

The lateral reticular nucleus: a precerebellar centre providing the cerebellum with overview and integration of motor functions at systems level. A new hypothesis

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Abstract The lateral reticular nucleus (LRN) is a major precerebellar centre of mossy fibre information to the cerebellum from the spinal cord that is distinct from the direct spinocerebellar paths. The LRN has traditionally been considered to provide the cerebellum with segregated information from several spinal systems controlling posture, reaching, grasping, locomotion, scratching and respiration. However, results are presented that show extensive convergence on a majority of LRN neurons from spinal systems. We propose a new hypothesis suggesting that the LRN may use extensive convergence from the different input systems to provide overview and integration of linked motor components to the cerebellum. This integrated information is sent in parallel with the segregated information from the individual systems to the cerebellum that finally may compare the activity and make necessary adjustments of various motor behaviours.

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Abbreviations bVFRT, bilateral ventral reflex tract; DF, dorsal funiculus; iFT, ipsilateral forelimb tract; LRN, lateral reticular nucleus; PNs, propriospinal neurons; VSCT, ventral spinocerebellar tract.

Introduction

The lateral reticular nucleus (LRN) is a precerebellar mossy fibre relay of information from the spinal cord, trigeminal afferents, motor cortex, red nucleus and superior

colliculus. Physiological work has described segregated effects in LRN neurons mediated by activation of different peripheral limb nerves, stimulation of labyrinthine and neck receptors, and induction of fictive locomotion and scratching (reviewed by Ito, 1984, and references therein).

Bror Alstermark studied medicine at Göteborg University and completed a MD/D Phil in 1983 on the functional role of propriospinal neurones in the control of forelimb movements, supervised by Anders Lundberg, Department of Physiology, Göteborg, Sweden. In 1992, he became professor in physiology at Umeå University. His research activity focuses on discrete neural circuits controlling reaching, grasping and posture. He is currently addressing questions concerned with internal feedback control to understand how the cerebellum may regulate movements. **Carl-Fredrik Ekerot** studied electrical engineering, computer science and medicine at Lund University and completed a MD/D Phil in 1982 on interactions between the cerebellar climbing fiber and mossy fiber systems under supervision of Olof Oscarsson. Ekerot has worked as research assistant and professor at Lund University and the research aims at understanding the function of the cerebellar neuronal network and afferent and efferent pathways. His recent work focuses on properties and role of climbing fiber induced plasticity in parallel fiber synapses on Purkinje cells and molecular layer interneurons.



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The aim of the present review is to synthesize the available results and to propose a new hypothesis in which the LRN provides the cerebellum with an overview and integration of motor functions at systems level (Fig. 1).

Inputs to the LRN

Spinal pathways. Three distinct spinal systems have been identified physiologically: the bilateral ventral reflex tract (bVFRT), the ipsilateral forelimb tract (iFT) and the C3–C4 propriospinal system. LRN neurons located in the ventral part of the nucleus receive input from the bVFRT, which is characterized by bilateral activation from multimodal afferents in hindlimb and forelimb nerves (Clendenin *et al.* 1974; Ekerot 1990c), and strong activation from the lateral vestibulospinal tract. These

bVFRT neurons are located in lumbar, thoracic and cervical segments, and their axons cross the midline segmentally, ascend in the contralateral ventrolateral funiculus and terminate successively in more ventromedial parts of the LRN, but with extensive overlap.

It has been proposed that the bVFRT pathway may signal information regarding activity in spinal circuits regulating posture during standing, locomotion and scratching (Clendenin *et al.* 1974). It was suggested that the bVFRT neurons are mainly active during the extensor phase, in contrast to the direct ventral spinocerebellar tract (VSCT) neurons, which are active during the flexion phase, suggesting that the two systems signal activity about complementary populations of spinal interneurons controlling rhythmic activity such as scratching (Arshavsky *et al.* 1978a,b). However, fig. 3A in the article by Arshavsky *et al.* (1978a) and fig. 9B by Arshavsky *et al.* (1978b) both show that more than half (15 of 27) of the recorded LRN neurons were active during the flexion phase, and the remaining (12) cells were active during the extensor phase. Thus, it appears that the VSCT system is mainly involved in signalling information during the flexion phase, whereas the bVFRT–LRN system provides information about the entire scratch cycle. This is further corroborated by the finding that during fictive locomotion, many LRN neurons fired during both flexion and extension (Ezure & Tanaka, 1997) whereas VSCT neurons were mainly active during flexion (Fedirchuk *et al.* 2013).

