SUPRASPINAL CONTROL OF AUTOMATIC POSTURAL RESPONSES: WHICH PATHWAY DOES WHAT?

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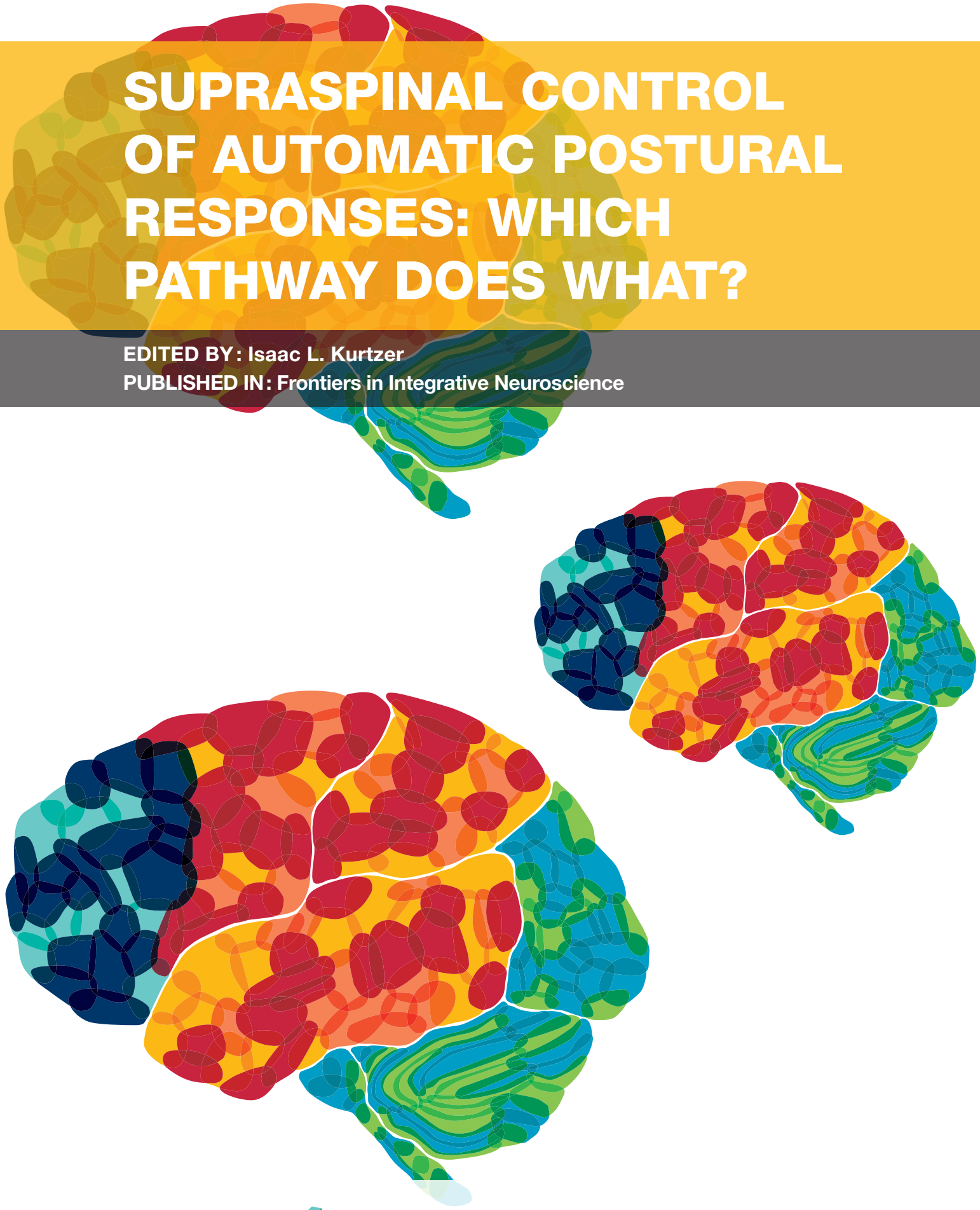

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SUPRASPINAL CONTROL OF AUTOMATIC POSTURAL RESPONSES: WHICH PATHWAY DOES WHAT?

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Contribution of supraspinal systems to generation of automatic postural responses

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Different species maintain a particular body orientation in space due to activity of the closed-loop postural control system. In this review we discuss the role of neurons of descending pathways in operation of this system as revealed in animal models of differing complexity: lower vertebrate (lamprey) and higher vertebrates (rabbit and cat). In the lamprey and quadruped mammals, the role of spinal and supraspinal mechanisms in the control of posture is different. In the lamprey, the system contains one closed-loop mechanism consisting of supraspino-spinal networks. Reticulospinal (RS) neurons play a key role in generation of postural corrections. Due to vestibular input, any deviation from the stabilized body orientation leads to activation of a specific population of RS neurons. Each of the neurons activates a specific motor synergy. Collectively, these neurons evoke the motor output necessary for the postural correction. In contrast to lampreys, postural corrections in quadrupeds are primarily based not on the vestibular input but on the somatosensory input from limb mechanoreceptors. The system contains two closed-loop mechanisms – spinal and spino-supraspinal networks, which supplement each other. Spinal networks receive somatosensory input from the limb signaling postural perturbations, and generate spinal postural limb reflexes. These reflexes are relatively weak, but in intact animals they are enhanced due to both tonic supraspinal drive and phasic supraspinal commands. Recent studies of these supraspinal influences are considered in this review. A hypothesis suggesting common principles of operation of the postural systems stabilizing body orientation in a particular plane in the lamprey and quadrupeds, that is interaction of antagonistic postural reflexes, is discussed.

Keywords: balance control, postural reflexes, reticulospinal neurons, pyramidal tract neurons, rubrospinal neurons, unilateral labyrinthectomy, galvanic vestibular stimulation

INTRODUCTION

Various species from mollusk to man stabilize a particular body orientation in space due to the activity of a feedback postural control system. Any deviation from the desirable body orientation caused by external forces evokes an automatic postural response (corrective movement) aimed at restoration of the initial orientation. Maintenance of a specific body orientation in space (e.g., vertical or dorsal-side-up) is a vital motor function based on inborn neural mechanisms. Numerous studies have been devoted to different aspects of the control of body posture during standing in humans and in some animal models. These studies characterized the motor and EMG patterns of postural reactions, which allowed formulating a number of hypotheses about functional organization of the postural control system (for review see e.g., Horak and Macpherson, 1996; Massion, 1998; Massion et al., 2001; Bouisset and Do, 2008).

During last two decades we have studied the organization and operation of neuronal mechanisms responsible for stabilization of the body orientation in animal models of different complexity – mollusk, lamprey, rabbit, and cat. Comparison of the reactions to similar postural perturbations in evolutionarily remote species revealed some common principles in the organization and operation of their postural mechanisms, as well as some distinctions (Deliagina et al., 2006b). Experiments on simple animal models allow an in depth analysis of the postural neuronal networks, which at present is difficult to perform in higher vertebrates. In this review, we consider mainly the nervous mechanisms responsible for the dorsal-side-up orientation of the animal. Special attention is given to the contribution of supraspinal neuronal mechanisms to the generation of automatic postural responses.

CONTROL OF BODY ORIENTATION IN LAMPREY

POSTURAL BEHAVIOR

The lamprey (Cyclostome) is a lower vertebrate animal. The principal organization of its CNS is similar to that in higher vertebrates (Nieuwenhuys and Ten Donkelaar, 1996). This simple animal model presents a unique opportunity for studies of different neuronal mechanisms, including locomotor (see, e.g., Grillner et al., 1991, 1995) and postural networks, which have been analyzed in considerable detail.

The lamprey has two principal behavioral states – a quiescent state when the animal is attached to the substrate with its sucker mouth, and an active state, when it locomotes. The lamprey is capable of several forms of locomotion (Archambault et al., 2001;

Islam et al., 2006; Islam and Zelenin, 2008). However, it actively stabilizes the body orientation in space only during the main form of locomotion – fast forward swimming. During this locomotion, orientation of the animal in the sagittal (pitch) and transverse (roll) planes is stabilized in relation to the gravity vector by postural control systems driven by vestibular input (Deliagina et al., 1992a,b; Ullén et al., 1995b; Deliagina and Fagerstedt, 2000; Pavlova and Deliagina, 2002). Vestibular-driven mechanisms also contribute to stabilization of the swimming direction in the horizontal (yaw) plane (Karayannidou et al., 2007). Any deviations from the stabilized body orientation are reflected in vestibular signals, which cause corrective motor responses. In the pitch and yaw planes, these corrective responses occur due to the body bending in the corresponding plane (**Figure 1A**, Pitch and Yaw; Ullén et al., 1995a,b). In the roll plane, the corrections occur due to a change in the direction of locomotor body undulations, from the lateral (left–right) to the oblique one (**Figure 1A**, Roll; Zelenin et al., 2003a).

Usually, the lamprey stabilizes its dorsal-side-up and horizontal body orientation in the transverse and sagittal planes, respectively. However, under certain environmental conditions the stabilized orientation can be changed. For example, asymmetrical illumination of eyes causes a roll tilt of the body toward the more illuminated side (referred as "the dorsal light response") and this new orientation in the transverse plane is actively stabilized by the animal (Ullén et al., 1995b).

MAIN COMPONENTS OF POSTURAL CONTROL SYSTEM

Figure 1B shows basic components of the postural system in the lamprey. Vestibular afferents (through the neurons of vestibular nuclei) affect reticulospinal (RS) neurons. The RS tract is the main descending pathway in the lamprey (Bussières, 1994),

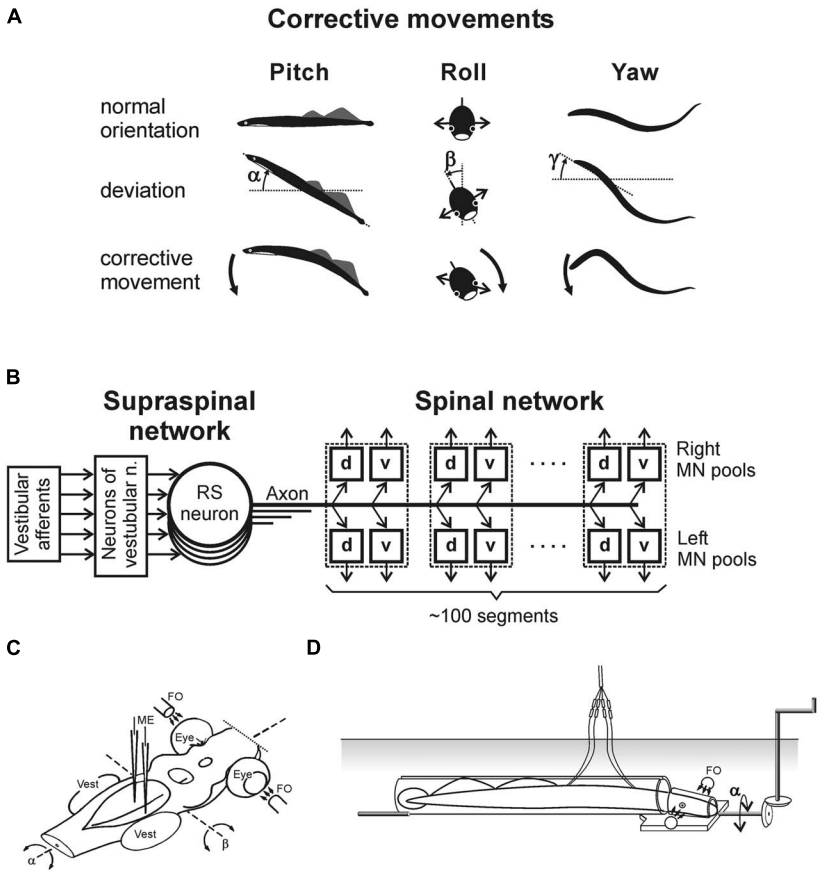

FIGURE 1 | Experiments on the lamprey. (A) During regular swimming, the lamprey stabilizes its orientation in the sagittal (pitch) plane, in the transverse (roll) plane, and in the horizontal (yaw) plane. Deviations from the stabilized orientation in these planes (angles α, β, and γ, respectively) evoke corrective motor responses (large arrows) aimed at restoration of the initial orientation. **(B)** Commands for correcting the orientation are formed on the basis of vestibular information, processed by neurons of vestibular nuclei, and transmitted from the brainstem to the spinal cord by axons of reticulospinal (RS) neurons. Motor output of each segment is generated by four motoneuron (MN) pools controlling the dorsal and ventral parts of a myotome on the two sides (*d* and *v* pools). **(C)** Design for *in vitro* experiments. The brainstem was isolated together with vestibular organs (Vest) and eyes. Vestibular stimulation was performed by rotating the preparation around the longitudinal (α) or transverse (β) axes. Visual stimulation was performed by fiber optic (FO). RS neurons (or vestibular afferents) were recorded by microelectrodes (ME). **(D)** Design for *in vivo* experiments. The lamprey was positioned in a narrow tube preventing body movements. Activity of reticulospinal neurons was recorded from their axons in the spinal cord by means of chronically implanted electrodes. Vestibular stimulation was performed by rotation of the setup in the roll plane. Similar setups were used to rotate the animal in the pitch and yaw planes.

which transmits all commands from the brainstem to the spinal cord, including commands for postural corrections. The majority of RS neurons receiving a specific vestibular input (that is responding to rotation in a definite plane) are active only during fast forward swimming, when the animal actively stabilizes the body orientation in space (Zelenin, 2011). Vestibulospinal pathways in the lamprey are poorly developed, contain small number of fibers, terminate in the rostral spinal segments (Bussières, 1994), and produce very weak effects on the motor output (Zelenin et al., 2003b).

The spinal network is responsible for the transformation of RS commands into the motor pattern of postural corrections. This network includes interneurons, as well as four motoneuron (MN) pools in each segment (**Figure 1B**) that innervate the dorsal and ventral parts of a myotome on the two sides. The spinal mechanisms transforming RS commands into the motor pattern of postural corrections are rather complex. For example, signals from intraspinal stretch receptor neurons monitoring the lamprey's body configuration can modify the spinal networks decoding these commands. Thus, the effects of RS commands may depend on the phase and amplitude of locomotor body undulations (Hsu et al., 2013).

SENSORY INPUTS TO NEURONS OF POSTURAL NETWORKS

To analyse operation of the postural networks, the following questions were addressed: (i) how individual vestibular afferents respond to a deviation of the body from the desirable orientation, (ii) how individual RS neurons respond to this vestibular input, (iii) how postural commands transmitted by individual neurons are decoded in the spinal cord, which results in the generation of postural corrections. To answer these questions, a number of animal preparations and experimental techniques have been developed (**Figures 1C,D** and **3A**; Deliagina et al., 1992a,b, 2000a; Orlovsky et al., 1992; Deliagina and Fagerstedt, 2000; Pavlova and Deliagina, 2002; Karayannidou et al., 2007).

As with other vertebrates, the lamprey has canal and otolith afferents (Lowenstein et al., 1968). The canal afferents respond to a change in orientation with a high-frequency burst (Deliagina et al., 1992b). In the transverse plane, they respond to rotation toward ipsi-side down. Pitch tilt revealed two groups of canal afferents responding to rotation toward either nose-up or nose-down. The otolith afferents respond both to a change of position and to a maintained new position. These afferents were classified in several groups according to their zones of sensitivity (**Figures 2A,B**). For roll, the largest group has maximal sensitivity around a 90° tilt to the ipsilateral side (**Figure 2A**). For pitch, there are groups responding with maximal sensitivity at 90° nose-down and 90° nose-up (**Figure 2B**). In addition, a group responding at up-side-down position (180°) was revealed (**Figures 2A,B**). A minority of afferents are active during normal (dorsal-side-up) orientation and during contralateral roll.

Most RS neurons respond to the contralateral roll tilt and have both dynamic and static response components. The zones of spatial sensitivity differ in different reticular nuclei; together they cover the whole range of possible inclinations in the transverse plane (**Figure 2C**). The roll-sensitive RS neurons are driven mainly by excitatory contralateral vestibular input (Deliagina and Pavlova, 2002). They also receive weak input from the ipsilateral labyrinth, which supplements the contralateral one (Deliagina and Pavlova, 2002). In addition, they receive excitatory and inhibitory inputs from the ipsilateral and contralateral eye, respectively, which affect the magnitude of their response to roll (Deliagina et al., 1993; Deliagina and Fagerstedt, 2000).

In the pitch plane, most RS neurons respond either to the nose-up pitch tilt, or to the nose-down pitch tilt (Deliagina et al., 1992a; Orlovsky et al., 1992; Pavlova and Deliagina, 2002). The neurons of these two populations reside in all reticular nuclei, but in different proportions (**Figure 2D**). The RS neurons responding to nose-up pitch tilt are driven mainly by an excitatory input from the contralateral labyrinth. By contrast, nose-down RS neurons receive excitatory inputs from both labyrinths (Pavlova and Deliagina, 2003). About a quarter of RS neurons respond to both roll and pitch tilts suggesting that these neurons are partly shared by the pitch and roll control systems (Pavlova and Deliagina, 2003; Zelenin et al., 2007).

Finally, in the yaw plane, most RS neurons respond to contralateral turn due to an excitatory input mainly from the contralateral labyrinth (Karayannidou et al., 2007).

ENCODING AND DECODING OF RS POSTURAL COMMANDS

To characterize the sensory-motor transformation in postural neuronal networks, a special technique was developed to assess both vestibular inputs and motor effects of individual RS neurons (**Figure 3**; Zelenin et al., 2001, 2007).

The motor effects of individual neurons were qualitatively the same along the whole extent of the axon (Zelenin et al., 2001), and thus could be characterized by a combination of influences on the four MN pools in any segment (muscle synergy; **Figure 1B**).

The majority (68%) of RS neurons with specific vestibular inputs and specific motor effects respond to rotation only in one of the three main planes, as the neuron in **Figure 3B**. This neuron fires spikes in response to contralateral roll tilts, and does not respond to rotation in the yaw and pitch planes. Thus, it belongs to the roll control system. Motor effects of this neuron are shown in **Figure 3C**. They include activation of the MN pools projecting to the ipsi-ventral and contra-dorsal myotomes, and inhibition of those projecting to the ipsi-dorsal and contra-ventral myotomes. In the swimming lamprey, this pattern would lead to a change in the direction of locomotor body undulations, from lateral to oblique, resulting in a roll torque directed opposite to the initial turn (**Figure 1A**, Roll; Zelenin et al., 2007). In the majority of RS neurons there is a strong correlation between vestibular inputs and motor effects, as in the neuron shown in **Figure 3B** (Zelenin et al., 2007). Most often, the neuron produced a motor pattern causing a torque, which would oppose the initial rotation that activated the neuron.

