showed that preventing limb use in cats aged between 14 and 30 weeks resulted in a decreased representation of joints at multijoint sites in M1. Thus, the redistribution of multijoint RN map might assist the refinement of dexterous distal motor skills during the later phase of development.

Subsequently, Williams et al. (2014) inject anterograde tracers into the RN to characterize the contralateral spinal terminations of developing RST, either in the intermediate zone or the motor pool for the forelimb muscles in the ventral horn. This aims to determine how the changes in the organization of RST terminations could be related to the RN motor map development. They quantify varicosities, defined as punctate axonal swellings with a diameter of more than three times the diameter of the nonvaricose axon that are considered putative presynaptic sites, in the intermediate zone and the motor pools. Starting from week 3 there is a richness of RST axons varicosities
throughout the intermediate zone. However contrary to their previous findings in the CST (Li and Martin 2001), the topography of RST axons in the intermediate zone does not change significantly between week 3 and adulthood. Particularly, there is no age-dependent correlation in the density of RST intermediate zone varicosities. The previous study in the CST showed a protracted age-dependent development of the CST segmental axon terminals in the spinal gray matter of the intermediate zone (Li and Martin 2001). In contrast, Williams et al. (2014) find an age-dependent development of RST terminations in the motor pool (ventral horn) that paralleled the RN motor map development, which is in contrast to the CST where there is a age-dependent decrease in axonal terminations and varicosity densities (Li and Martin 2002).

For the first time Williams et al. (2014) provide evidence and suggest that there are two distinct phases of functional maturation of the lateral motor system, a “precorticospinal” phase characterized by a primary role of the RST system to early proximal and distal control of forelimb movement, and a subsequent “cocorticospinal” phase where RST and CST pathways are synergistically important for the development of limb motor skills (Fig. 1). There is evidence supporting the idea that skillful limb movements require refinement of both the CST and RST, given that in maturity both seem to have an important role on movement execution (Martin and Ghez 1988).

One common form of significant childhood motor disability is cerebral palsy (CP), caused by a brain injury around birth, in many instances of the CST resulting in substantial difficulties in motor development, more so in the distal limbs. While it has been found that after CST injury the RST may show some plasticity and provide a neural substrate for motor functions (Takenobu et al. 2014), it is still unclear what is the role of
RST in recovery when the developing CST is damaged. Recently in a kitten model of unilateral spastic CP it has been shown that early intense training during development is critically important for recovery of motor function mediated by neuroplastic changes of the corticospinal system (Friél et al. 2012). In humans with CP, during developmental years, the CST can still undergo changes to contribute to motor skill improvements following intense training such as Constraint-Induced Movement Therapy or Bimanual Training (Gordon et al. 2007), indicating a remarkable neuroplastic mechanism even in the presence of substantial damage. Furthermore, while uninjured CST development is known to be sensitive to experience-dependent training (Bengtsson et al. 2005), it is not known if such training can influence postnatal development of the rubrospinal system in either an uninjured and injured state.

It would be imperative to understand if the protracted “cocorticospinal” phase of RN/RST development, when the refinement of motor skills are being established synergistically with the CST can show facilitatory neuroplastic changes in the event of early damage of the CST. Therefore, the findings by Williams et al. (2014) open promising avenues to further understand the parallel contributions and interactions of RN/RST and CST during the period of postnatal development. This could provide possible translational therapeutic interventions for recovery and promotion of motor function following a perinatal cortical injury, such as cerebral palsy.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).
Author contributions

M.B. and S.D. drafted manuscript; M.B. and S.D. edited and revised manuscript; M.B. and S.D. approved final version of manuscript.

References


Fig. 1. Timelines of postnatal maturation of corticospinal (CST) and reticulospinal (RST) tracts. In the reviewed article, Williams et al. (2014) show that early on, RST development provides rudiments of motor skills prior to the start of CST development (Postnatal week 5-8, precorticospinal phase) and continues in parallel with the CST development (Postnatal week 8-16, cocorticospinal phase). The interaction between the two during the period of co-development might be important for control of limb movement, particularly in case of a perinatal cortical injury such as cerebral palsy.
Perinatal Brain Injury

Forelimb Control

PW5  PW8  PW16
Time (weeks)

CST  RST

Precorticospinal Phase
Cocorticospinal Phase