In contrast to the bVFRT input, LRN neurons located in the dorsal region of the nucleus receive input from the iFT, which is characterized by multimodal activation from forelimb afferents restricted to the ipsilateral side (Clendenin *et al.* 1974; Ekerot, 1990b). The iFT neurons are located in the forelimb segments; their axons ascend ipsilaterally in the ventral part of the lateral funiculus and they terminate in the dorsal part of the LRN. It is not known to what extent the iFT neurons are activated by descending pathways, but it has been suggested that some may receive input from the cortico- and rubrospinal tracts (Ekerot, 1990b). The function of the iFT system is not known, but it has been proposed that it may signal information from spinal interneuronal systems involved in the control of the forepaw in digit grasping movements (Ekerot, 1990b).

A third spinal system providing input to the LRN consists of propriospinal neurons (PNs) located mainly in the C3–C4 segments (Alstermark & Lundberg 1992). The C3–C4 PN interneurons mediate disynaptic effects from several major descending systems, including the cortico-, rubro-, reticulo- and tectospinal tracts, to forelimb motoneurons (Illert *et al.* 1977). The PNs have bifurcating axons; one branch descends to motoneurons in the forelimb segments C6–Th1, and the other branch ascends to the LRN and terminates on neurons in the dorsal and

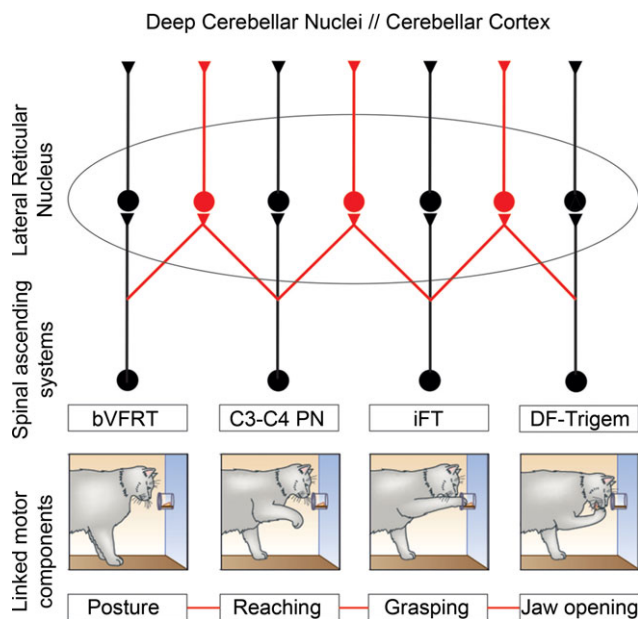


Figure 1. The lateral reticular nucleus (LRN): a precerebellar nucleus that provides cerebellar circuits with an overview and integration of systems-level motor functions

A new physiological hypothesis is proposed for the LRN. The old concept of segregated inputs and outputs, respectively, to and from the LRN is indicated by black lines, and the new hypothesis proposing comparison across systems is shown in red. For simplicity, the behaviour is limited to posture, reaching, grasping and jaw opening, but does include other components such as eye and head movements. It is assumed that these different motor components are closely linked and need to be coordinated. Information about each motor component is signalled by distinct systems to the LRN: the bVFRT, C3–C4 PN, iFT and DF–trigeminal systems. There is extensive convergence between all of these systems, including excitation and inhibition to the LRN, but for clarity, only subsets of the diverging and converging paths are shown. The multiple convergence is simplified schematically by the combined red synapses to LRN neurons. The panels showing behaviour are from fig. 3 in Alstermark and Isa (2012; reproduced with permission of the Annual Review Organisation).

mainly caudal half of the nucleus (Illert & Lundberg, 1978; Alstermark *et al.* 1981). These projections are strictly ipsilateral and the axons are located in the ventral part of the lateral funiculus. Behavioural experiments have shown that the C3–C4 PNs can mediate the descending command for visually guided forelimb reaching in the cat and monkey, and for precision grip with the thumb and index finger in the monkey (Alstermark & Lundberg, 1992; Alstermark & Isa, 2012).