About quarter of RS neurons responded to rotation in more than one plane (as the neuron shown in **Figure 3D**). This neuron responded to left (contralateral) roll tilts and to nose-up pitch tilts but did not respond to rotation in the yaw plane. The neuron excited the ipsilateral ventral MNs and inhibited the ipsilateral dorsal MNs (**Figure 3E**), thus contributing to postural corrections caused by the left roll tilt (that is activation of the right ventral and left dorsal myotomes, and inhibition of right dorsal and left ventral

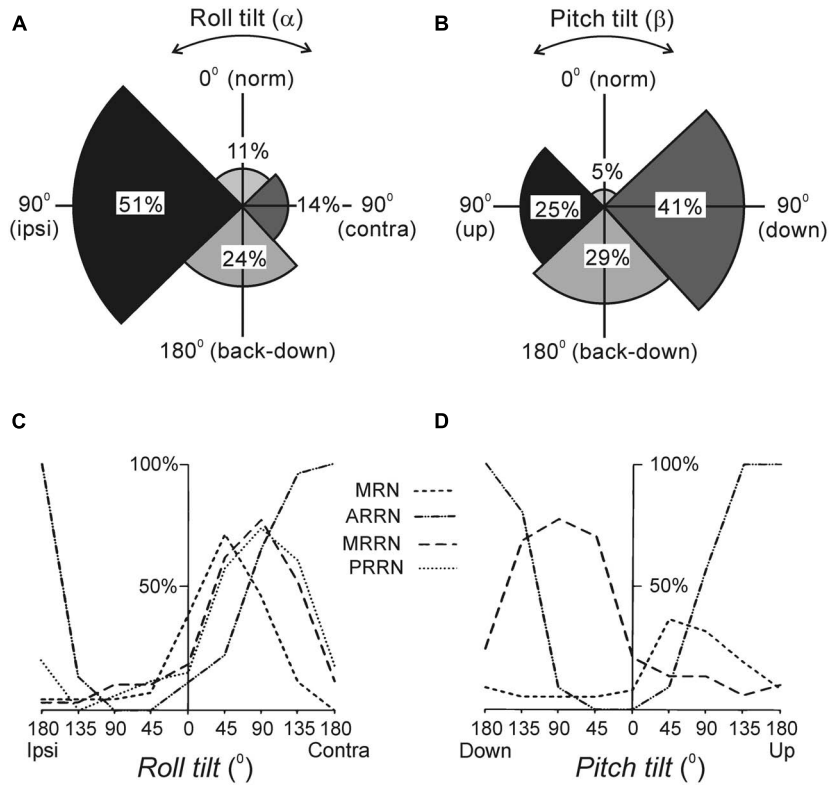

FIGURE 2 | Reactions of supraspinal network to rotation in the transverse (roll) and sagittal (pitch) planes. (A,B) Proportion of otolith afferents with different zones of spatial sensitivity in the roll **(A)** and pitch **(B)** planes. Angular zones of sensitivity and percentage of afferents in each zone are indicated. **(C,D)** Summary diagrams of responses to roll and pitch in different reticular nuclei. The relative number of neurons active at different positions is presented as a function of roll **(C)** and pitch **(D)**. For simplicity, neither the group of MRRN neurons sensitive to nose-up pitch tilt nor the groups of PRRN neurons with zones of sensitivity distributed over the whole space are shown in **(D)**. Designations of reticular nuclei: PRRN, posterior rhombencephalic; MRRN, middle rhombencephalic; ARRN, anterior rhombencephalic; MRN, mesencephalic.

myotomes), as well as to the nose-up pitch tilt (that is activation of both ventral myotomes and inhibition of both dorsal myotomes). Most of the neurons responding to rotation in more than one plane produced the motor pattern contributing to postural corrections in the corresponding planes.

Thus, individual RS neurons transform sensory information about the body orientation into motor commands that produce corrections of orientation. The closed-loop microcircuits formed by individual RS neurons belonging to a particular (roll, pitch, or yaw) postural system operate in parallel to generate the resulting motor responses that counteract the postural disturbances (**Figure 4**).

These results support a point of view that each type of postural corrections in humans and quadrupeds is based on a combination of specific muscle synergies (for review, see Ting, 2007). One can suggest that, similar to the lamprey, in other vertebrates these synergies are also activated by specific descending neurons.

FUNCTIONAL MODEL OF POSTURAL SYSTEM

The aforementioned data allowed to formulate conceptual models of the postural systems responsible for stabilization of the body orientation in the roll, pitch, and yaw planes (Deliagina and Orlovsky, 2002; see also Deliagina and Fagerstedt, 2000; Zelenin et al., 2001; Pavlova and Deliagina, 2002; Karayannidou et al., 2007; Zelenin et al., 2007).

The functional model of the roll control system is shown in **Figure 5A**. The key elements of the model are two subgroups of RS neurons, the left (RS-L), and the right (RS-R). Due to vestibular inputs, the activity of RS neurons is orientation-dependent with its peak at approximately 90° of contralateral roll tilt (**Figure 5B**). The two subgroups also receive an excitatory input from the ipsilateral eye and an inhibitory input from the contralateral eye. Each of the subgroups, via spinal mechanisms, elicits ipsilateral rotation of the lamprey (**Figures 5A,B**, the white and black thick arrows). The system stabilizes an orientation with equal activities of RS-L and RS-R. At normal environmental conditions this occurs at the dorsal-side-up orientation of the body in the roll plane (equilibrium point in **Figure 5B**). The stabilized orientation can be changed by adding an asymmetrical bias to RS-L and RS-R activities, for example, through asymmetrical visual inputs to RS neurons. Illumination of an eye causes additional excitation of the ipsilateral RS neurons and inhibition of the contralateral ones; this will result in a shift of the equilibrium point of the system toward the illuminated eye and stabilization of the new tilted orientation (**Figure 5C**). These predicted modifications in RS-L

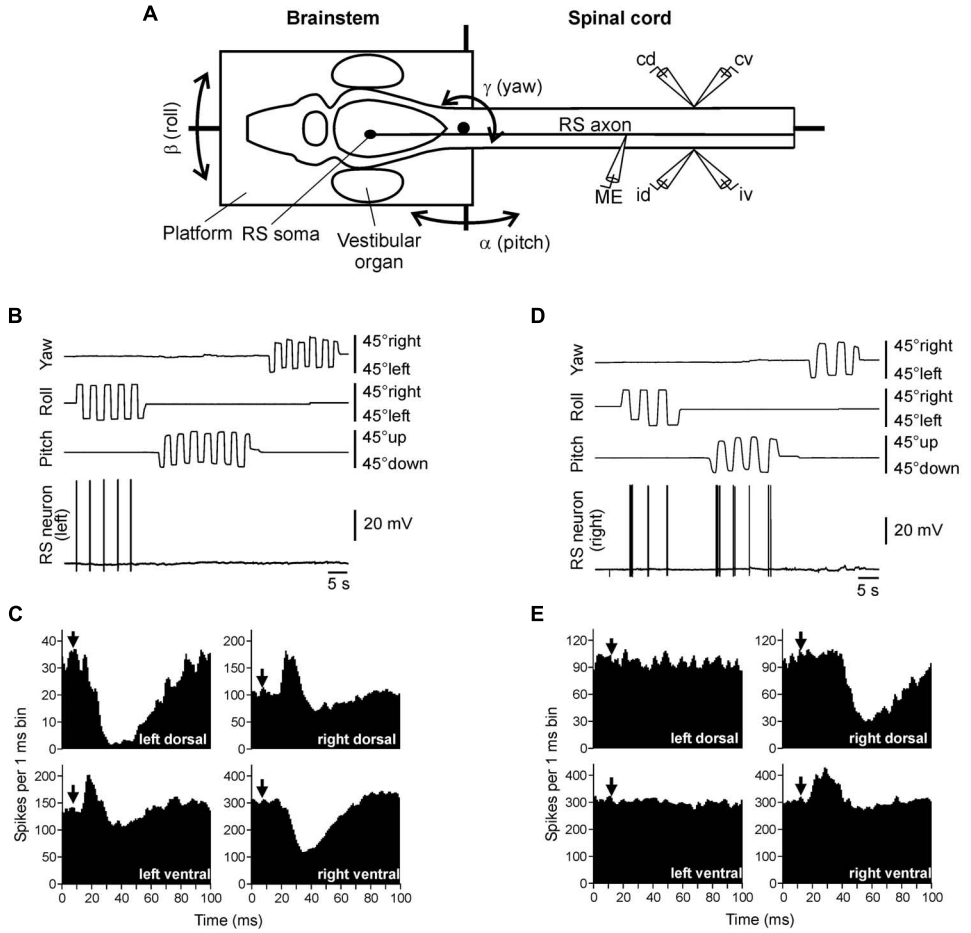

FIGURE 3 | Vestibular inputs and motor outputs of individual RS neurons. (A) The brainstem – spinal cord preparation with vestibular organs was used for studying vestibular inputs to individual RS neurons and their motor effects. The preparation was positioned in a chamber and perfused with Ringer solution. The brainstem with vestibular organs could be rotated around three axes: transverse (pitch), longitudinal (roll), and vertical (yaw). D-glutamate was applied to the spinal cord to elicit fictive locomotion. Individual neurons were recorded from their axons in the spinal cord. To stimulate a neuron, positive current pulses were passed through the recording intracellular microelectrode (ME). Activity of MNs was recorded bilaterally in the segment 30 by suction electrodes, from the dorsal and ventral branches of a ventral root (*id*, ipsilateral dorsal branch; *iv*, ipsilateral ventral; *cd*, contralateral dorsal; *cv*, contralateral ventral). **(B,C)** An RS neuron that contributed only to stabilization of the body orientation in the transverse plane. The neuron fired spikes in response to right (contralateral) roll tilts only **(B)**. The neuron evoked excitation in the left (ipsilateral) ventral and right (contralateral) dorsal branches of the ventral roots and inhibition in the right ventral and left dorsal branches **(C)**. **(D,E)** An RS neuron that contributed to stabilization of the body orientation in both transverse and sagittal planes. The neuron fired spikes in response to left (contralateral) roll tilts and nose-up pitch tilts **(D)**. The neuron evoked excitation in the ipsilateral ventral branch of the ventral root and inhibition in the ipsilateral dorsal branch **(E)**. In panels **(C,E)**, a post-RS-spike histogram was generated for the spikes of motoneurons recorded in the dorsal and ventral branches of the left and right ventral roots. The moment of RS spike occurrence at the stimulated site was taken as the origin of the time axis in the histogram. Arrows indicate the time of arrival of the RS spike to segment 30 (where motor output was monitored). Typically, responses to several thousands of RS spikes were used for generation of a histogram.

and RS-R activities caused by asymmetrical illumination of eyes were found experimentally (Deliagina and Fagerstedt, 2000). This explains the neural mechanism of the dorsal light response, that is, a roll tilt toward the illuminated eye (**Figure 5C**, inset; Deliagina et al., 1992a, 1993; Ullén et al., 1996).

The model can also explain motor deficits in the lamprey caused by the unilateral labyrinthectomy (UL). It is known that UL severely impairs locomotion and postural control in vertebrates. The main deficit caused by UL in the lamprey is rolling, i.e., continuous rotation of the swimming animal around the longitudinal body axis (Deliagina, 1995, 1997a). As shown in **Figure 5D** by a black interrupted line, due to abolition of the excitatory input from the removed right labyrinth, RS-L neurons become inactivated. As a result, the RS-R and RS-L curves do not intersect, the equilibrium point is absent, and RS-R neurons cause continuous rolling to the right. The rolling can be stopped by rising RS-L activity (red interrupted line) so that the two activity curves intersect again. Activation of RS-L neurons can be done either by asymmetrical visual input (illumination of the left eye), or by continuous electrical stimulation of the right vestibular or left optic nerve (Deliagina, 1997b). The changes in activity of RS-L and RS-R neurons predicted by the model were later demonstrated

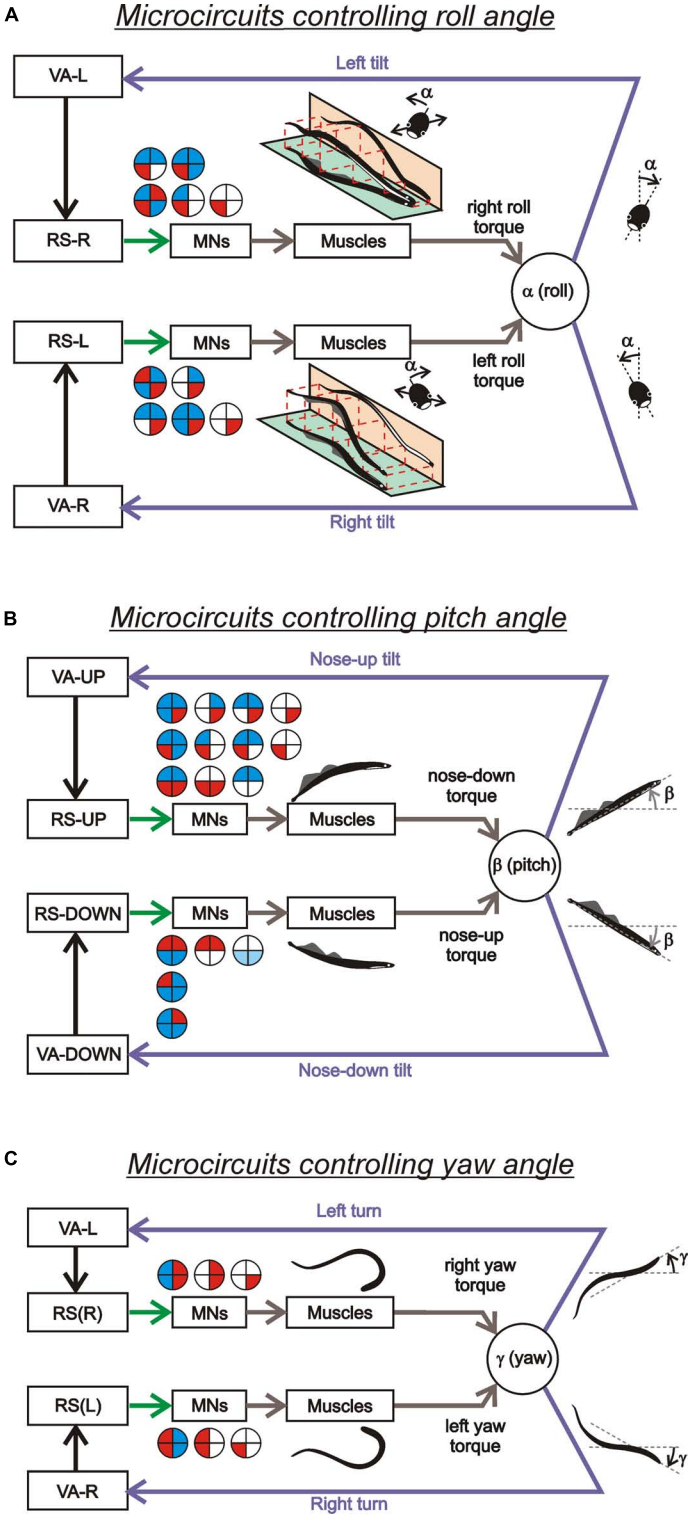

FIGURE 4 | Sensory-motor transformation in neuronal networks underlying operation of the roll, pitch, and yaw control systems. Relationships between vestibular responses and motor effects in individual RS neurons of the roll **(A)**, pitch **(B)**, and yaw **(C)** control systems. The neurons were divided into groups [RS-L, RS-R, RS-UP, RS-DOWN, RS(L), and RS(R)] according to their inputs (vestibular responses). For each group, the patterns of motor effects in its neurons are shown as circle diagrams, with the quadrants representing the motoneuronal pools (MNs) projecting to the corresponding parts of the myotomes. Different colors designate the type of effect (excitation – red, inhibition – blue, no effect – white). Each RS neuron evoked a motor pattern (or a part of the pattern) opposing the initial turn that activated the neuron.

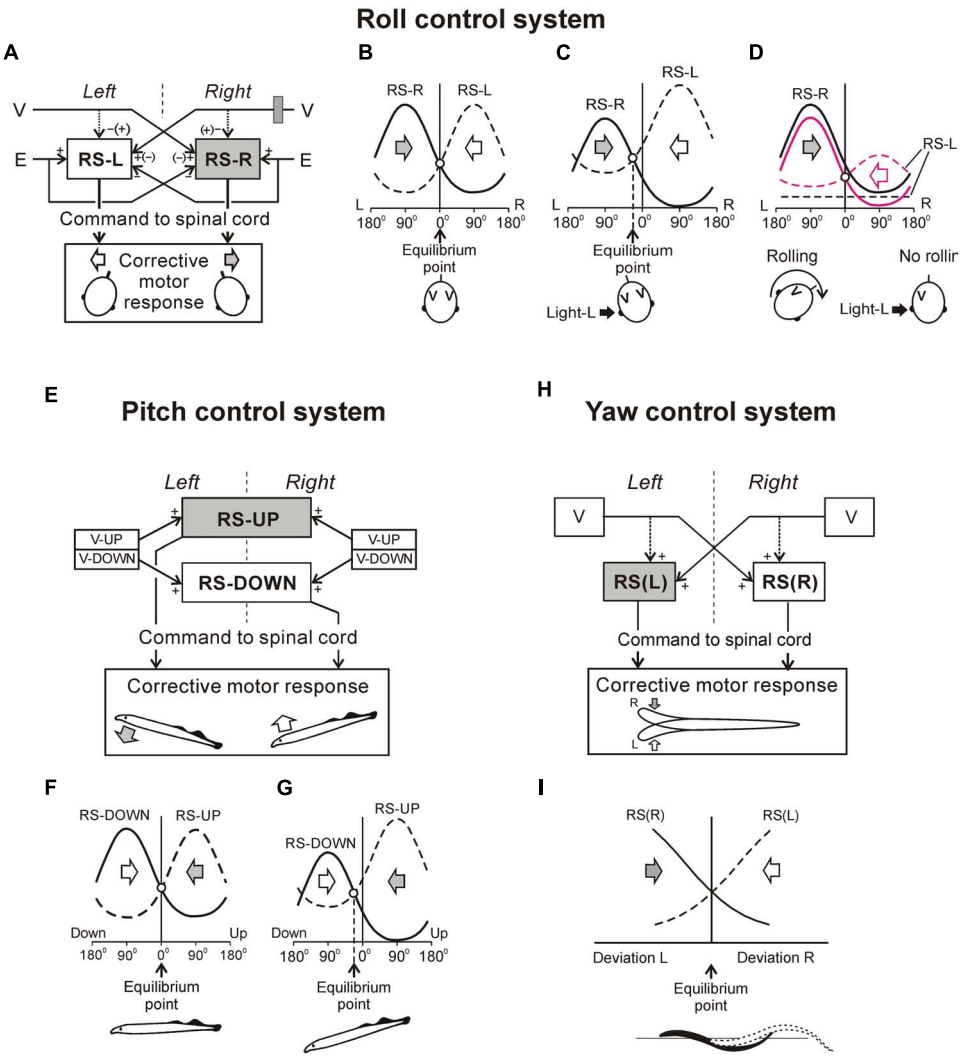

FIGURE 5 | Conceptual models of systems controlling orientation in different planes. (A–D) Roll control system. **(A)** Two groups of RS neurons (RS-L and RS-R) receive inputs from the labyrinths (V) and eyes (E); they affect the spinal networks to evoke rolling of the lamprey. The signs (+ and –) indicate the major effects on RS neurons produced by sensory inputs, the signs in brackets – the minor effects. **(B)** Operation of the system when driven only by vestibular inputs. The curves represent activity in RS-R and RS-L as a function of roll angle (L, left tilt; R, right tilt). Vestibular input causes activation of RS-R and RS-L with the contralateral tilt. Direction of rolling caused by RS-R and RS-L is indicated by the gray and white arrows, respectively. The system has an equilibrium point at 0° (dorsal-side-up orientation). **(C)** Operation of the system when the left eye is illuminated. This visual input (a black arrow; Light-L) causes a shift of the equilibrium point to the left and the corresponding tilt of the animal. **(D)** Effect of the right unilateral labyrinthectomy (indicated by gray rectangle in **A**). The RS activity after the right labyrinthectomy is shown by black solid and interrupted lines. The system has no equilibrium point and the animal continuously rolls to the right. Rolling could be abolished by means of left eye illumination causing activation of RS-L and some inactivation of the RS-R (shown by red interrupted and solid lines, respectively) resulting in re-creation of the equilibrium point. **(E–G)** Pitch control system. **(E)** Two groups of RS neurons, RS-UP and RS-DOWN, receive excitatory inputs from vestibular afferents activated by nose-up (V-UP) and nose-down (V-DOWN) pitch tilt, respectively. Each of the RS-UP and RS-DOWN groups sends a command to the spinal cord causing downward and upward turning of the lamprey, respectively, (gray and white arrows). **(F)** Operation of the system during horizontal swimming. Curves represent the activity of RS-UP and RS-DOWN and their motor effects as a function of the pitch angle. Vestibular input causes activation of the groups with upward and downward tilt, respectively. Direction of turning caused by RS-UP and RS-DOWN is indicated by gray and white arrows, respectively. System has an equilibrium point at 0° (horizontal orientation). **(G)** Operation of the system under high water temperature (the activity of RS-UP increased relative to that of RS-DOWN). Equilibrium point is displaced toward the down pitch angles. Insets in **(F,G)** show the stabilized body orientation. **(H,I)** Yaw control system. **(H)** Two groups of RS neurons, RS(R) and RS(L), are driven by vestibular afferents from the left and right vestibular organs (V). As a result of these inputs, RS-R and RS-L respond to the left and right yaw turn, respectively. RS-R and RS-L affect the spinal network and cause right and left corrective lateral turn of the lamprey, respectively, (gray and white arrows). Solid lines indicate the major effects on RS neurons produced by vestibular organs; interrupted lines indicate the minor effects. **(I)** Operation of the system during swimming. Two curves represent the activity of RS-R and RS-L groups caused by a dynamic deviation of the head movement from the rectilinear one. Motor effect of each RS group is proportional to its activity. Direction of turning caused by RS-R and RS-L is indicated by the gray and white arrows, respectively. System has an equilibrium point where the effects of RS-R and RS-L are equal to each other.

experimentally (Deliagina and Pavlova, 2002). One of the methods for restoration of equilibrium control after UL (electrical stimulation of the stump of the transected vestibular nerve) developed for the lamprey was successfully tested on the rat (Deliagina et al., 1997), suggesting a similarity of the roll control mechanisms in these evolutionary remote species.

The validity of the functional model of the roll control system under dynamic close-to-normal conditions was tested in experiments with a neuro-mechanical model (Zelenin et al., 2000). The lamprey's body was attached to a platform, orientation of which was controlled by RS-L and RS-R neurons recorded by implanted electrodes. The system was able to maintain the dorsal-side-up body orientation, as well as to reproduce the effects of UL, of asymmetrical illumination of eyes, etc.

A functional model of the pitch control system is shown in **Figures 5E–G** (Pavlova and Deliagina, 2002). Two antagonistic subgroups of RS neurons, RS-UP and RS-DOWN, are driven by vestibular afferents responding to the nose-up pitch tilt (V-UP) and nose-down pitch tilt (V-DOWN), respectively. Due to these vestibular inputs, the activity of RS-UP and RS-DOWN and their motor effects are orientation-dependent (**Figure 5F**). The RS-UP subgroup causes a downward turn of the lamprey, whereas RS-DOWN causes an upward turn (gray and white arrows in **Figures 5E–G**). The system stabilizes the orientation with equal activities of the RS-UP and RS-DOWN groups. Normally this occurs at the zero pitch angle (the horizontal orientation of the body in the pitch plane, equilibrium point in **Figure 5F**). The stabilized orientation can be changed by adding an asymmetrical bias to RS-UP and RS-DOWN activities. A factor, which presumably causes a downward turn of the animal (higher temperature), affects the vestibular responses in RS-UP and RS-DOWN differently (Pavlova and Deliagina, 2002). This results in an increase in the ratio of RS-UP activity to RS-DOWN activity. Because of the increase in the UP/DOWN ratio, an intersection of the two activity curves is shifted from 0° toward the downward tilt angles (**Figure 5G**). This new pitch angle (equilibrium point) is stabilized by the pitch control system.

Figures 5H,I presents a conceptual model of the yaw control system (Karayannidou et al., 2007). Two subgroups of RS neurons (RS-L and RS-R) are driven by vestibular inputs mainly from the contralateral labyrinth (**Figure 5H**), so that they are activated with contralateral yaw turn (**Figure 5I**). When activated, RS-L and RS-R subgroups evoke a corrective yaw turn, that is, rotation opposite to the initial turn. If, for example, an external force turns the lamprey to the left, the RS-R subgroup is activated by vestibular input and elicits a corrective turn of the animal to the right, resulting in restoration of the initial orientation in the yaw plane. Thus the yaw control system counteracts any deviations from the rectilinear swimming caused by external factors.

MAINTENANCE OF LATERAL STABILITY DURING STANDING IN QUADRUPEDS

Maintenance of lateral stability during standing and locomotion is an important function of the postural system in terrestrial quadrupeds. In this section we consider the neural mechanisms responsible for stabilization of the dorsal-side-up body orientation in the rabbit and cat during standing. We will then compare these mechanisms with the roll control system in the lamprey considered above.

Nervous mechanisms responsible for lateral stability in quadrupeds during locomotion (Matsuyama and Drew, 2000; Karayannidou et al., 2009a; Musienko et al., 2014), or during voluntary movements (Schepens et al., 2008; Yakovenko et al., 2011; Cullen, 2012) are out of the scope of this review.

POSTURAL REACTIONS ENSURING LATERAL STABILITY IN QUADRUPEDS

In standing animals, a lateral tilt of the support surface causes a lateral body sway and evokes a compensatory postural reaction – extension of the limbs on the side moving down and flexion of the limbs on the opposite side. These limb reactions reduce the lateral body sway and move the dorso-ventral trunk axis toward the vertical (**Figures 6A,B**; Deliagina et al., 2000b, 2006a; Beloozerova et al., 2003a). These limb movements are caused by an increase in the limb extensor activity on the side moving down and its decrease in the opposite limb (**Figure 6C**). The somatosensory inputs from the limbs play a major role for elicitation of the postural reactions (Deliagina et al., 2000b; Beloozerova et al., 2003a), except for the case of very high tilt velocity (Macpherson et al., 2007). Usually the system for trunk stabilization operates as a unit, but under certain environmental conditions it dissociates into two relatively independent sub-systems responsible for stabilization of the anterior and posterior parts of the trunk, respectively, (**Figure 6D**). They are driven by somatosensory inputs from the corresponding limbs (Beloozerova et al., 2003a; Deliagina et al., 2006a). Coordination between these sub-systems is primarily based on influences of the anterior sub-system on the posterior one (Deliagina et al., 2006a). It was demonstrated that each subsystem contains two mechanisms – limb controllers for the right and left limbs, generating a part of the corrective limb movement in response to sensory input from the same limb; another part is formed on the basis of sensory influences from the contralateral limb (Deliagina et al., 2006a). Such a functional organization is similar to that of the locomotor system in quadrupeds; it was suggested that a control system consisting of semi-autonomous subsystems better adapts to complicated environmental conditions (Orlovsky et al., 1999).

Besides postural reactions to lateral tilts, reactions to some other perturbations of balance in the standing cat were investigated, including the reaction to lateral translation of the supporting platform (Macpherson, 1988a,b), to lateral push (Karayannidou et al., 2009a), and to drop of support under one of the limbs (Dufossé et al., 1982; Stapley and Drew, 2009). All these perturbations affect balance in the transverse plane, but it is rapidly compensated due to postural reactions caused by specific muscle synergies. As in the tilt task, these reactions are mainly due to somatosensory input from the limbs. It was reported (Honeycutt et al., 2007, 2008) that input from Group I and II muscle spindle afferents is critically important for directionally appropriate muscle activation in response to horizontal translation of one limb. Thus, in the translation task, the functional organization of the system seems to be similar to that in the tilt task, in which a considerable part of the corrective movement of the

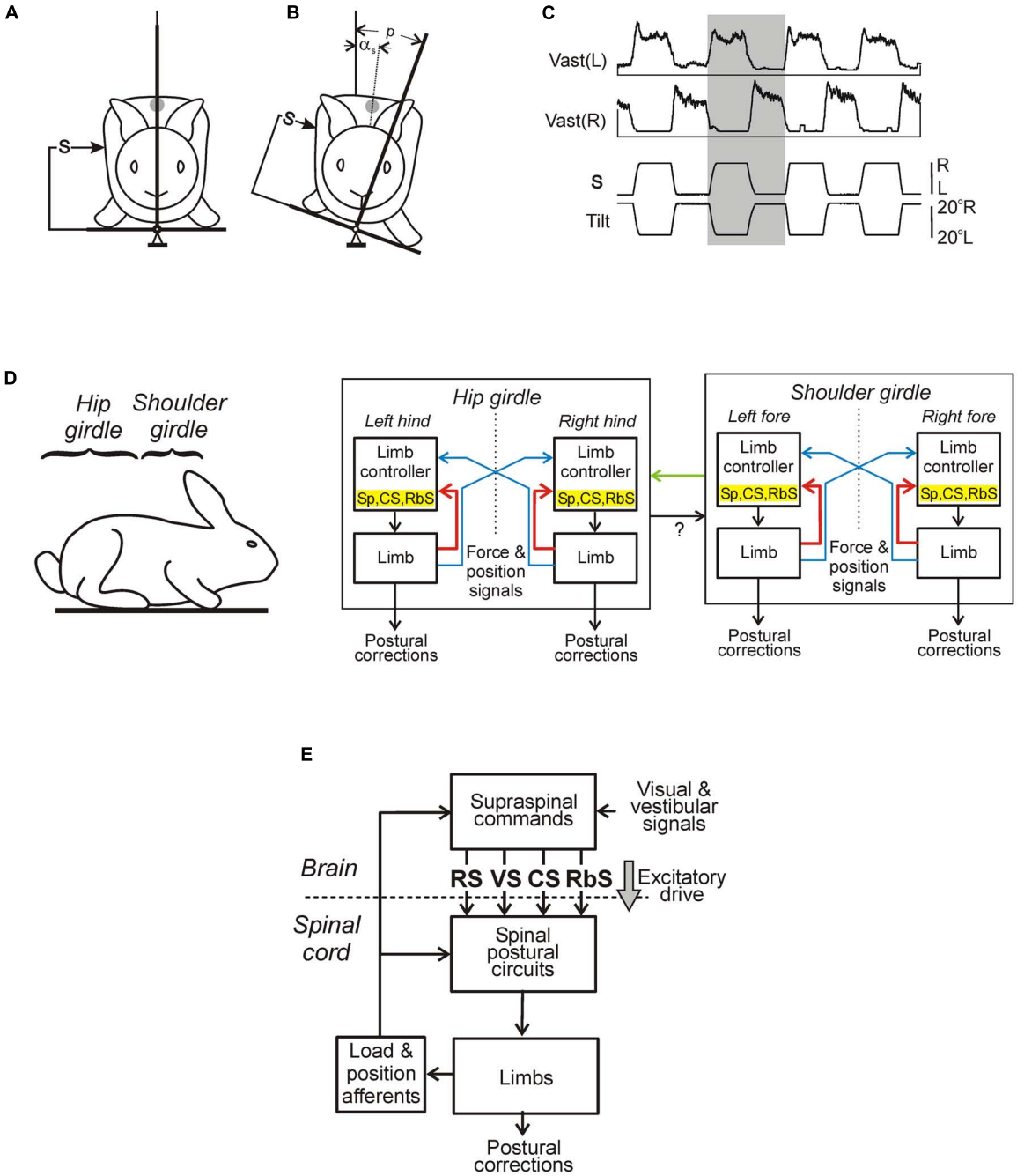

FIGURE 6 | Maintenance of body orientation in the transverse plane in the standing rabbit. (A,B) Experimental design for testing postural responses to lateral tilts of the support surface. The platform tilt (p), the trunk tilt after execution of postural correction (α_S), as well as the position of mechanical sensor (S) measuring the lateral displacement of the trunk in relation to the platform (the trunk corrective movement) are indicated. **(C)** Motor and EMG responses to trapezoidal tilts. Vast(L) and Vast(R) are left and right m. vastus lateralis, respectively. **(D)** Functional model of the postural system stabilizing the trunk orientation in the transverse plane. Lateral stability of the anterior and posterior parts of the body (shoulder and hip girdles) is maintained by two relatively independent sub-systems. Each sub-system contains two controllers (for the right and left limbs) generating a part of corrective limb movement in response to sensory input from the same limb (red lines), spinal postural limb reflexes (Sp), corticospinal (CS), and rubrospinal (RbS) neurons are parts of this mechanism. Another part of corrective limb movement is produced in response to influences from the contralateral limb (blue lines). Coordination between these subsystems is primarily based on influences of the anterior sub-system on the posterior one (green lines). **(E)** Main components of the postural system in quadrupeds. Two closed-loop mechanisms participate in the postural control. Spinal circuits generate postural limb reflexes, and their effects are added to the effects of supraspinal commands, which are generated on the basis of sensory information, and transmitted by the major descending tracts reticulospinal (RS), vestibulospinal (VS), corticospinal (CS), and rubrospinal (RbS). A gray arrow indicates the tonic supraspinal drive that activates the spinal postural circuits.

limb is generated in response to sensory input from the same limb (**Figure 6D**).

In humans, postural reactions to different perturbations (including lateral tilts and lateral translations of support) have been characterized in a number of studies (e.g., Henry et al., 1998; Carpenter et al., 1999). These data show that the reactions are due to the feedback mechanisms driven, to a large extent, by the somatosensory input from the limbs, similar to quadrupeds. However, in contrast to quadrupeds, vestibular input significantly contributes to their generation (Carpenter et al., 2001).

MAIN COMPONENTS OF POSTURAL CONTROL SYSTEM

The main components of the sub-systems maintaining the dorsal-side-up orientation of the trunk are shown in **Figure 6E**. Somatosensory information from the limbs affects the spinal networks directly; it is also sent to the brain where it contributes to formation of supraspinal postural commands transmitted to the spinal cord through different descending pathways. The fact that the premammillary decerebrated rabbit generates postural corrections in response to lateral tilts of the support surface (Musienko et al., 2008) suggests that basic postural networks reside in the brainstem, cerebellum, and spinal cord, and the forebrain contributions are not crucial. However, the value of these corrections is reduced, indicating that input from the forebrain increases excitability of the basic postural networks. An essential part of limb reactions to tilts is postural limb reflexes (PLRs) driven by stretch and load receptors of the limbs; they were studied in the decerebrate rabbit (**Figure 7**; Musienko et al., 2010; Hsu et al., 2012). The EMG pattern of PLRs can be evoked in acute spinal rabbits subjected to the epidural electrical stimulation of the spinal cord (Musienko et al., 2010). This finding suggests that the spinal cord contains the networks generating PLRs, and in intact animals they are activated by the tonic supraspinal drive from the posture-related brain structures (such as the ventral tegmental field and mesencephalic locomotor region; Musienko et al., 2008). However, spinal PLRs are very weak (Mori, 1987; Musienko et al., 2010), suggesting a crucial role of phasic supraspinal commands in the generation of postural corrections.

The conclusion about a crucial role of the brainstem-cerebellum-spinal mechanisms for lateral stability was supported by Honeycutt and colleagues (Honeycutt et al., 2009; Honeycutt and Nichols, 2010) who demonstrated the persistence of essential features of postural reactions to support translation in decerebrate cats.

There are some indirect evidences suggesting that in humans, cortex does not contribute to triggering the initial (short-latency) phase of postural responses to external perturbations (Dietz et al., 1984, 1985; Quintern et al., 1985; Ackermann et al., 1990, 1991; Berger et al., 1990). Thus, it seems likely that in humans (as in terrestrial quadrupeds) the brainstem–cerebellum–spinal cord mechanisms are responsible for the initiation of postural reactions.

Chronic spinal cats can be trained to stand and produce postural reactions to support translation (Fung and Macpherson, 1999). However, the underlying muscle synergies are distorted, the response latencies are longer than normal, and the response amplitude is small (Macpherson and Fung, 1999; Chvatal et al., 2013). This further demonstrates a crucial role of supraspinal phasic commands and tonic drive for normal functioning of the spinal postural networks.

NEURONS OF SPINAL POSTURAL NETWORKS

Two groups of spinal interneurons (F and E) were found, activity of which strongly correlated with PLRs, suggesting their participation in PLRs generation (Hsu et al., 2012; Zelenin et al., 2013). F-neurons were excited in-phase with extensors of the ipsilateral limb, while E-neurons – in anti-phase (as the neuron in **Figure 7D**). Presumably, at least some F-neurons and E-neurons participate, respectively, in the excitation and inhibition of extensor motoneurons (EMNs) of the ipsilateral limb. The modulation of F- and E-neurons was primarily determined by somatosensory input from the ipsilateral limb. In the framework of the functional model of the postural system stabilizing trunk orientation in the transverse plane (**Figure 6D**) these neurons belong to the feedback mechanism generating corrective limb movements on the basis of sensory information from the same limb.

The recently developed method of "reversible spinalization" (a temporary cold block of the signal transmission in spinal pathways) allowed studying the contribution of supraspinal influences to the activity of individual F- and E-neurons (**Figure 7**; Zelenin et al., 2013). Elimination of supraspinal commands produced diverse but mostly inhibitory effects on F- and E-neurons (**Figure 7E**). A small proportion of neurons was activated during cooling, suggesting a relative weakness of inhibitory supraspinal influences on these neurons as compared to excitatory ones. In the overwhelming majority of neurons, cooling did not affect their phase of response, suggesting that these neurons belong to the networks generating the spinal component of PLRs, and that supraspinal postural commands strongly affect these neurons. In 19% of neurons non-modulated before cooling, the modulation appeared during cooling, suggesting that supraspinal influences reduce activity in the reflex arcs transmitting somatosensory information to these neurons, and thus affected processing of sensory information in the spinal cord. The proportion of F-neurons inactivated during cooling was significantly larger than found in E-neurons (79% vs. 48%), suggesting that excitatory supraspinal drive to F-neurons is considerably stronger than to E-neurons, which can explain an increase in extensor activity and enhancement of PLRs. In the activated and inactivated F- and E-neurons, cooling affected both the mean burst frequency and mean interburst frequencies (**Figure 7F**), suggesting that most neurons received, respectively, inhibitory and excitatory supraspinal drive during both phases of the tilt cycle. A population of F-neurons residing in the ventromedial part of the gray matter was revealed, which exhibited a dramatic (>80%) decrease in their activity during cooling. It was suggested that elimination of the excitatory supraspinal drive to these neurons is responsible for disappearance of extensor tone and PLRs during spinal shock (Zelenin et al., 2013).