Brainstem pathways. Multimodal input to the magnocellular region of the LRN is also conveyed from interneurons that receive input from forelimb afferents via a pathway in the dorsal funiculus (DF) and from the face via trigeminal afferents (Clendenin *et al.* 1975). It was proposed that these interneurons are located in the lower brainstem, although the exact location remains unknown (Clendenin *et al.* 1975). These authors proposed that the DF–trigeminal system may provide information about forelimb and head movements. Convergence was also found with the cervical component of the bVFRT system. Notably, LRN neurons with input from the cervical bVFRT often received activation from the DF- and trigeminal pathways, whereas such activation was rare among neurons with input from the lumbar bVFRT (Clendenin *et al.* 1975). These findings indicate that integration of posture of the forelimbs with head and face movements is one function of the LRN. LRN neurons are also activated by respiratory centres in the brainstem (Ezure & Tanaka, 1997), by the vestibular system in combination with neck input (Kubin *et al.* 1980) and by the neurons in the oculomotor region (Qvist, 1988).

Projections from motor cortex, red nucleus and superior colliculus. There is a direct projection from the contralateral sensorimotor cortex to LRN neurons (Bruckmoser *et al.* 1969) that is separate from the corticospinal tract (Alstermark & Lundberg, 1992; Matsuyama & Drew, 1997). In addition, neurons in the contralateral red nucleus project to the LRN, but it is not known if these projections are separate from the rubrospinal tract (see references in Ito, 1984). Both the cortico-reticular and the rubro-reticular efferent fibres terminate mainly in the dorsal part of the magnocellular division of the LRN (Brodal *et al.* 1967), and stimulation of these pathways evokes monosynaptic excitation in LRN neurons (Kitai *et al.* 1974). Convergence from the iFT, cervical bVFRT and C3–C4 PN systems is common among LRN neurons receiving monosynaptic cortico-reticular excitation (Alstermark & Ekerot, 1992). Finally, projections to the LRN from the intermediate layers of the contralateral superior colliculus (Kawamura *et al.* 1974) and from the oculomotor region (Qvist, 1988)

have been described, but the regions of termination in the LRN are not known.

Outputs from the LRN

Origin and projection of LRN neurons. The results described above suggest a somatotopical organization of spinal pathways and cortico- and rubral inputs to the LRN. Despite some overlap of terminations, this input organization is to some extent preserved in the LRN output to the cerebellar cortex. LRN neurons with input from lumbar bVFRT terminate more rostrally in the anterior lobe of the cerebellum than those with inputs from thoracic and cervical bVFRT. In contrast, terminations of LRN neurons receiving convergent input from multiple cervical and lumbar systems were larger in the intermediate regions than in the vermis, whereas the opposite was the case for the thoracic systems (Clendenin *et al.* 1974). All of these LRN populations have bilateral terminations in the cerebellum. In contrast, LRN neurons with input from iFT neurons project almost exclusively to the forelimb areas of the ipsilateral intermediate zone and the ipsilateral paramedian lobule (Clendenin *et al.* 1974). The cerebellar cortical termination of LRN neurons with input from the C3–C4 PNs has not been investigated, but because of similar organization within the LRN between the PN and iFT systems, it is tentatively assumed that these LRN neurons have similar cerebellar output organization to those involved with the iFT system (Alstermark & Ekerot, 1992).

In addition to the cerebellar cortical projections, LRN neurons have collateral projections to the deep cerebellar (fastigial, interpositus and dentate) nuclei as well as to the vestibular nuclei (Matsushita & Ikeda, 1976; Dietrich & Walberg, 1979; Ito *et al.* 1982; Parenti *et al.* 1996; Wu *et al.* 1999). Electrophysiological investigations of LRN neurons have shown that they can fire reliably up to frequencies of 1 kHz (Kitai *et al.* 1974), and it was proposed that LRN neurons provide a tonic excitatory drive to the deep cerebellar nuclei upon which the Purkinje cell-mediated inhibition could act to modify specific functions (Kitai *et al.* 1974). Interestingly, single LRN neurons often terminate in several deep cerebellar nuclei as well as in different folia of the cerebellar cortex, indicating a more complex termination pattern than for single olivo-cerebellar fibres (Wu *et al.* 1999). By tracing the projection and termination of single axons, the same authors found no obvious correspondence between the LRN termination within the cerebellar cortex and the well-circumscribed microzones defined by the climbing fibre inputs (Wu *et al.* 1999). However, this view has recently been challenged by using retrograde tracing of LRN neurons projecting to defined microzones (Pijpers *et al.* 2006). These authors found a considerable overlap in mossy and climbing fibre terminations.