To reveal the spinal pathways critically important for maintenance of lateral stability, lesion studies were performed in rabbits (Lyalka et al., 2005, 2009, 2011). After lateral or

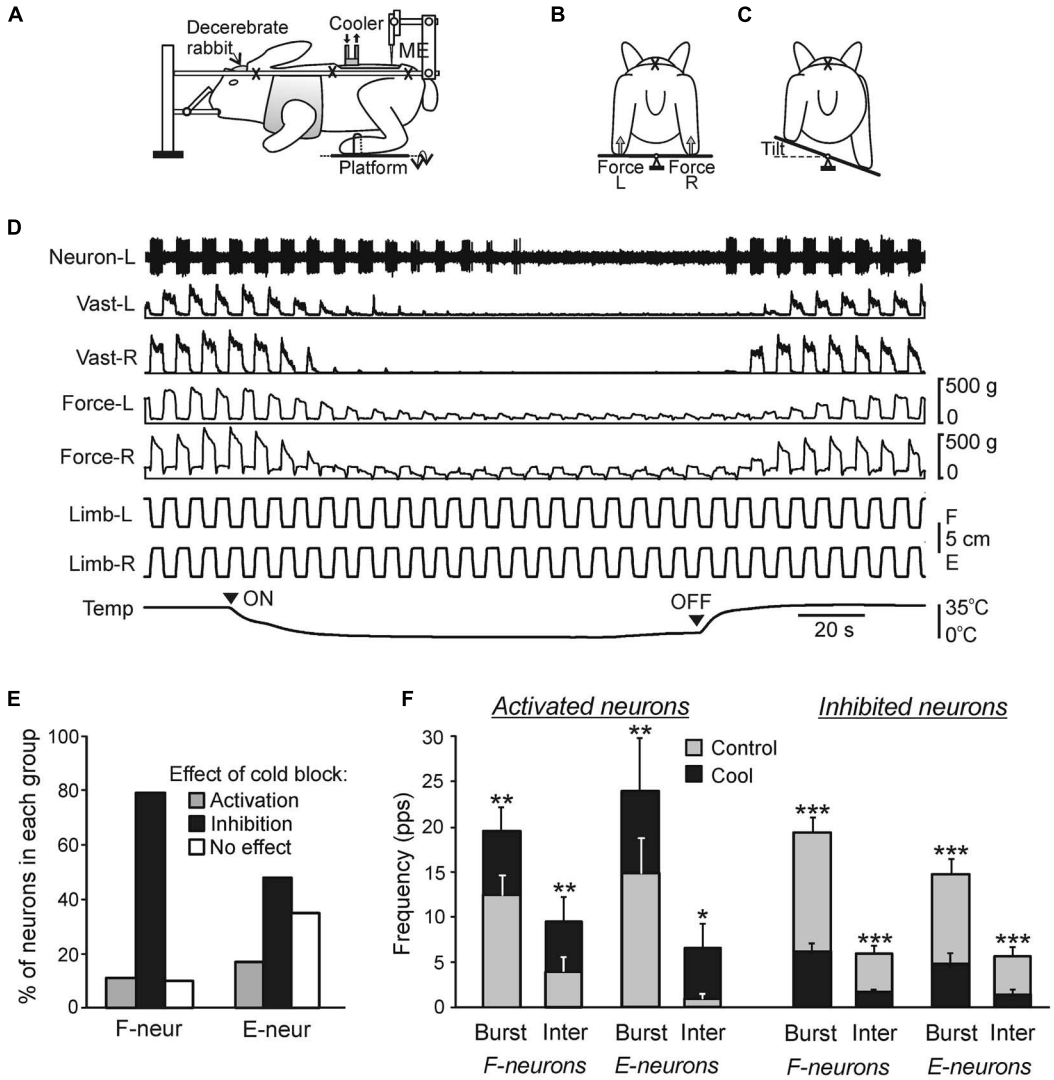

FIGURE 7 | Effects of reversible spinalization on postural limb reflexes and spinal neurons presumably mediating these reflexes. **(A–C)** Details of the experimental design. **(A)** The decerebrate rabbit was fixed in a rigid frame (crosses indicate the fixation points). Activity of spinal neurons from L5 was recorded by a microelectrode (ME). To evoke PLRs, the hindlimbs were positioned on a platform **(B)** periodically tilted in the transverse plane **(B,C)**. The contact forces under the left and right hindlimbs were measured by the force sensors (**B**, Force L and Force R, respectively). **(D)** An example of the effect of reversible spinalization on PLRs and on the activity of a neuron recorded on the left side of spinal segment L5. During the experiment, periodical anti-phase loading/unloading and flexion/extension movements of the left and right limbs were produced by tilting the support platform. The contact force and the EMG of vastus lateralis (Vast) were recorded bilaterally along with the activity of the neuron. Trace *Temp* shows temperature of a cooler placed on the dorsal surface of the spinal cord at T12. Arrowheads ON and OFF indicate the onset of cooling and the onset of re-warming, respectively. Before cooling, tilts of the platform caused PLRs, i.e., activation of extensors during limb flexion/loading and decrease in their activity during limb extension/unloading (left part of recording). Note the disappearance of PLRs (EMG, force), and neuron responses to tilts during cooling, and their re-appearance during re-warming. **(E,F)** Effects of the reversible spinalization on spinal neurons mediating PLRs. **(E)** Proportion of F- and E-neurons activated, inactivated, or unaffected by could block. **(F)** Effect on the mean burst and interburst frequencies of F- and E-neurons activated and inactivated by the cold block. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, *t*-test.

dorsal hemisection of the spinal cord at T12, postural corrective responses to lateral tilts recovered in 1–3 weeks, whereas after the ventral hemisection they disappeared completely and did not recover. These findings suggest that RS and vestibulospinal pathways descending in the ventral quadrants are crucially important for the generation of postural reactions.

TONIC SUPRASPINAL DRIVE

One of the important functions of supraspinal systems is to provide tonic drive to spinal postural networks necessary for their activation. One of the sources of tonic activity of different descending systems (vestibulospinal, RS, etc.) is unspecific tonic inflow from the continuously firing vestibular afferents, which affects them through the vestibular nuclei. Activated by this tonic inflow,

the vestibulospinal drive determines a high level of excitability of EMNs during standing and, therefore, a high tonus in the extensor muscles, which is a necessary condition for supporting the body during standing (Duysens et al., 2000), as well as for generation of postural corrections.

Recently, the effects of manipulation with tonic supraspinal drive by means of galvanic vestibular stimulation (GVS) on the postural system were studied (Hsu et al., 2012). The GVS excites and inhibits vestibular afferents on the side of the negative (cathode) and positive (anode) electrode, respectively, (Goldberg et al., 1984; Minor and Goldberg, 1991). Thus the left/right asymmetry in tonic supraspinal drive is created, which results in a lateral body sway toward the anode observed in all studied species including humans (e.g., Séverac Cauquil et al., 2000; Beloozerova et al., 2003a; Gorgiladze, 2004). Analysis of GVS effects in humans shows that the sway is caused mainly by activation of canal afferents (Mian et al., 2010), its direction and amplitude depend on the polarity and strength of the current stimulating the left and right labyrinths, as well as on the initial subject's posture (Marsden et al., 2002). A model of GVS effects was proposed (Day et al., 2011).

In the standing rabbit, the GVS-caused new body orientation is actively stabilized (Beloozerova et al., 2003a) due to the change in the set-point of the postural system. The GVS strongly affects the magnitude of PLRs (**Figure 8A**): the extensor EMGs and the force developed during limb flexion are considerably increased when the cathode is ipsilateral to the limb, and decreased when the anode is ipsilateral to the limb (Hsu et al., 2012). Thus, GVS, by creating asymmetry in the tonic left and right supraspinal drive, changes the set-point of the postural system through the change of the gain in antagonistic PLRs. It was also demonstrated that in the caudally decerebrated rabbit, an artificial feedback based on GVS could restore normal postural reactions and lateral stability (Zelenin et al., 2012).

Similar results were obtained in humans: an artificial GVS-based feedback considerably improved lateral stability during standing (Scinicariello et al., 2001). These results suggest similarity in organization of the system responsible for balance during standing in humans and quadrupeds.

The effects of GVS on the activity of spinal interneurons mediating PLRs were analyzed (Hsu et al., 2012). It was shown that

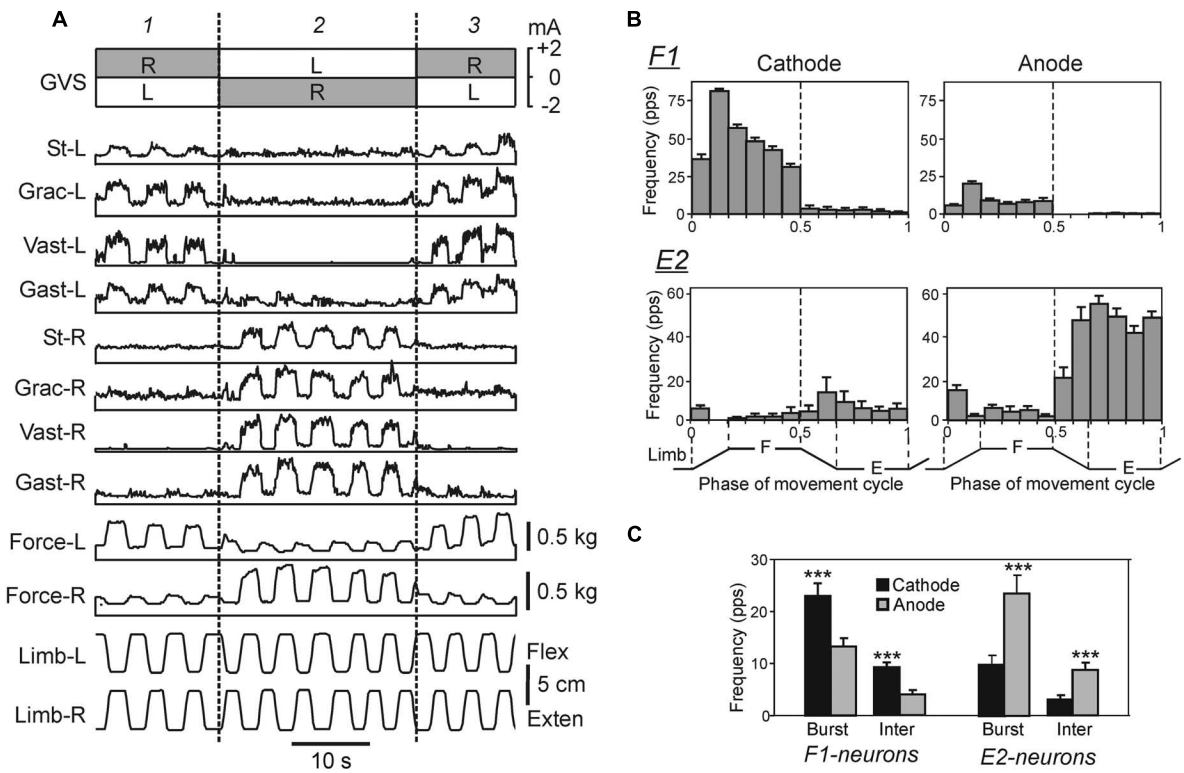

FIGURE 8 | Effects of galvanic vestibular stimulation on postural limb reflexes and on spinal neurons presumably mediating these reflexes. (A) An example of GVS effects on PLRs. The configuration of GVS was repetitively changed, so that the anode was on the right side (R) and cathode was on the left side (L) during time periods *1*, and *3*; the position of anode and cathode was opposite during period *2*. The reflex responses of the limb (the EMG value in eight tested muscles and the force magnitude) were much larger when the cathode was ipsilateral to the limb than when the anode was ipsilateral to this limb. St, semitendinosus; Grac, gracilis; Gast, gastrocnemius. **(B)** Examples of the neurons from F1 and E2 subgroups presumably mediating the effects of GVS on PLRs. For each neuron, a histogram of its activity in the F/E cycle of the ipsilateral limb was obtained under two conditions, with ipsilateral cathode and with ipsilateral anode. In F1 neurons, the activity was significantly higher with ipsilateral cathode than with ipsilateral anode. In E2 neurons, the activity was significantly higher with ipsilateral anode than with ipsilateral cathode. **(C)** The effects of GVS on the mean burst and mean interburst frequencies of F1 and E2 neurons under two conditions: with ipsilateral anode (gray bars) and with ipsilateral cathode (black bars). $^{***}p < 0.001$, *t*-test.

asymmetry in the tonic supraspinal drive (caused by GVS) produces diverse effects on the activity of individual F- and E-neurons. Two sub-groups of spinal interneurons presumably mediating the effect of GVS on PLRs were found. The activity in F1-neurons increased with cathodal GVS and decreased with anodal GVS (**Figures 8B,C**), as the activity of EMNs. By contrast, E2-neurons exhibited responses to GVS that were opposite to those in EMNs (**Figures 8B,C**). It was suggested that the F1 and E2 neurons regulate the degree of activation and inactivation of EMNs during PLRs, respectively, in accordance with supraspinal drive (determined by the GVS polarity). Neurons of F1 and E2 subgroups are located mainly in the intermediate and ventral part of the gray matter, respectively, that is in the areas of termination of the vestibulospinal tract (Nyberg-Hansen and Mascitti, 1964; Petras, 1967), and thus can receive direct vestibulospinal influences.

Two chains of antagonistic PLRs, as well as the effects of GVS on these chains are schematically shown in **Figure 9A**. This scheme reflects also an important finding (Grillner and Hongo, 1972) that the vestibulospinal tract can excite the EMNs both directly and indirectly, through spinal interneurons (presumably subgroups F1 and E2) that integrate descending and afferent information. **Figures 9B–E** illustrates presumed effects of the two antagonistic reflex chains in the unrestrained standing rabbit. The effects without GVS are shown in **Figure 9B**. Any deviation of the dorso-ventral body axis from the vertical (lateral sway) causes opposite changes in PLR-R and PLR-L (solid and interrupted lines, respectively). In turn, PLR-R and PLR-L produce opposite motor effects – they cause body sway in opposite directions as indicated by black and white arrows, respectively. With symmetrical PLRs (as in **Figure 9B**), the two curves intersect at 0° (no lateral sway). This orientation (**Figure 9C**, 1) is stabilized, i.e., the rabbit will return to this orientation after any deflection caused, e.g., by the lateral push (**Figure 9C**, 2 and 3).

Continuous GVS (e.g., with Cathode-R, Anode-L) causes an increase in PLR-R and a decrease in PLR-L (**Figure 9D**). Now the two curves intersect not at 0° but at some angle of the left sway. This tilted orientation (**Figure 9E**, 1) will be stabilized, i.e., the rabbit will return to this orientation after any deflection from it (caused, e.g., by lateral push, **Figure 9E,** 2 and 3). Thus, GVS changes the set-point in the control system. A similar principle of balance control, as well as a similar mechanism underlying a change of stabilized orientation were found in simpler animals – a mollusk (*Clione*) and a lower vertebrate, lamprey (**Figures 5A–C**; Deliagina et al., 1998, 2006b; Deliagina and Fagerstedt, 2000).

As in the lamprey, the immediate effect of UL in higher vertebrates is the loss of lateral stability, and continuous rolling toward the damaged side (e.g., Smith and Curthoys, 1989; Deliagina et al., 1997). As in the lamprey, electrical stimulation of the vestibular nerve terminates rolling and restores lateral stability in the rat. By changing the strength of stimulation, the stabilized body orientation in the transverse plane can be regulated (Deliagina et al., 1997). One can suggest that as in the lamprey (**Figure 5D**) UL causes strong asymmetry in the tonic supraspinal drive. This leads to a dramatic decrease in the gain of PLRs on the damaged side, resulting in disappearance of a set-point in the postural system operating in the transverse plane. The activity of PLR network on the intact side leads to rolling toward the damaged side. Electrical stimulation of the vestibular nerve restores the symmetry in supraspinal drive. This results in an increase in the gain of PLRs on the damaged side, reappearance of the set-point of the system, and restoration of the lateral stability.

One can expect that in humans the principles of operation of the postural system responsible for stabilization of the body orientation in the frontal plane is similar to that revealed in animal models, and a lateral body sway caused by GVS (Séverac Cauquil et al., 2000) can be explained by a shift of the equilibrium point of the control system.

PHASIC SUPRASPINAL POSTURAL COMMANDS

Reticulospinal system

The activity of RS neurons during postural reactions to drop of support under one of the limbs was analyzed in the cat (Stapley and Drew, 2009). In the standing cat, this perturbation produces postural reactions, which result in transition from quadrupedal to tripedal standing (Dufossé et al., 1985; Rushmer et al., 1987; Stapley and Drew, 2009). The initial postural changes in the supporting limbs are caused by sensory information from the dropping limb (Stapley and Drew, 2009). The majority of RS neurons respond to this perturbation with a short latency preceding the initial change in EMGs, suggesting that their discharge represents a postural command contributing to initiation of the postural corrective reaction.

The striking result is that only about 10% of neurons respond to drop of only one of the limbs, suggesting that they encode a command contributing to initiation of only one specific postural reaction. The majority of RS neurons respond to drop of different limbs, thus contributing to generation of different specific postural reactions.

About three quarters of the RS neurons are activated by perturbation of any of two or three limbs. Drop of the support under one of the limbs causes a specific disturbance of body orientation in both pitch and roll planes. One may hypothesize that, as in the lamprey, individual RS neurons in the cat produce motor output contributing to generation of postural correction in a particular vertical plane. For example, RS neurons contributing to rotation of the trunk to the left in the roll plane will be activated by drop of the surface under right forelimb and right hindlimb, and inhibited by drop of the surface under left forelimb and left hindlimb. Neurons with reciprocal responses to the right and left perturbations of the trunk orientation comprised about 25% of the RS population.

Finally, about 15% of RS neurons are activated by the support drop under any of the limbs. One can suggest that these RS neurons generate a "GO" command, and the motor response to this command depends on the current state of spinal networks affected by specific supraspinal and somatosensory inputs.

Thus, the study by Stapley and Drew (2009) has clearly demonstrated that RS neurons may contribute to the compensatory postural reactions that follow an unexpected perturbation. This study also presented arguments against a contribution of the RS system to the specification of the detailed postural reaction required for the compensation. This role most likely belongs to the corticospinal and rubrospinal systems.

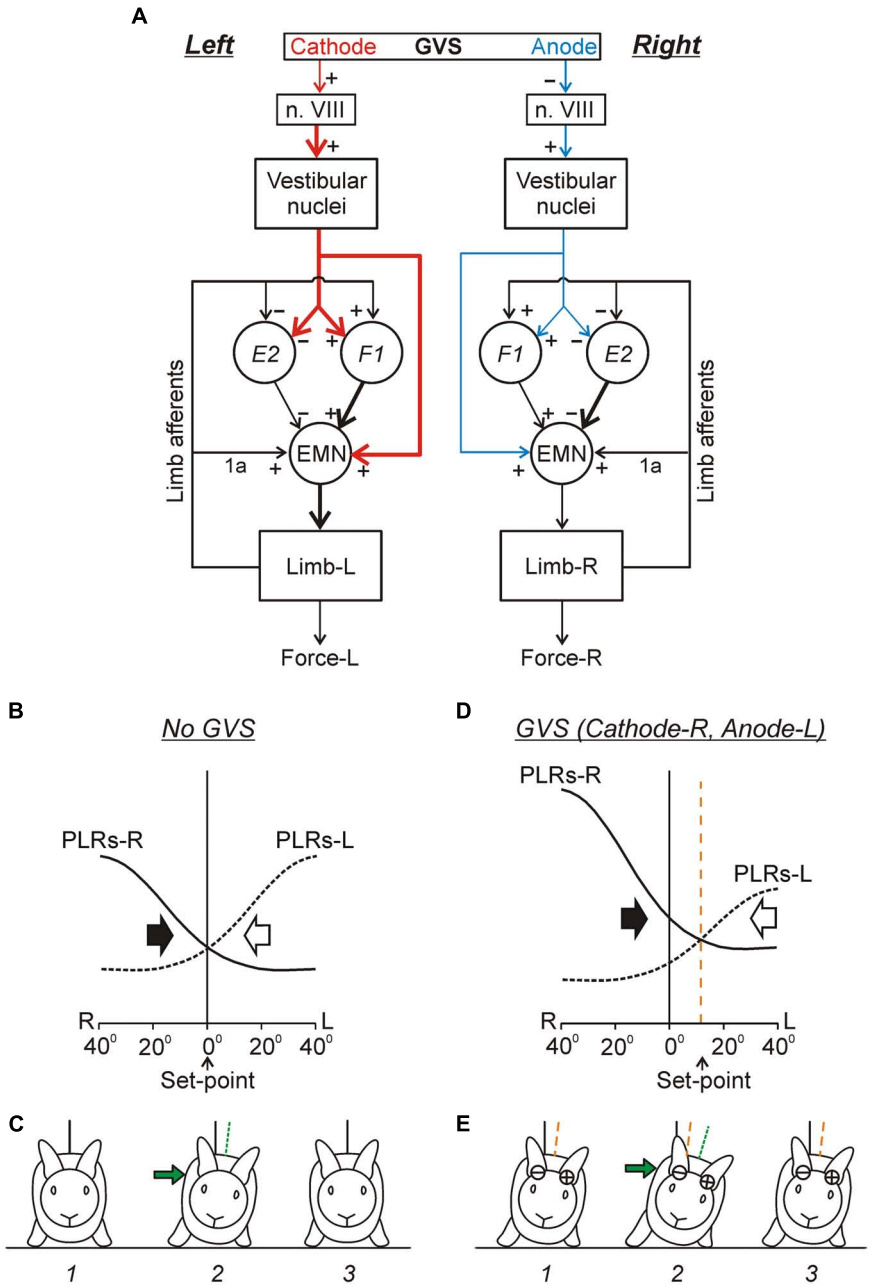

FIGURE 9 | Conceptual model of the trunk stabilization system and effects of galvanic vestibular stimulation. (A) Schematic representation of two chains of PLRs (Left and Right), as well as the effects of GVS on these chains. In each chain, flexion/loading of the limb activates afferents of this limb. They excite extensor motoneurons (EMNs) through monosynaptic pathways (group 1a afferents) and through polysynaptic pathways mediated by spinal interneurons (groups F1 and E2). Extensor motoneurons activate extensor muscles, which counteract the limb flexion. The GVS causes asymmetry of the two chains (indicated by different size and thickness of the corresponding red and blue arrows). With cathode on the left side, GVS activates vestibular afferents in the left VIII nerve (n. VIII), which activate neurons of the left vestibular nuclei. These neurons, through the left vestibulospinal tract, affect the spinal postural reflexes on the left side (for simplicity, crossed-effects are not considered). Due to this changed descending drive, excitability of extensor motoneurons and F1-interneurons is increased, and excitability of E2-interneurons is decreased (as compared to the right side). **(B–E)** Presumed effects of the two antagonistic reflex chains in the unrestrained standing rabbit, without GVS **(B,C)** and during GVS with cathode-R and anode-L **(D,E)**. **(B,D)** The abscissa shows a deviation of the dorso-ventral body axis from the vertical (lateral sway); the ordinate shows the value of PLR-R and PLR-L (solid and interrupted line, respectively). Black and white arrows indicate the motor effect (lateral sway) caused by PLR-R and PLR-L, respectively. **(C,E)** The stabilized orientation (1), a deviation due to a lateral push (2), and the restored orientation (3). The stabilized body orientation and the body orientation immediately after the push are indicated by the orange and green interrupted lines, correspondingly. (See text for details).

Corticospinal and rubrospinal systems

Despite the fact that integrity of the cerebral cortex is not critical for the ability to maintain lateral stability (Musienko et al., 2008), in intact animals and humans the cortical mechanisms supplement the basic brainstem-cerebellum-spinal cord mechanisms during maintenance of the basic body posture (for review see, e.g., Jacobs and Horak, 2007). Recording activity of different classes of neurons (**Figure 10A**) of the motor cortex (MC) in awake rabbits, while the animals maintained balance on a laterally tiling platform, have shown that activity of descending corticofugal neurons of layer V (CF5s) [which includes pyramidal tract neurons (PTNs)] and one class of GABA-ergic inhibitory interneurons (SINs) was strongly correlated to the postural corrections (Beloozerova et al., 2003b; **Figures 10B,C**). In contrast to CF5 and SINs, the proportion of corticofugal neurons of layer VI (CF6s) and of cortico-cortical neurons with ipsilateral (CCIs) and cortico-cortical neurons with contralateral (CCCs) projections that were active during postural corrections was relatively small (**Figure 10B**), and their discharge frequencies were low (**Figure 10C**). This suggests that cortico-cortical interactions, both within a hemisphere (mediated by CCIs) and between hemispheres (mediated by CCCs), as well as cortico-thalamic interactions via CF6 neurons are not essential for motor coordination during postural corrections.

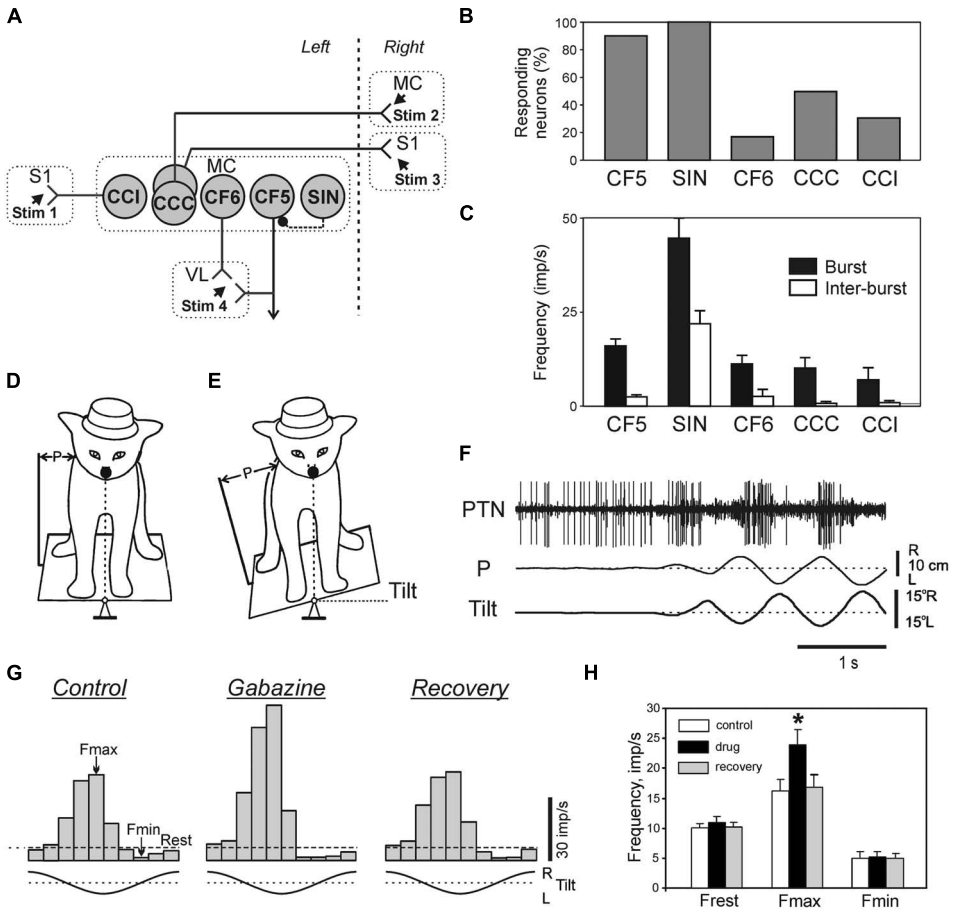

FIGURE 10 | Activity of different classes of neurons in the motor cortex during postural corrections caused by lateral tilts of the platform. (A) Types of neurons which were recorded in the forelimb representation of the left motor cortex (MC) in rabbits. CCI, cortico-cortical neurons projecting to the ipsilateral primary somatosensory cortex (S1); CCC, cortico-cortical neurons projecting to the contralateral motor (MC) or primary somatosensory cortex (S1); CF6, corticofugal neurons of layer VI projecting to the ventrolateral thalamus (VL); CF5, corticofugal neurons of layer V with collaterals projecting to the ventrolateral thalamus (these neuron types were identified by their antidromic responses to electrical stimulation of the corresponding structures, Stim 1–Stim 4); SIN, putative inhibitory interneurons (identified by their high-frequency orthodromic responses to stimulation of ventralateral thalamus or a cortical site). **(B)** Proportion of neurons responding to tilts in different classes of cortical neurons. **(C)** Mean burst and mean interbust frequencies of modulated neurons in different classes of cortical neurons. **(D,E)** Experimental design for recording the activity of pyramidal tract neurons (PTNs) during postural corrections. PTN activity was recorded along with platform tilts (Tilt) and postural corrections (P). **(F)** An example of PTN responses to tilts. **(G)** The effect of gabazine on postural responses of a PTN. Histograms of the PTN activity during tilts for each of three conditions: Control, before application; Gabazine, 2 min after gabazine application; Recovery, 15 min after application. Fmax and Fmin, the maximum and minimum frequencies in the histogram. **(H)** Effects of GABA-A receptor antagonists on PTN population activity: Frest, Fmax, and Fmin. $*p < 0.05$, *t*-test.

The tilt-related signals from the spinal cord and brainstem can reach the MC and affect its output neurons (CF5) via different routes. One of these is an input via ventro-lateral thalamus, a part of which is mediated by SINs (Strick and Sterling, 1974; White, 1989; Swadlow, 2002). Since activity of SINs is rhythmically modulated during postural corrections, one can hypothesize that they contribute to shaping of cortical output. The activity of individual PTNs in the cat maintaining balance on a tilting platform (**Figures 10D,F**) was recorded both before and after local iontophoretic application of the GABA-A receptor antagonists at the site of recording (Tamarova et al., 2007). It was found that the GABA-ergic system of the MC attenuates the posture-related responses of PTNs but plays little role in determining the response timing (**Figures 10G,H**).

Activity of individual neurons of two supraspinal systems (corticospinal and rubrospinal) was studied in awake cats maintaining balance on the tilting platform (**Figures 10D,E**; Beloozerova et al., 2005; Karayannidou et al., 2008, 2009b; Zelenin et al., 2010). It was found that activity of these two systems in the postural task has many features in common.

First, a considerable proportion of neurons in both systems are phasically modulated by tilts (**Figure 10F**), though the proportion of modulated rubral neurons is smaller (46%) than the cortical ones (90%). Modulated PTNs and rubrospinal neurons (RbNs) can be forelimb- or hindlimb-related. A half of PTNs have a positional response to tilt, i.e., their activity depends on the value of stationary tilt. Taken together these results suggest that the MC and red nucleus send postural commands to the spinal cord and medulla. The MC along with other descending systems including reticulo- and vestibulospinal ones (Matsuyama and Drew, 2000), participates in execution of both principal postural functions: the maintenance of a definite body configuration and the maintenance of equilibrium (Horak and Macpherson, 1996).

Second, in both corticospinal and rubrospinal systems, the phases of activity of individual neurons were distributed over the entire tilt cycle, and the role of RbNs and PTNs in the postural task is difficult to assess on the basis of a simple correlation between the population activity and the motor pattern.

Third, the contribution of tilt-related sensory inputs from individual limbs to posture-related modulation of individual RbNs and PTNs was examined by eliminating tilt-related sensory input from one, two or three limbs (**Figures 11A–F**). In the presented example, the forelimb-related RbN from the left red nucleus has the same phase and depth of modulation in all those tests in which the right forelimb is standing on the tilting platform, and thus tilt-related somatosensory input from this limb is present. The amplitude and phase of responses to platform tilts in the majority of RbNs and PTNs are determined primarily by sensory input from the corresponding (fore or hind) contralateral limb, whereas inputs from the other limbs make a much smaller contribution to their modulation (**Figures 11G–J**). Thus, in the sub-systems responsible for stabilization of the anterior and posterior parts of the trunk in the transverse plane, PTNs and RbNs are elements of the feedback mechanism generating corrective limb movement on the basis of sensory information from the same limb (**Figure 6D**).

Fourth, in the majority of PTNs and RbNs, the afferent signals that they presumably receive from their receptive fields during tilts cannot be even partially responsible for the generation of neuronal reactions to tilts (Beloozerova et al., 2003b, 2005; Zelenin et al., 2010). Most likely, in these neurons the somatosensory input from the receptive field determined at rest, is replaced or complemented by other inputs during active postural behavior. This hypothesis is further supported by the view that the signals from limb mechanoreceptors are processed in the spinal and brainstem networks before they reach the MC, and in the cerebellum and MC before they reach rubral neurons (Massion, 1967; Toyama et al., 1968; Landgren and Silfvenius, 1971; Asanuma, 1989).

Thus, in quadrupeds, all studied descending tracts transmit postural commands to the spinal cord. One can expect that postural commands in humans are also transmitted through many descending pathways.

CONCLUDING REMARKS

During the last decade, the use of different animal models and novel techniques has enabled considerable progress to be made in understanding the functional organization of postural mechanisms and in analysis of the underlying neuronal networks. Some differences in organization but remarkable similarities in principles of operation of the postural control system in the lamprey and in the quadrupeds have been revealed.

(1) The postural system in the lamprey and quadrupeds responds to numerous destabilizing factors by producing specific postural corrections. These corrections in the lamprey and quadrupeds are caused by different types of sensory information – vestibular in the lamprey and mainly somatosensory (from limb mechanoreceptors) in quadrupeds. This difference reflects different environmental conditions for aquatic and terrestrial animals.

(2) In the lamprey, there is only one system that controls the postural orientation of the whole body. In quadrupeds, the trunk stabilization system can dissociate into two independent subsystems controlling orientation of the anterior and posterior body parts. This is important in the cases of complex configuration of the support surface, but irrelevant for the lamprey living in a homogeneous medium (water).

(3) In both lampreys and quadrupeds, stabilization of body orientation in the transverse plane is based on the interaction of two antagonistic reflexes (vestibulospinal reflexes in the lamprey and PLRs in quadrupeds). The animal stabilizes its orientation at the point at which these reflexes are equal to each other.

(4) In both lampreys and quadrupeds, these antagonistic reflexes are mediated by neurons of supraspinal systems. Phasic postural commands, transmitted by supraspinal neurons to the spinal cord, play a crucial role in the generation of postural corrections. In the lamprey, supraspinal commands are responsible for elicitation of postural corrections, and the role of spinal networks is transformation of these commands into an appropriate motor pattern. In quadrupeds, this mechanism also exists but it is supplemented with spinal postural networks (generating spinal PLRs), which are regulated by the supraspinal tonic drive. One of the lines of future studies is the

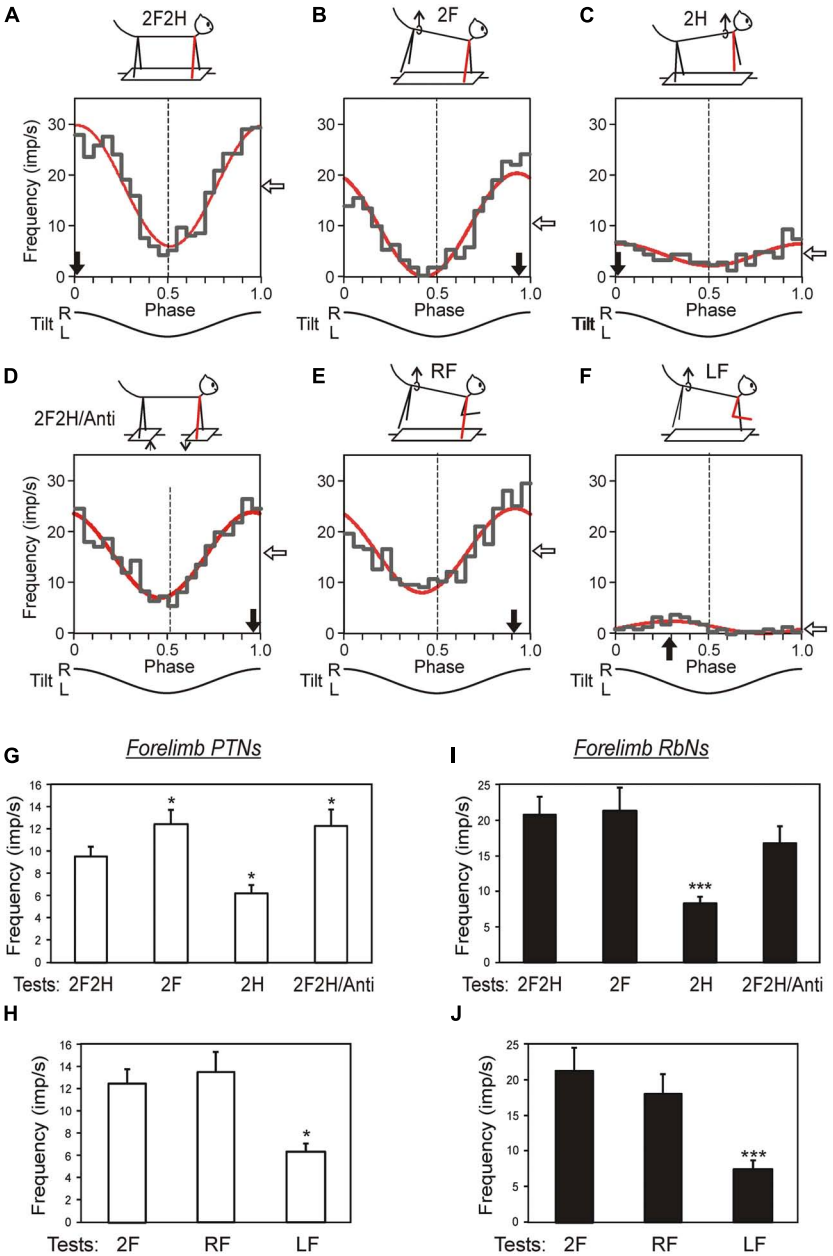

FIGURE 11 | Activity of corticospinal and rubrospinal neurons in the cat during postural corrections. (A–F) Activity of forelimb-related RbS neuron from left red nucleus during different postural tests. The neuron was related to the right forelimb (indicated by blue). **(A)** Control, standing on all four limbs (test 2F2H). **(B)** Standing on two forelimbs (test 2F). **(C)** Standing on two hindlimbs (test 2H). **(D)** Antiphase tilts of the platforms under the forelimbs and hindlimbs (test 2F2H/Anti). **(E)** Standing on the right forelimb (test RF). **(F)** Standing on the left forelimb (test LF). For each test the following are shown: (1) the phase histogram of spike activity in the tilt cycle (gray line), (2) the first harmonic of Fourier image (red line), (3) the mean frequency of discharge (white arrow), and (4) the preferred phase (black arrow). **(G–J)** Population characteristics of forelimb PTNs **(G,H)** and RbSNs **(I,J)** in tests revealing influences from shoulder and hip girdles **(G,I)**, and in tests revealing influences from individual limbs of the same girdle **(H,J)**. Mean value of modulation depth, that is the peak-to-peak value of the first harmonic, is shown. $*p < 0.05$, $***p < 0.001$, *t*-test.

analysis of operation of spinal neuronal networks in different postural tasks, as well as search for the factors enhancing their efficacy in subjects with spinal cord injury. Another line is to understand how the capability of the spinal cord for sophisticated processing of somatosensory information is used in postural mechanisms.

(5) In both lampreys and quadrupeds, the stabilized body orientation can be changed through a change of the gain in antagonistic reflex chains, which causes a shift of the equilibrium point of the control system. In both lamprey and quadrupeds, supraspinal mechanisms are responsible for this function. In the lamprey, the neuronal mechanisms

underlying the shift of the equilibrium point were revealed. The goal of future studies is to reveal these mechanisms in quadrupeds.

(6) In the lamprey, postural commands to the spinal cord are transmitted by the only developed descending system, the RS one. The mechanisms of encoding and decoding of these commands have been revealed. In quadrupeds, postural commands are transmitted by many descending pathways. In a few examined postural tasks, phasic postural commands transmitted by corticospinal, rubrospinal, and RS systems were analyzed, and a difference in function has been revealed between corticospinal and RbNs on one hand, and RS neurons on the other. The goal of future studies is to understand the neuronal mechanisms of formation of supraspinal postural commands in quadrupeds, as well as their processing by the spinal networks, which results in the corrective motor response.

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Neurons in red nucleus and primary motor cortex exhibit similar responses to mechanical perturbations applied to the upper-limb during posture

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Primary motor cortex (M1) and red nucleus (RN) are brain regions involved in limb motor control. Both structures are highly interconnected with the cerebellum and project directly to the spinal cord, although the contribution of RN is smaller than M1. It remains uncertain whether RN and M1 serve similar or distinct roles during posture and movement. Many neurons in M1 respond rapidly to mechanical disturbances of the limb, but it remains unclear whether RN neurons also respond to such limb perturbations. We have compared discharges of single neurons in RN (n = 49) and M1 (n = 109) of one monkey during a postural perturbation task. Neural responses to whole-limb perturbations were examined by transiently applying (300 ms) flexor or extensor torques to the shoulder and/or elbow while the monkeys attempted to maintain a static hand posture. Relative to baseline discharges before perturbation onset, perturbations evoked rapid (<100 ms) changes of neural discharges in many RN (28 of 49, 57%) and M1 (43 of 109, 39%) neurons. In addition to exhibiting a greater proportion of perturbation-related neurons, RN neurons also tended to exhibit higher peak discharge frequencies in response to perturbations than M1 neurons. Importantly, neurons in both structures exhibited similar response latencies and tuning properties (preferred torque directions and tuning widths) in joint-torque space. Proximal arm muscles also displayed similar tuning properties in joint-torque space. These results suggest that RN is more sensitive than M1 to mechanical perturbations applied during postural control but both structures may play a similar role in feedback control of posture.

Keywords: red nucleus, primary motor cortex, upper-limb muscle, perturbation, optimal feedback control

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Introduction

It is well established that primary motor cortex (M1) and red nucleus (RN) form parallel pathways for motor control as both structures have axonal projections to the spinal cord including direct connections to motoneurons (Fetz and Cheney, 1980; Buys et al., 1986; Cheney et al., 1991; Mewes and Cheney, 1991, 1994; Belhaj-Saif et al., 1998; McKiernan et al., 1998; Park et al., 2004). Furthermore, M1 and RN, together with the cerebellum, form an extensively

interconnected premotor network involved in the control of upper limb movement (reviewed in Kennedy, 1990; Houk et al., 1993; Keifer and Houk, 1994). Understanding the common and distinct contributions of M1 and RN is important to our understanding of volitional motor control.