Functional role of the LRN; a new hypothesis

From the description above it is clear that neurons in the LRN receive multifaceted inputs with regard to motor control. A traditional view has been to focus each investigation on a single or only a few inputs, which has led to the idea that there are functional subdivisions in the LRN that provide the cerebellum only with segregated information. However, volitional movements require sequential stages of motor control. A schematic sequence of motor acts that must be conjointly controlled in time is shown in Fig. 1. Initially, the standing postural position must be adjusted before a reach can be properly initiated and at the onset of lifting the extensor tonus of the supporting limbs must increase. It is postulated that this control is governed by the bVFRT system. Next, reaching can be initiated by descending commands via the C3–C4 PN system and this control must be intimately integrated with the posture. Likewise, grasping should not be executed until the forepaw has entered the tube containing the food. This control is postulated to be mediated by the iFT system. Finally, before eating, jaw opening needs to be timed to the position of the food held by the digits near the mouth. This motor component is postulated to be controlled by the DF–trigeminal system.

In Fig. 1, it can be seen that the head and neck are lifted upwards during reaching. It is easy to imagine that any uncontrolled change of posture may severely affect the success of subsequent reaching and grasping and, thus, it would be advantageous if the cerebellum received postural information that is weighted and evaluated against reaching and grasping information. Moreover, the cat keeps its visual focus on the target during reaching and therefore compensatory eye movements must occur. Thus, postural adjustments and oculomotor information need to be integrated with reaching during movement.

We propose a new hypothesis that begins with the observations that there is extensive convergence onto single LRN neurons from several different spinal systems. In fact the convergence between three spinal systems, the bVFRT, the C3–C4 propriospinal system and the IF tract, was tested in 42 LRN neurons (Alstermark & Ekerot, 1992). Only 10 (24%) of the LRN cells were innervated by a single spinal system whereas the rest received a convergent input from two systems (62%, $n = 26$) and six (14%) from all three systems. Our hypothesis may equally well be applied for those parts of the LRN involved in the control of rhythmic movements such as locomotion, scratching and respiration, as well as autonomic functions, since there is certainly a need for the cerebellum to obtain integrated information about these functions. For example, it has been suggested that the cerebellum may control homeostatic adjustments of respiratory movements during locomotion (Baker *et al.* 1993).

For simplicity, we limit the description to the four above-mentioned systems, the bVFRT, iFT, C3–C4 PN and DF–trigeminal systems. It has been proposed that individual spinocerebellar neurons, such as the VSCT (Lundberg & Weight, 1971) and dorsal spinocerebellar tract (Hantman & Jessell, 2010), may monitor the activity of a given system by measuring the balance of excitation against inhibition. LRN neurons receive parallel excitatory and inhibitory inputs from the DF–trigeminal, bVFRT, iFT (Ekerot, 1990*a,b,c*) and C3–C4 PN systems (Alstermark & Ekerot, 1992). By using such comparison of excitation and inhibition, the LRN could sample the activity level of each system. After assessment of the net activity, the LRN could then use this convergent information to compare the activity across the different systems. In this way, the LRN may provide an overview of inter-related motor components and signal this integrated information to the deep cerebellar nuclei and cerebellar cortex. This integrated information is sent in parallel with the segregated information from the individual systems to cerebellum that finally may compare the activity and make necessary adjustments of motor behaviour. We also postulate that the LRN may provide the cerebellum with the necessary information to correctly time the different motor components. It is interesting that LRN neurons may convey timing signals that could be used by the cerebellum to keep track of when to start the next motor component (Xu *et al.* 2012).

To test the proposed hypothesis further, it would be desirable to investigate the input patterns to granule cells and deep cerebellar neurons from LRN neurons that receive convergent input from the bVFRT, iFT, C3–C4 PN and DF–trigeminal systems. Future experiments may benefit from new technologies using optogenetic techniques to selectively manipulate the various subpopulations of inputs to the LRN and outputs from the LRN in a behavioural context, as shown in Fig. 1. Also, it would be desirable to use experiments involving multiple and simultaneous recordings of subtypes of LRN neurons during the whole sequence of movements. Understanding the underlying mechanisms operating at a precerebellar level seems important for further analysis on the role of cerebellar control of movements.

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Additional Information

Competing interests

None declared.

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