The patterns of activity observed in RN are generally similar to those observed in M1. Neural activity M1 is correlated with the timing and magnitude of upper-limb muscle activity (Smith et al., 1975; Bennett and Lemon, 1996; Scott, 1997; Holdefer and Miller, 2002), as is the activity of neurons in RN (Miller et al., 1993; Mewes and Cheney, 1994; Miller and Houk, 1995; Belhaj-Saif et al., 1998; Miller and Sinkjaer, 1998). Neural activity in M1 can reflect either kinematic (motion) or kinetic (forces) features of movement (reviewed in Scott, 2003), a feature that is also observed in RN (Kohlerman et al., 1982; Gibson et al., 1985a,b; Kennedy, 1987; Cheney et al., 1988; Mewes and Cheney, 1994). More recent studies suggest that RN may be specialized for controlling grasping movements coupled with reaching (Sinkjaer et al., 1995; van Kan and McCurdy, 2001, 2002a,b).

A recent hypothesis proposes that the volitional motor system may act like an optimal feedback controller (Todorov and Jordan, 2002; Todorov, 2004). This framework highlights the importance of afferent feedback for voluntary control of movement and predicts that feedback will be modified based on the goal of the behavioral task (Scott, 2004, 2012). Examination of muscle stretch responses highlight that the long-latency response is modified by limb mechanics (Kurtzer et al., 2008, 2009, 2014), motor intention (Pruszynski et al., 2008; Dimitriou et al., 2012; Crevecoeur et al., 2013), motor learning (Cluff and Scott, 2013), and features of the goal and environment (Nashed et al., 2012, 2014; Omrani et al., 2013). The fact that these context dependent responses occur during long, but not short latency responses is significant because it suggests that they are generated supraspinally.

Supraspinal involvement in feedback control of volitional movement is also supported by electrophysiological studies of M1 neurons in awake, behaving monkeys. These studies have observed that M1 neurons respond to passive joint motion (Fetz et al., 1980; Lemon, 1981; Scott, 1997; Scott and Kalaska, 1997) and exhibit rapid responses to mechanical perturbations applied to a single (Evarts, 1973; Evarts and Fromm, 1977; Wolpaw, 1980a; Flament and Hore, 1988; Bauswein et al., 1991) or multiple joints (Herter et al., 2009). Importantly, perturbation responses in M1 consider the influence of limb mechanics (Pruszynski et al., 2011b), motor intention (Conrad et al., 1974, 1975; Evarts and Tanji, 1974; Wolpaw, 1980b; Pruszynski et al., 2014), and whether the animal is actively engaged in a motor task (Omrani et al., 2014). Furthermore, rapid responses to perturbations have been observed in M1 neurons with identified projections to the pyramidal tract (Evarts and Tanji, 1976; Fromm et al., 1984), including M1 neurons with direct connections onto spinal motor neurons (Cheney and Fetz, 1984).

It remains unclear, however, whether neurons in monkey RN exhibit rapid motor responses similar to those observed in M1. Some studies have found that most neurons in RN respond to passive joint movements (Larsen and Yumiya, 1980) and torque perturbations (Mewes and Cheney, 1994) of the upper-limb. However, other studies have found that sensory stimulation evokes weak or negligible responses in RN neurons (Gibson et al., 1985a; Kennedy et al., 1986). The present study uses a multi-joint paradigm to investigate whether mechanical perturbations evoke rapid sensorimotor responses in RN neurons that are similar to those observed in M1 and upper-limb muscles. We hypothesized that neurons in RN would exhibit rapid responses to mechanical perturbations with directional tuning features that are similar to M1 neurons and upper-limb muscles. To test this hypothesis, we compared rapid responses of RN neurons, M1 neurons and upper-limb muscles evoked by multi-joint perturbations (transient mechanical torques at elbow and/or shoulder joints) applied while monkeys maintained a constant arm posture. Here we show that directional tuning features of RN and M1 neurons were similar to those observed in upper-limb muscles.

Methods

Subjects and Apparatus

Four male rhesus monkeys (*Macaca mulatta*, 6–10 kg) were trained to perform whole-limb visuomotor tasks while wearing KINARM (BKIN Technologies, Kingston, ON, Canada), a robotic exoskeleton that supports the arm, permits planar shoulder and elbow motion, and can apply mechanical torques at the shoulder and/or elbow (Scott, 1999; **Figure 1A**). A virtual reality system presented visual targets within the limb's movement plane while permitting the monkeys to view their entire limb. The Queen's University Animal Care Committee approved all procedures.

Behavioral Task

The monkeys performed a postural perturbation task (Herter et al., 2009). Mechanical perturbations were transiently applied to the monkeys' right arms while they maintained their right hand at a visual target (6 mm radius) displayed near the center of the arm's workspace (30° shoulder flexion, 90° elbow flexion) where passive viscoelastic forces are relatively small (Graham et al., 2003). The monkeys initiated each trial by moving their right hand to the visual target and holding it within an acceptance window (8 mm radius) for 1000–1500 ms. One of nine perturbations was then transiently applied to the monkeys' arm for 300 ms. The nine perturbation conditions included four single-joint torques (shoulder flexion, *SF*; shoulder extension, *SE*; elbow flexion, *EF*; elbow extension, *EE*), four multi-joint torques (*SF* + *EF*, *SF* + *EE*, *SE* + *EF*, *SE* + *EE*), and an unloaded condition (**Figure 1B**). The magnitude of torque applied at each joint was fixed at either ±0.12 Nm (Monkeys A–C) or ±0.32 Nm (Monkey D), producing a uniform distribution in joint-torque space but a torque magnitude that was $\sqrt{2}$ greater in multi-joint than single-joint conditions. Each perturbation (except the unloaded condition) pushed the monkeys' hand from the target's acceptance window and the monkeys were required to return their hand to the visual target within 1500 ms and hold it there for

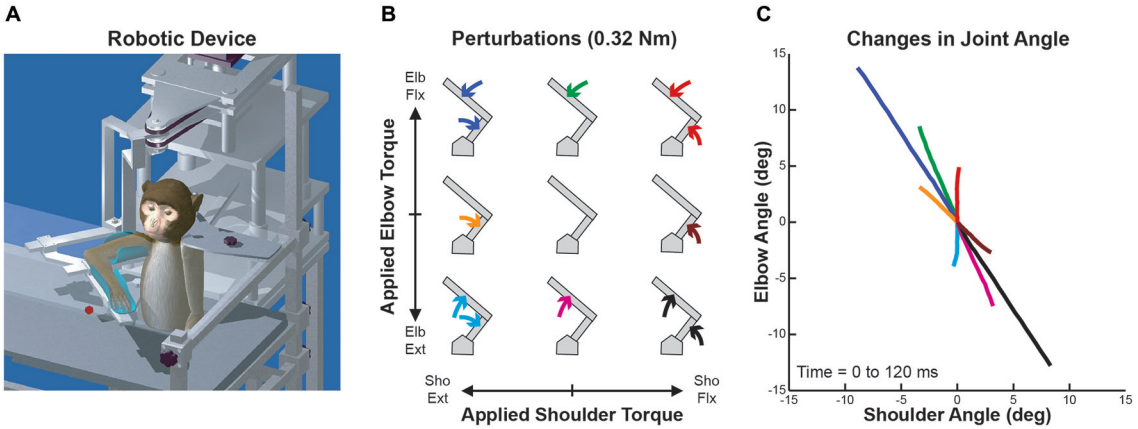

FIGURE 1 | Robotic device, perturbation conditions and perturbation-evoked kinematics. **(A)** Schematic representation of the KINARM exoskeleton robot used in the study. **(B)** Arrangement of the nine perturbation conditions applied to the monkey's upper-limb. Joint torques imposed at the shoulder and elbow joints are represented along the *x* and *y* axes, respectively (joint-torque space: flexor torque positive and extensor torque negative). Modified from Herter et al. (2009). **(C)** Joint motion evoked by each perturbation condition. Changes in shoulder and elbow angle in first 120 ms after perturbation onset are represented along the *x* and *y* axes, respectively (flexion positive and extension negative). Colors of each line are associated with the respective perturbation conditions in **(B)**. Modified from Herter et al. (2009).

another 1000–1500 ms to receive a liquid reward. The nine perturbation conditions were presented in a pseudo-random block design with each block repeated five times for a total of 45 trials.

Data Collection

Neural data was collected from the left RN of one monkey (Monkey D) using standard extracellular recording techniques developed for recording from brainstem structures (Marino et al., 2008). Microelectrodes were advanced through guide tubes that were placed inside a grid mounted within a stainless steel recording chamber (Crist Instruments, Hagerstown, MD) that was implanted over the stereotaxic coordinates of the RN. The recording chamber was centered on the midline and angled 35° posterior of vertical, which allowed us to identify the superior and inferior colliculus during penetrations into the rostral and caudal RN, respectively. Neural data was collected from the left M1 of all four monkeys using standard extracellular recording techniques for cortical neurons (Herter et al., 2007). However, M1 data from Monkey D only is presented in the current report because RN data was collected from Monkey D only. For penetrations into both RN and M1, microelectrodes were advanced until neural activity was observed in response to active or passive arm movements. Single neurons were then isolated and neural activity was recorded from all neurons that were related to active or passive movements of the shoulder and/or elbow, but not the wrist and/or fingers.

Electromyographic (EMG) activity was collected from proximal arm muscles involved in flexion or extension at the shoulder and/or elbow (Graham and Scott, 2003) using standard techniques (Loeb and Gans, 1986; Kurtzer et al., 2006a). Acute recordings were obtained from all four monkeys using pairs of single-strand wires that were percutaneously inserted approximately 5 mm apart in the muscle belly. Chronic recordings were attained from Monkeys A and C using bipolar multi-strand electrodes that were subcutaneously implanted within the superficial muscle belly. EMG activity was recorded from 11 different upper-limb muscles, including shoulder flexors (Anterior Deltoid, Pectoralis Major), shoulder extensors (Posterior Deltoid, Medial Deltoid), elbow flexors (Brachialis, Brachioradialis, Extensor Carpi Radialis Longus), elbow extensors (Triceps lateral head, Triceps medial head), biarticular flexors (Biceps long head, Biceps short head), and biarticular extensors (Triceps long head, Dorsoepitrochlearis). Electrode placement in each muscle was verified using micro-stimulation through the recording electrode.

During recording sessions, EMG signals were band-pass filtered (100–3,000 Hz) and recorded at 1 kHz (Monkeys A–C) or 4 kHz (Monkey D). During the subsequent offline analysis, signals were full-wave rectified and integrated into 5 ms bins. Muscles were only included in the analyses if they obtained a score of $\geq$3 on a subjective rating scale of signal quality (1 = poor, 5 = excellent; Kurtzer et al., 2006a). EMG data from the four monkeys was included in our analyses for the current report.

Joint angles, velocities, and applied torques were recorded at 1 kHz (Monkeys A–C) or 4 kHz (Monkey D). Cartesian hand positions and tangential hand speed were calculated from joint angles and velocities.

Data Analyses

Neural Activity

Analyses of RN and M1 neurons were restricted to perturbation-related neurons, defined as neurons that: (1) exhibited onset latencies between 10 and 100 ms after perturbation onset; and (2) exhibited significant directional-tuning in joint-torque space during the epoch lasting from 20 to 120 ms after perturbation onset. Onset latencies were obtained from spike frequencies that were averaged across the three spatially adjacent perturbation

conditions with the highest mean activity during the post-perturbation epoch (n = 15 trials). Spike frequencies that were calculated at 5 ms intervals with an asymmetric spike density filter (Thompson et al., 1996; Herter et al., 2009). Each neural spike was convolved with a double exponential kernel that mimics a post-synaptic potential (1 ms rise and 20 ms fall). Onset latency was determined as the first time that spike frequency increased for at least three consecutive points (15 ms) and extended beyond 4 SD of the mean during the period of 100 ms preceding perturbation onset.

Directional tuning in joint-torque space (SF = 0°, EF = 90°, SE = 180°, EE = 270°) was obtained by examining changes in neural activity as a function of perturbation direction in joint-torque space. Directional tuning features were calculated with the plate method, which describes several features of directional tuning without assuming an underlying tuning function (Gribble and Scott, 2002). This method characterizes the "mass distribution" of torque-related activity by assuming that activity changes linearly between sampled torque directions and that torque magnitude is equal for each torque direction. To use this method, the lowest activity across all trials was subtracted so that all values were greater or equal to zero. Significance of directional tuning was determined using a nonparametric "bootstrapping" test (Scott and Kalaska, 1997), in which the distance of the center mass from the origin (i.e., magnitude of the centroid) was compared with bootstrap values of the centroid obtained by randomly reassigning the neural activity across all trials. A neuron was considered to have significant directional tuning if fewer than 100 of 10,000 bootstrap values of the centroid were greater than the actual value of the centroid ($p < 0.01$).

For all perturbation-related neurons, the centroid was used to calculate four directional tuning features (Herter et al., 2007). (1) *Preferred-torque direction* (PTD), which describes the angle associated with the greatest increase in activity, was calculated as the direction of the centroid relative to the origin in joint-torque space. (2) *Torque-slope* (TS), which expresses the sensitivity to loads, was calculated by normalizing the magnitude of the centroid by the torque magnitude (0.32 Nm). (3) *Tuning Width* was calculated as the ratio of changes in activity perpendicular to the PTD axes relative to changes in activity along the PTD axes. This method of computing tuning width yields values ranging from 0 (narrow) to 1 (broad), where a cosine obtains a tuning width of 0.44. (4) *Excitation-Inhibition Ratio* (EIR) describes the relationship between changes in activity (relative to the unloaded baseline condition) for the load condition nearest to the preferred-torque direction (ΔPTD) and for the load condition opposite the preferred-torque direction (ΔOPP). EIRs were computed as:

$$EIR = \frac{(\Delta PTD + \Delta OPP)}{(\Delta PTD - \Delta OPP)} \quad (1)$$

Note that changes in activity relative to the unloaded baseline condition are generally excitatory (positive) for load conditions near the PTD and inhibitory (negative) for load conditions opposite the PTD. As a result, EIRs values typically range from −1 to 1, where positive (negative) EIRs occur when the magnitude of excitation at the PTD is greater (lesser) than the magnitude of inhibition opposite the preferred-torque direction. Values near 0 occur when the magnitudes of excitation and inhibition are similar. In some cases, EIRs can go beyond 1 (−1) if both ΔPTD and ΔOPP exhibit excitation or inhibition.

Rayleigh tests were used to determine if distributions of PTDs were statistically unimodal or bimodal relative to a uniform distribution (Batschelet, 1981). This statistic is based on mean vector length, which describes similarity across a sample of angles (e.g., PTDs). A mean vector length of 0 is obtained if all angles are uniformly distributed and a value of 1 is obtained if all angles are identical. The value of a mean vector length along this continuum provides an index that is compared with a Rayleigh distribution. For a population with a significantly unimodal distribution, the mean orientation of the distribution determines the preferred direction of the population. For the bimodal Rayleigh test, all PTDs are multiplied by two, which creates a unimodal distribution if the underlying distribution is symmetrically bimodal. For a population with a significantly bimodal distribution, a preferred axis is obtained by dividing the average orientation by two.

Muscle Activity

To compare and contrast the patterns of activity of RN and M1 neurons with proximal arm muscles, the preceding analyses were also carried out on the EMG activity of our sample of proximal arm muscles. Note that TSs of muscles could not be directly compared with TSs obtained from neurons because muscle EMG was an arbitrary unit.

Statistical Comparisons

Onset latencies and PTDs of RN and M1 neurons were compared statistically with those of upper-limb muscles using t-tests ($p < 0.05$). For PTDs with a significant bimodal distribution, we multiplied each PTD by two to produce unimodal distributions that could be quantitatively compared with t-tests.

Assuming that activation of neurons in RN and M1 initiate muscle activity that produces movement, we expected the onset latencies of RN and M1 neurons would be shorter than onset latencies of upper limb muscles but similar to each other. Given similarities in their anatomical connections with the motor periphery (see Discussion), we also predicted that RN neurons, M1 neurons, and upper–limb muscles would exhibit similar bimodal distributions of PTDs biased towards whole limb flexor torques (elbow flexor and shoulder extensor) and whole limb extensor torques (elbow extensor and shoulder flexor). Given our *a priori* predictions, we did not correct for multiple comparisons for these tests of onset latencies and PTDs.

To capture the temporal evolution of neural and muscular activities, means were computed for each of the directional tuning properties (TSs, tuning widths, EIRs) in five 20 ms bins between 20 and 120 ms. Each of these tuning features was then compared statistically using two-way (3 × 5) ANOVA ($p < 0.05$) that examined the effects of cell population (RN, M1, muscle) and temporal epoch (20–40 ms, 40–60 ms, 60–80 ms, 80–100 ms, 100–120 ms). We did not have any strong *a priori* predictions regarding these directional-tuning properties, thus we used the

Bonferroni method (alpha divided by the number of t-tests) to correct for multiple comparisons.

Prior to statistical testing, onset latencies and directional tuning properties (PTDs, TSs, tuning widths, EIRs) of RN and M1 neurons and upper limb muscles were examined for normality using Lilliefors' test ($p < 0.05$). When necessary, parametric statistics (e.g., t-tests and ANOVAs) were replaced with equivalent nonparametric statistical tests (e.g., Wilcoxon rank sum tests and Freidman's tests).

Results

Kinematics of the Perturbation Task

Although the applied loads were uniformly distributed in joint-torque space (**Figure 1B**), joint motion was highly nonuniform due to intersegmental dynamics (**Figure 1C**). Over the first 120 ms, each single-joint torque produced multi-joint motion (brown, green, orange and magenta lines) and two of the multi-joint torques generated single-joint motion (red and cyan lines). In addition, the magnitude of joint motion resulting from these two multi-joint torques was much smaller than the other two multi-joint perturbation conditions (blue and black lines).

Responses of RN Neurons to Perturbations

We examined the activity of 49 neurons recorded in the upper-limb region of RN of Monkey D. After the recording sessions were completed, the monkey was euthanized and the brainstem was removed and sectioned for histological examination. Based on the location of the recording tracks, we confirmed that some penetrations targeted the RN. Over half of these neurons (n = 28, 57%) exhibited perturbation-related activity; i.e., their activity was significantly modulated at relatively short latencies (onset latency of 20–100 ms) and exhibited significant directional tuning in joint-torque space (bootstrap test, $p < 0.01$). **Figures 2A,B**, illustrate spike rasters and spike frequency histograms showing perturbation-related activity of two exemplar RN neurons. Both neurons showed markedly greater increases in activity for some perturbations conditions than others. The first neuron responded greatest to perturbations that required the monkey to generate an extensor torque at the shoulder and a flexor torque at the elbow (PTD = 139°, **Figure 2C**). The second neuron was most sensitive when the monkey produced extensor torques at the elbow and flexor torques at the shoulder (PTD = 290°, **Figure 2D**). Both neurons displayed large differences in modulation between preferred and non-preferred perturbation conditions, which resulted in substantial TSs of 120 and 115 (sp/s)/Nm, respectively (**Figures 2C,D**). Despite this similarity, the first neuron exhibited increases in activity for several perturbation conditions and decreases in a few directions, resulting in a tuning width that was slightly greater than cosine tuning (tuning width = 0.56, **Figure 2C**, right). In

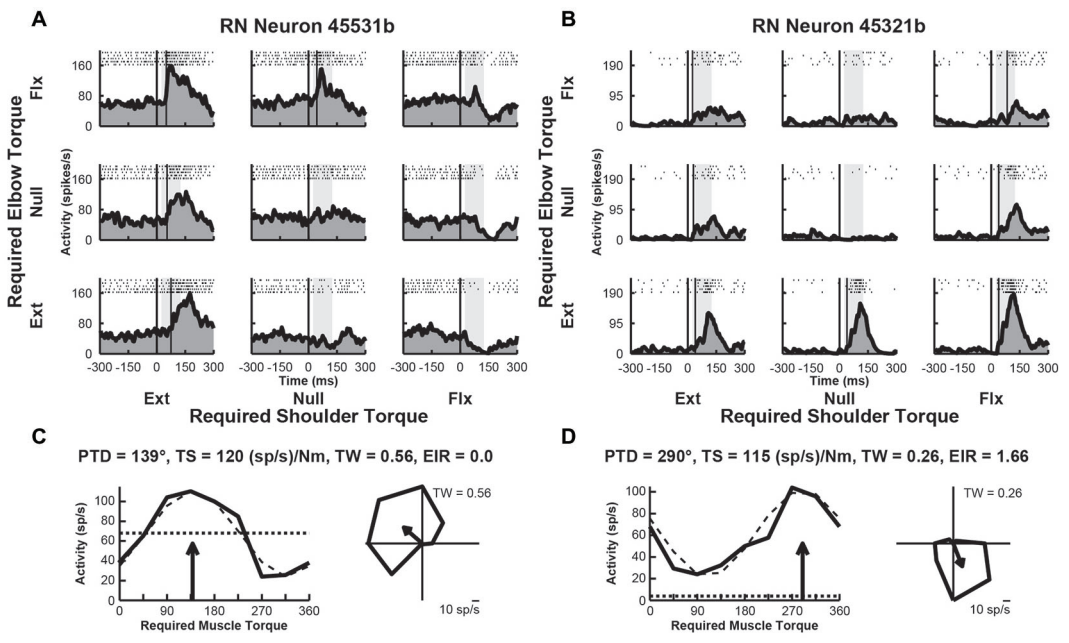

FIGURE 2 | Activity of exemplar RN neurons. **(A)** Rasters and histograms for each perturbation condition (arranged in joint-torque space) displaying the activity of an RN neuron that responded maximally to perturbations that required an extensor torque at the shoulder and a flexor torque at the elbow to counter the applied torques. **(B)** Activity of a RN neuron that responded maximally to perturbations that required a flexor torque at the shoulder and an extensor torque at the elbow. **(C,D)** Directional tuning of the corresponding RN neurons. Left sub-panels illustrate linear plots of overall activity vs. joint-torque angle. Unloaded baseline activities and cosine fits are shown as dotted and dashed lines, respectively. Right sub-panels show polar plots of the perturbation-related activity (baseline removed) in joint-torque space. PTD, preferred-torque direction; TS, torque-slope; TW, tuning width; EIR, excitation-inhibition ratio.

contrast, the second neuron showed large increases in activity for only a few perturbation conditions, resulting in narrow tuning relative to a cosine (tuning width = 0.26, **Figure 2D**, right). Relative to the unloaded baseline condition, the first neuron also showed similar increases (excitation) and deceases (inhibition) in activity in response to the various perturbations (excitation-inhibition ratio = 0.0, **Figure 2C**, left). The second neuron, however, exhibited excitation in response to each perturbation, though the extent of excitation differed between the perturbation directions (excitation-inhibition ratio = 1.66, **Figure 2D**, left).

Responses of M1 Neurons to Perturbations

We examined the activity of 109 neurons recorded in the shoulder-elbow region of M1 of Monkey D. Data from these neurons were presented in a previous publication that compared the activity of M1 neurons in the current task with their activity during static postural maintenance (Herter et al., 2009). Close to half of these neurons (n = 43, 39%) displayed perturbation-related activity (onset latency, 20–100 ms; bootstrap test, $p < 0.01$). **Figures 3A,B**, illustrate spike rasters and spike frequency histograms showing perturbation-related activity of two exemplar M1 neurons. Similar to the exemplar RN neurons seen previously, both exemplar M1 neurons showed large increases in activity for some perturbations. The first M1 neuron responded greatest to perturbations that required the monkey to generate an extensor torque at the shoulder and a flexor torque at the elbow (PTD = 114°, **Figure 3C**). The second neuron was most sensitive for loads that required production of extensor torques at the elbow (PTD = 283°, **Figure 3D**). Compared to the exemplar RN neurons, the first M1 neuron displayed smaller differences in modulation between preferred and non-preferred perturbation conditions (torque-slope = 62 (sp/s)/Nm, **Figure 3C**). The second M1 neuron was more sensitive to loads though still less sensitive than the two RN neurons (torque-slope = 91 (sp/s)/Nm, **Figure 3D**). Similar to the second RN neuron, both M1 neurons exhibited tuning widths that were slightly narrower than a cosine (tuning widths = 0.35 and 0.28, **Figures 2C,D**, right). Both M1 neurons showed similar diversity of excitation and inhibition that was seen in the exemplar RN neurons. Relative to baseline, the first M1 neuron showed increases and deceases in activity in response to the various perturbations, though excitation was greater than inhibition (excitation-inhibition ratio = 0.36, **Figure 3C**, left). Like the second RN neuron, the second M1 neuron exhibited excitation in response to each perturbation, though the extent of excitation varied across perturbation directions (excitation-inhibition ratio = 0.0, **Figure 3D**, left).

Responses of Upper-Limb Muscles to Perturbations

We examined the activity of 33 EMG samples recorded from 33 different sites (1 sample per site) in 11 proximal arm muscles of

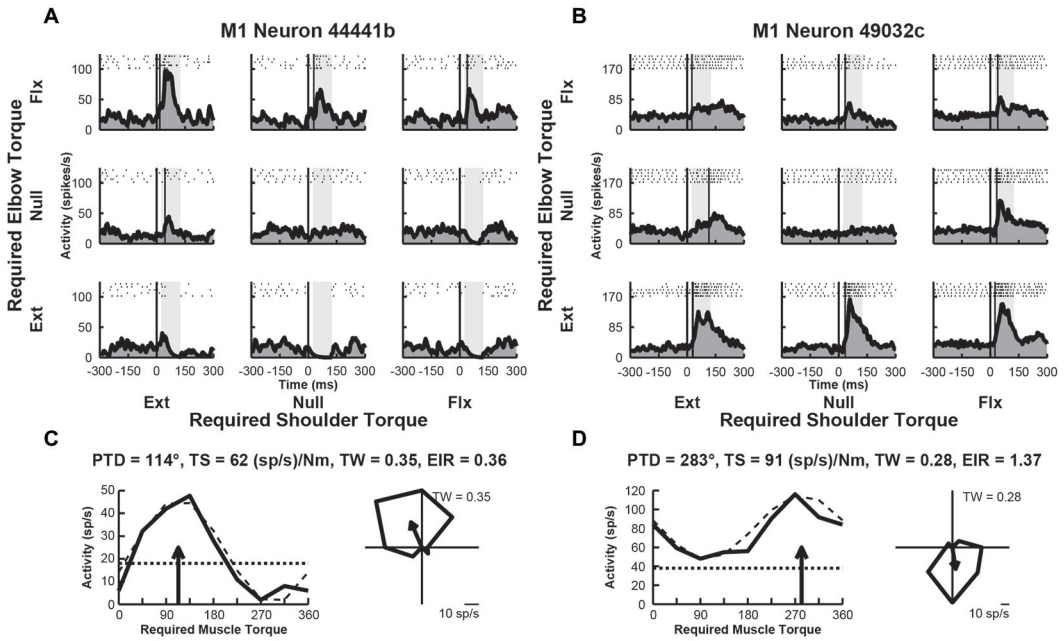

FIGURE 3 | Activity of exemplar M1 neurons. (A) Rasters and histograms for each perturbation condition (arranged in joint-torque space) displaying the activity of an M1 neuron that responded maximally to perturbations that required a flexor torque at the elbow. **(B)** Activity of a neuron that responded maximally to perturbations that required an extensor torque at the elbow. **(C,D)** Directional tuning of the corresponding M1 neurons. Left sub-panels illustrate linear plots of overall activity vs. joint-torque angle. Unloaded baseline activities and cosine fits are shown as dotted and dashed lines, respectively. Right sub-panels show polar plots of the perturbation-related activity (baseline removed) in joint-torque space. PTD, preferred-torque direction; TS, torque-slope; TW, tuning width; EIR, excitation-inhibition ratio.

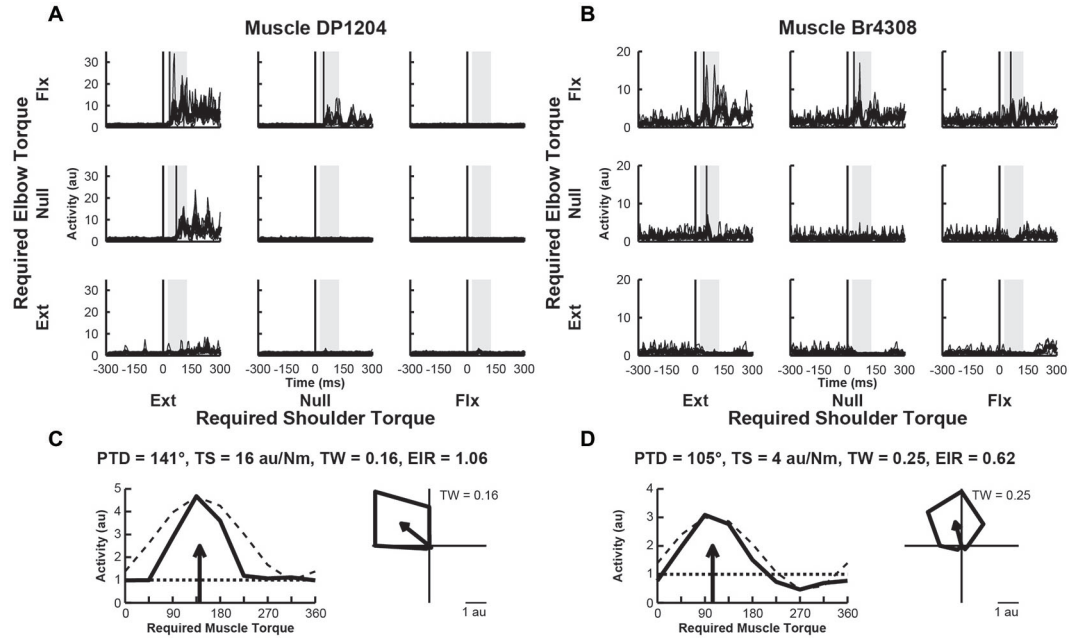

FIGURE 4 | Activity of exemplar upper-limb muscles.
(A) Electromyographic (EMG) activity of a posterior deltoid sample in each perturbation condition (arranged in joint-torque space). The posterior deltoid sample responded maximally to perturbations that required an extensor torque at the shoulder and a flexor torque at the elbow. **(B)** EMG Activity of a brachioradialis sample that responded maximally to perturbations that required a flexor torque at the elbow. **(C,D)** Directional tuning of the corresponding muscle samples. Left sub-panels illustrate linear plots of overall activity vs. joint-torque angle. Unloaded baseline activities and cosine fits are shown as dotted and dashed lines, respectively. Right sub-panels show polar plots of the perturbation-related activity (baseline removed) in joint-torque space. PTD, preferred-torque direction; TS, torque-slope; TW, tuning width; EIR, excitation-inhibition ratio.

Monkeys A–D. We found that two thirds of the muscles (n = 22, 67%) exhibited perturbation-related activity (onset latency, 20–100 ms; bootstrap test, $p < 0.01$). **Figures 4A,B**, illustrate perturbation-related activity obtained from two exemplar upper-limb muscles. An EMG recording from a posterior deltoid sample showed increases in activity in response to loads that required production of extensor torques at the shoulder and flexor torques at the elbow (PTD = 321°, **Figure 4C**). Similarly, an exemplar EMG recording from brachioradialis showed increases in activity for responses requiring flexor torques at the elbow and extensor torques at the shoulder (PTD = 105°, **Figure 4D**). Both of these patterns are consistent with activities that would bring the hand back to the target in response to their stretch. Both muscles exhibited narrow tuning relative to a cosine (tuning widths = 0.16 and 0.25, **Figures 4C,D**, right). Both muscles also showed far greater excitation than inhibition, relative to their baseline activities (excitation-inhibition ratios = 1.06 and 0.62, **Figures 4C,D**, left).

Comparison of Onset Latencies

We compared the response latencies of RN neurons, M1 neurons and upper limb muscles (**Figure 5**). As indicated above, many RN neurons (57%), M1 neurons (39%) and upper-limb muscles (67%) exhibited rapid responses (20–100 ms), suggesting that their activity is tightly coupled to the mechanical (sensory) stimulus. We found that the mean onset latencies of RN (44 ± 14 ms) and M1 (46 ± 19 ms) neurons were not significantly different from each other (Wilcoxon rank sum test, $p > 0.1$). By comparison, the mean onset latency of upper-limb muscles (55 ± 22 ms) was significantly longer than RN neurons (one-tailed t-test, $p < 0.05$) but did not differ significantly from M1 neurons, (Wilcoxon rank sum test, $p > 0.1$).

Comparison of Tuning Properties

A common characteristic of M1 neurons is that their torque-related activity exhibits a bimodal distribution of PTDs that mirrors the distribution observed in upper-limb muscles (reviewed in Kurtzer and Scott, 2007). Specifically, PTDs of M1 neurons and upper-limb muscles are both biased towards whole-limb flexor (EF + SE) and whole-limb extensor (EE + SF) torques. **Figure 6** investigates whether the RN neurons, M1 neurons and upper-limb muscles examined in the current study exhibit similar bimodal distributions of PTDs. Consistent with our previous studies, bimodal distributions of PTDs were seen in M1 neurons (**Figure 6B**, unimodal Rayleigh test, $p > 0.1$; bimodal Rayleigh test, $p < 0.01$, r = 0.53, PTD axes = 132–312°) and upper-limb muscles (**Figure 6C**, unimodal Rayleigh test, $p > 0.1$; bimodal Rayleigh test, $p < 0.01$, r = 0.66, PTD axes = 125–305°). In contrast, RN neurons exhibited similar results for unimodality and bimodality. RN neurons exhibited a unimodal distribution that was marginally insignificant (unimodal Rayleigh test,

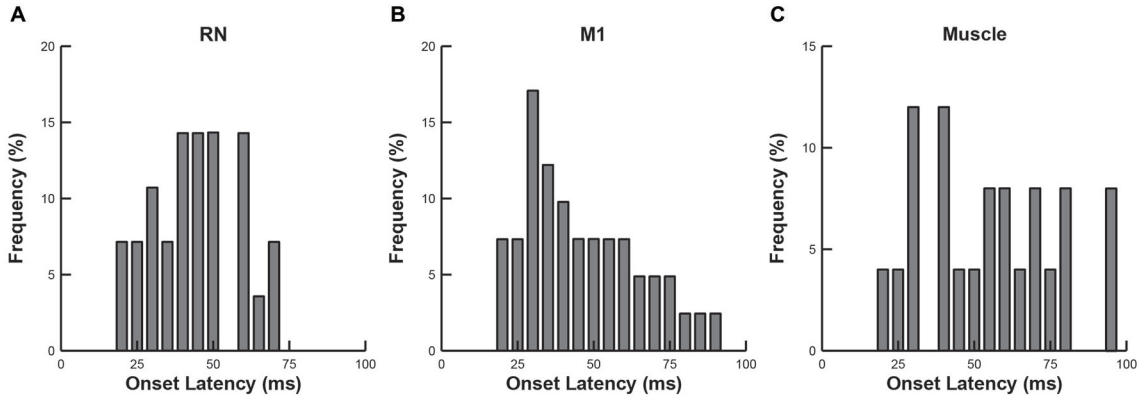

FIGURE 5 | Frequency histograms of onset latencies. **(A)** RN neurons. **(B)** M1 neurons. **(C)** Upper-limb muscles.

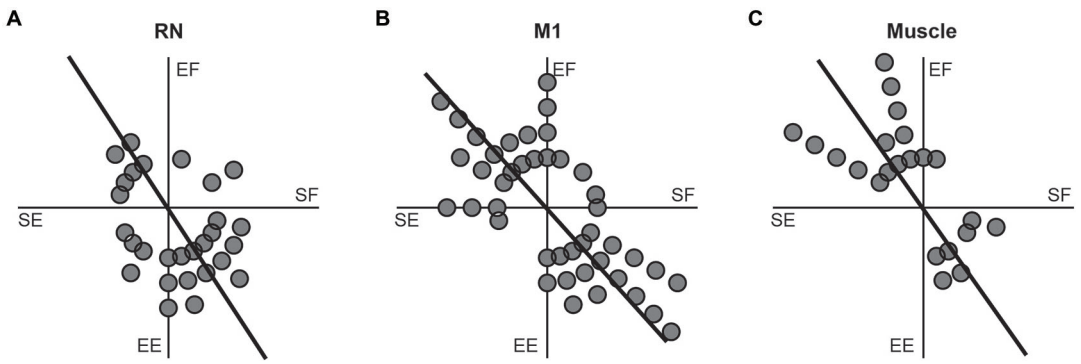

FIGURE 6 | Frequency histograms of preferred-torque directions. **(A)** RN neurons. **(B)** M1 neurons. **(C)** Upper-limb muscles. Each filled circle shows one neuron or muscle with a PTD within a 15° bin. Thick lines show the bimodal axes for each distribution of PTDs.

$p = 0.06$, $r = 0.31$, PTD = 288°), whereas the bimodal distribution was marginally significant (**Figure 6A**; bimodal Rayleigh test, $p < 0.05$, $r = 0.33$, PTD axes = 123–303°). Importantly, the distributions of RN neurons, M1 neurons and upper-limb muscles did not differ significantly from one another (*t*-tests, all $p > 0.1$).

In addition to comparing PTDs, we also examined whether the temporal evolution of other directional tuning properties in RN and M1 were similar to upper-limb muscles. Note that, because of the difference in units, TSs of neurons (discharge frequency) could not be directly compared with TSs obtained from EMG activity in muscles (arbitrary units). However, we found the mean TS in both brain regions and upper-limb muscles increased over time following perturbations (**Figure 7A**, linear regressions, all $p < 0.05$). Furthermore, the mean TS in RN was significantly greater than in M1 (**Figure 7A**, ANOVA, $p < 0.01$), indicating that firing frequencies of RN neurons increased more than M1 neurons in response to perturbations. Comparisons of tuning widths revealed that tuning widths were significantly narrower in upper-limb muscles than neurons in M1 and RN (ANOVA, $p < 0.01$), though the tuning widths were generally narrower than cosine tuning in all three (**Figure 7B**). Finally, we found that EIRs were broadly distributed in both RN and M1 (**Figure 7C**), including many neurons that exhibited reciprocal excitation and inhibition ($-1 <$ EIR < 1) and many neurons that were excited by all perturbations but in differing amounts (EIR > 1). By comparison, most muscles exhibited reciprocal excitation and inhibition in which excitation was greater than inhibition ($0 <$ EIR < 1). Despite these differences in the breadth of excitation and inhibition, we did not observe a significant difference in EIRs between RN neurons, M1 neurons and upper-limb muscles (**Figure 7C**, ANOVA, $p > 0.1$).

Discussion

The goal of the present study was to investigate whether mechanical perturbations evoke rapid sensorimotor responses in RN neurons that are similar to those observed in M1 neurons and upper-limb muscles. In general, perturbation responses in RN neurons were qualitatively similar to those observed in M1, with broad tuning and preferred torque directions biased towards whole limb flexor torques (elbow flexor and shoulder extensor) and whole limb extensor torques (elbow extensor and shoulder flexor). Timing of perturbation responses was also

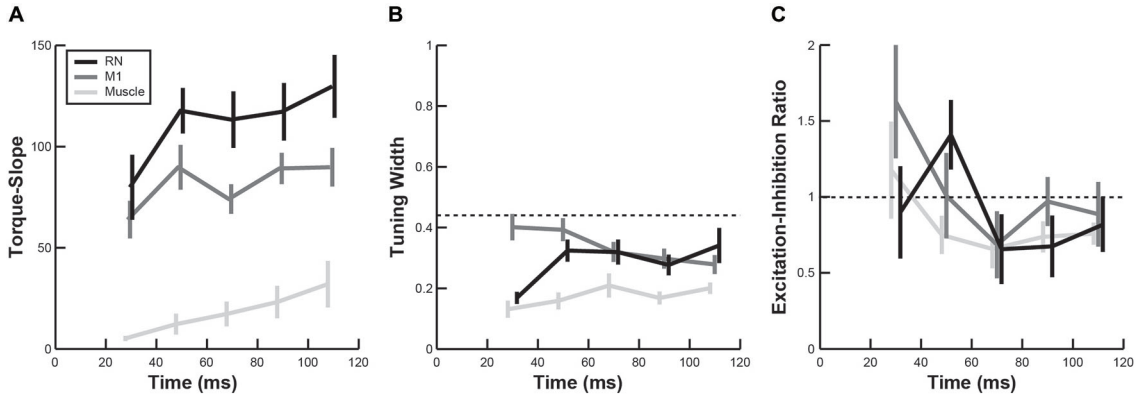

FIGURE 7 | Temporal evolution of perturbation-related activity. **(A–C)** Plots show changes in torque-slope **(A)**, tuning width **(B)** and activation-inhibition ratio **(C)** of RN neurons (black), M1 neurons (dark gray) and upper-limb muscles (light gray) during the first 120 ms after perturbation onset (mean ± sem).

similar across the two regions, with onsets beginning at ∼20 ms after perturbations were applied. However, RN neurons tended to display larger perturbation responses than M1 neurons with regards to the absolute change in discharge.

Both RN and M1 exhibited distributions of PTDs that were skewed towards one of two quadrants in joint-torque space, shoulder extensor torque coupled with elbow flexor torque (whole-limb flexor torque) and shoulder flexor torque coupled with elbow extensor torque (whole-limb extensor torque) (**Figures 6A,B**). However, RN neurons exhibited similar vector lengths for the unimodal (r = 0.31) and bimodal distributions (r = 0.32). The unimodal PTD of 288° indicates that more RN neurons were related to whole-limb extensor torques, which is consistent with several studies on RN (Gibson et al., 1985a; Cheney et al., 1988; Mewes and Cheney, 1994; Sinkjaer et al., 1995; Belhaj-Saif et al., 1998; Park et al., 2004). Similar to M1 and RN, PTDs of shoulder and elbow muscles were also skewed towards whole-limb flexor and whole-limb extensor torques (**Figure 6C**) even though some muscles spanned only one joint (i.e., monoarticular) and those muscles that spanned both joints (i.e., biarticular muscles) possess pulling actions in the opposite quadrants (Graham and Scott, 2003). A similar bias has also been observed in M1 and upper-limb muscles when continuous loads were applied to the shoulder and/or elbow during static posture (Cabel et al., 2001; Kurtzer et al., 2005, 2006a; Herter et al., 2007, 2009), as well as for dynamic or static loads applied to the limb during reaching (Gribble and Scott, 2002; Kurtzer et al., 2005, 2006b).

These biases in the distribution of PTDs exhibited by RN and M1 neurons appear to reflect the anatomical properties of the musculoskeletal system (Kurtzer et al., 2006a,b; Lillicrap and Scott, 2013). Both mathematical and neural network models highlight that the bias in the distribution of PTDs was only observed when biarticular muscles were included in the models. This provides strong evidence that the patterns of activity observed in RN and M1 neurons reflect constraints imposed by the anatomical organization of the musculoskeletal system (Kurtzer and Scott, 2007).

In theory, proximal limb muscles should exhibit relatively rapid perturbation responses (within 25 ms) due to spinal level feedback. However, only a few muscles displayed perturbation responses below 30 ms. The late muscle responses likely reflect the fact that minimal muscle activity is required to overcome passive limb forces in the middle of the workspace (Graham et al., 2003). Short latency stretch responses increase with baseline activity, but are small or not present when the muscle is inactive prior to the perturbation (Pruszynski et al., 2011a). Muscles were also commonly modulated by only two to three load conditions, whereas neurons in RN and M1 were generally modulated by three to four load conditions. Stated otherwise, muscles were rarely activated by flexor and extensor torques at a joint, whereas neurons were commonly activated by flexor and extensor torques at one of the two joints.

Perhaps the largest difference between RN and M1 neurons was in their mean discharge rates, as measured by TSs (**Figure 7A**). Although neurons in both structures exhibited steady increases in TS over the first 100 ms following perturbations (mirroring upper-limb muscles), the neurons in RN exhibited systematically higher TS values than neurons in M1. Perturbation responses were approximately 50% larger in RN neurons as compared to M1 neurons. Higher firing rates have also been observed in brainstem regions (superior colliculus) compared to cortical regions (frontal eye fields) during saccadic eye movements (Jantz et al., 2013).

The present study shows that both M1 and RN receive rapid feedback from the motor periphery. The dorsal column system provides the primary source of feedback to M1, including direct inputs from thalamus and indirect inputs via primary somatosensory cortex (Brinkman et al., 1978; Horne and Tracey, 1979; Asanuma et al., 1980). Projections from cerebellum also contribute sensory information to M1 (Massion, 1976; Asanuma et al., 1983; Butler et al., 1992). The dorsal column system is also the principle source of sensory information for RN (Berkley et al., 1986; Boivie, 1988). Importantly, RN is a site of significant convergence on sensory and motor inputs from both cortex and cerebellum, suggesting that M1, RN

and cerebellum form a recurrent network that is involved in feedback control of voluntary motor actions. This is further supported by observations that perturbation-related activity in M1 is modulated by behavioral context (Conrad et al., 1974, 1975; Evarts and Tanji, 1974, 1976; Wolpaw, 1980b; Omrani et al., 2014; Pruszynski et al., 2014). It remains to be explored if perturbation responses in RN are similarly modulated by the behavioral goal.

The RN contains two regions, magnocellular and parvocellular, with the latter projecting principally to the inferior olivary nucleus creating a circuit with the cerebellum, and the former providing the origin of the rubrospinal tract (Houk et al., 1993). The corticospinal tract is much larger than rubrospinal tract in non-human primates and this difference is even greater in humans (Larsen and Yumiya, 1980; Nathan and Smith, 1982). Although we did not identify whether our sample of RN neurons were in the magnocellular or parvocellular regions of RN, it would be interesting to know if there was any substantive difference in the perturbation response properties in these sub-regions of RN.

Author Contributions

TMH helped design the study, performed the data analysis, and wrote the manuscript. TT assisted with the data analysis. DPM helped design the study and assisted with data collection. SHS helped design the study, assisted with the data analysis, and participated in writing of the manuscript. All authors approved the final version of the manuscript.

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Interactions between stretch and startle reflexes produce task-appropriate rapid postural reactions

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Neural pathways underpinning startle reflex and limb stretch reflexes evolved independently and have served vastly different purposes. In their most basic form, the pathways responsible for these reflex responses are relatively simple processing units that produce a motoric response that is proportional to the stimulus received. It is becoming clear however, that rapid responses to external stimuli produced by human and non-human primates are context-dependent in a manner similar to voluntary movements. This mini review discusses the nature of startle and stretch reflex interactions in human and non-human primates and the involvement of the primary motor cortex in their regulation.

Keywords: long-latency stretch reflex, startle response, startReact, movement preparation, motor cortex

Like all animals, humans have inherited most of our anatomical structures and physiological functions from our ancestors. Some of these we have retained largely intact and some we have modified from their original form to suit our own purposes. We have also added some of own structures and functions that supersede or regulate those we have inherited. The purpose of this review is to discuss the contribution of stretch reflex and startle response circuits to the flexibility of rapid postural responses in humans and the possibility that rapid, goal-directed actions may be subserved by interactions between separate cortical and subcortical neural circuits. The focus of the review is on the generation, rather than the context-dependent modulation of these rapid responses.

I will begin by defining rapid postural responses as being muscular contractions that occur in response to an external perturbation, detected by one or more sensory modalities, and with a latency that is shorter than the most rapid voluntary response. This definition immediately raises the problem of how we determine that an action is voluntary and, although it is a somewhat unsatisfying resolution, I will define the most rapid voluntary actions as those that result from a person being asked to make a predefined response as rapidly as possible to a detectable, but not startling, stimulus. The magnitude of the stimulus becomes critical in any discussion of startle responses and we therefore arrive at a relative definition of voluntary actions that will suffice for the purposes of this review without being ideal. As I will discuss, distinctions between voluntary and involuntary responses are becoming blurred by discoveries about the flexibility of "involuntary" actions, and attempts to distinguish them may be futile.

EVOLUTIONARY FUNCTIONS OF RAPID MOTOR REACTIONS

Rapid, "involuntary" postural responses are not unique to humans. This type of motor action can be observed in early chordates, such as lampreys (Currie and Carlsen, 1985), with simple central nervous systems animals and even in animals with no central nervous system, such as jellyfish and other Cnidaria (Mackie, 1984). In these types of animals, the expression of rapid postural responses to startling stimuli often takes the form of an escape reflex to avoid predators. While the goal of these escape responses is consistent across a wide variety of animals, the pattern of muscle activation required to facilitate escape necessarily differs between animals with different body morphologies. In short-bodied aquatic animals for example, the escape response is characterized by all-or-none contraction of the muscles on one side of the body, resulting in the assumption of a C-type posture before contractions on the opposite side of the body produce the tail flick required for a rapid getaway (Eaton et al., 1977). In contrast, escape in long-bodied teleosts is enabled by co-contraction of muscles on both sides of the body, allowing rapid withdrawal of the head as the animal assumes a flattened S-shape posture (Rock, 1980). The pattern of muscle contraction required for this type of head withdrawal changes with the posture of the animal, and it has been shown that even larval lamprey have the capacity to modify the pattern of muscle activity of the escape response to compensate for changes in their initial posture (Currie and Carlsen, 1985). Escape responses in teleost fish, and presumably most animals, are also modified to account for differences in the location of the threatening stimulus (Eaton and Emberley, 1991). The flexibility of the escape response in even animals with simple nervous systems demonstrates the important role of multisensory

feedback for online adaptation of rapid postural and escape responses.

Given the need for rapid predator avoidance in animals with vastly different body types, the expression of these responses has been necessarily altered to suit the sensorimotor requirements of each anatomical form. Hale et al. (2002) have demonstrated that the expression of escape behavior is not conserved even across four species of fish with similar anatomy. The neural circuits mediating escape responses also appear to have undergone evolutionary adaptation, although perhaps less so, as several characteristics of the circuit have remained invariant. The need for rapid conduction from the sensory organs that detect a threat to the peripheral musculature that initiates escape appears to have constrained the type of neurons involved in the escape circuit to have axons of particularly large diameter [described as "giant fibers" in many animals] (Curtis and Cole, 1942; Mulloney, 1970; Eaton et al., 1977; Lingenhöhl and Friauf, 1992). These fast-conducting cells are invariably located within the brainstem or homologous hindbrain structure and often receive input from multiple sensory modalities including the auditory, visual and somatosensory systems. Even in mammals, who lack axons sufficiently large to be labeled as "giant," there exist populations of cells within the ventrocaudal part of the nucleus reticularis pontis caudalis with large soma and direct projections to the spinal cord (Mitani et al., 1988) that have been implicated in rapid responses to startling stimuli (startle reflexes) (Krasne and Edwards, 2002; Cluff and Scott, 2013; Safavynia and Ting, 2013).

The stimulus-driven reflexes initiated by giant brainstem cells can be suppressed or facilitated in a number of animals according to moment-to-moment functional requirements. An example of this type of reflex regulation can be found in the squid, which acquires the capacity for startle reflex inhibition during development to allow for the capture and consumption of small, fast-moving prey (copepods) (Preuss and Gilly, 2000). If squid do not encounter copepods in their environment during early development they do not acquire the ability to suppress the startle reflex. Similar types of startle reflex regulation, both inhibition and facilitation, are demonstrated by crayfish (Krasne and Edwards, 2002) and rats (Prosser and Hunter, 1936). The function of this startle reflex pathway has also been observed to change over an evolutionary time scale in Tahitian moths that have evolved in the absence of bats (Fullard et al., 2004). The startle reflex in these moths has been modified such that responses to high frequency auditory stimuli (similar to bat echolocation sounds) have been substantially reduced, although neural circuit underlying the startle reflex has been retained (Fullard et al., 2007). These examples demonstrate the potential for startle reflexes to be regulated rapidly and reversibly as well as very slowly but more permanently in animals with relatively simple nervous systems compared to the human nervous system. It is unsurprising then that the expression of rapid postural reactions in humans appears to be regulated in a manner that compensates for many postural and environmental factors.

CONTRIBUTIONS OF STRETCH REFLEXES TO RAPID MOTOR REACTIONS IN HUMANS

Humans are capable of producing rapid responses to large somatosensory, auditory or visual stimuli. In the upper limb, muscular responses to rapid stretch are detectable as early as 20 ms after the stretch begins, this response is referred to as the short-latency or myotatic stretch reflex (Liddell and Sherrington, 1924). If the muscle stretch lasts longer than 35 ms (±5.5 ms), a second muscle contraction can be observed, beginning 50–60 ms after the onset of muscle stretch (Lewis et al., 2005), referred to as the long-latency or transcortical stretch reflex. Both of these responses are assumed to be involuntary because the fastest voluntary muscular responses to smaller stimuli of the same type are initiated 90–100 ms after the stimulus (Hammond, 1955). In contrast to the short-latency stretch reflex, which is subserved entirely by cells within the spinal cord and peripheral nervous system, the long-latency stretch reflex appears to involve the primary motor area of the cortex (Matthews, 1991; Shemmell et al., 2009; Pruszynski et al., 2011) as well as other brain regions including the cerebellum (Vilis et al., 1976; Strick, 1983). The role played by the stretch reflex in postural maintenance and movement is not yet clear and has been the subject of debate in the scientific community for decades. Originally believed to be a mechanism by which postural perturbations were corrected, it has since been demonstrated that the muscle contractions produced by the stretch reflex are insufficient for this role (Crago et al., 1976). On this basis it has been argued that the purpose of the stretch reflex is to regulate muscle stiffness, and therefore limb impedance (Sinkjaer and Hayashi, 1989; Carter et al., 1990; Kearney et al., 1997). Some of the factors influencing the expression of the long-latency stretch reflex however, suggest that either its role is more complicated or that there are multiple mechanisms for postural regulation being invoked. Some of the major factors influencing the long-latency stretch reflex are outline below.

STABILITY OF THE LIMB AND ENVIRONMENT

Cortical regulation of the long-latency stretch reflex circuit appears to imbue this response with the capacity for subtle, task-appropriate modulation and coordination. For example, the amplitude of the long-latency stretch reflex is larger during interactions with compliant devices than those offering high levels of stiffness (Doemges and Rack, 1992; Dietz et al., 1994; Perreault et al., 2008). When environmental instability is greater in some directions than others, the amplitude of the long-latency stretch reflex in many muscles is greatest when the direction of greatest environmental instability aligns with the direction of greatest limb instability (Krutky et al., 2010). This reflex modulation allows changes in arm stiffness to rapidly compensate for instabilities in the environment (Kimura et al., 2006; Franklin et al., 2007; Wagner and Smith, 2008; Ahmadi-Pajouh et al., 2012; Cluff and Scott, 2013). That is, the long-latency stretch reflex appears to be regulated according to the levels of stability simultaneously offered by the environment with which one interacts and the configuration of the limb with which those interactions are made.

BODY AND LIMB POSTURE

Long latency stretch reflexes in soleus and tibialis anterior muscles have also been shown to be sensitive to changes in body posture, being substantially greater during standing than when lying supine despite equivalent levels of muscle activation in both conditions (Nakazawa et al., 2003). The long latency postural response in the upper limb also appears to be altered depending

upon the amplitude and direction of postural perturbations at limb segments distal to the recorded muscle (Kurtzer et al., 2008), demonstrating that rapid postural responses are distributed to muscles that have not been stretched or otherwise stimulated and that expression of the long latency response reflects an understanding of limb mechanics.

IMMINENT GOAL-DIRECTED MOVEMENTS

The long latency postural response, at least in the upper limbs, is also modulated according to the voluntary goal of an upcoming action (Pruszynski et al., 2008; Crevecoeur et al., 2013). Hammond was the first to demonstrate that perturbations of elbow posture could induce a response in the biceps brachii 50–60 ms after the onset of the perturbation (Hammond, 1955) that was alterable according to the intention of the participant to assist or resist the perturbation (Hammond, 1956). Evarts and colleagues were also able to demonstrate that pyramidal tract neurons originating in the motor cortex become active well in advance of such responses and that the firing rate of individual neurons was associated with the direction of the intended movement (Evarts and Tanji, 1974; Tanji and Evarts, 1976). It has since been shown that rapid perturbations of limb posture can hasten whole patterns of muscle activity that are appropriate for an intended movement, beginning at the time associated with the long-latency stretch reflex but also involving non-stretched muscles (Koshland and Hasan, 2000). Similarly, task-specific patterns of muscle activity have been observed in response to limb perturbations when the direction of the required response is unpredictable prior to the perturbation (Pruszynski et al., 2011; Omrani et al., 2014). The release of task-specific patterns of muscle activity has led to confusion as to whether the long-latency stretch reflex is a regulator of limb impedance to minimize postural disturbances (reaction) or whether it also plays a role in movement planning (action).

Some investigators have suggested that some of the confusion about the role of the long-latency stretch reflex may be caused by the superposition of two reflexive responses, one regulating limb impedance and one involved in the preparation and release of motor plans. Based initially on similarities in the timing of the long-latency stretch reflex and the startle response in many muscles, it has been suggested that activation of the startle response circuit may be responsible for releasing planned motor actions (Valls-Solé et al., 1999; Rothwell et al., 2002).

CONTRIBUTIONS OF STARTLE RESPONSES TO RAPID MOTOR REACTIONS IN HUMANS

For many animals, the neural circuit underlying responses to startling or immediately threatening stimuli involves connections from a number of sensory receptor systems onto large, rapidly conducting neurons in the brainstem (Mittenthal and Wine, 1978; Ritzmann and Camhi, 1978; Koto et al., 1981). This also appears to be true for humans, with the nucleus reticularis pontis caudalis identified by anatomical and electrophysiological studies as the most likely site at which auditory, vestibular and somatosensory stimuli summate to trigger the motor portion of the startle response (Davis et al., 1982; Lingenhöhl and Friauf, 1992; Yeomans and Frankland, 1995; Yeomans et al., 2002). In humans, triggering the startle response at rest with a loud auditory stimulus produces activity in many muscles throughout the body, almost always including both the orbicularis oculi (OO) and sternocleidomastoid (SCM) and with predominant flexor activity in limb muscles (Landis and Hunt, 1939). This pattern of muscle activity is altered radically when a startling auditory stimulus is applied before, or coincident with, a prepared voluntary action (Valls-Solé et al., 1999; MacKinnon et al., 2007; Ravichandran et al., 2013). When an action has been prepared, the pattern of muscle activity evoked by a loud auditory stimulus closely resembles that of the prepared movement, while also often involving activation of the OO and SCM muscles (Valls-Solé et al., 1999; Ravichandran et al., 2013). The major difference between prepared actions that are triggered by innocuous or startling auditory stimuli is the latency of the response, with startling auditory stimuli triggering the initiation of prepared forearm actions around 100 ms earlier than low volume stimuli (Valls-Solé et al., 1999). A similar hastening of prepared actions, with associated OO and SCM activity, has also been observed following rapid joint perturbations (Ravichandran et al., 2013) and whole-body postural perturbations (Campbell et al., 2013; Safavynia and Ting, 2013), confirming that rapid goal-directed responses: (i) are triggered by the same sensory modalities as startle responses, (ii) are initiated at the same time in limb muscles as startle responses and (iii) activate the muscles essentially involved in startle response expression (OO and SCM). This is consistent with the idea that auditory, vestibular and somatosensory inputs to the reticularis pontis caudalis are capable of activating startle circuitry and triggering rapid postural responses that resemble their voluntary counterparts. The electromyographic evidence accumulated to date therefore supports the involvement of the neural circuit underlying the startle reflex in the rapid expression of flexible postural responses to startling stimuli. This response has been termed the startReact response. An important caveat to this however, are observations that postural adjustments made prior to stepping can also be released early by non-startling stimuli (Delval et al., 2012), the likelihood of early release being related to the strength of the stimulus. This suggests a system of (at least) two response pathways in which the faster pathway is more likely to be engaged as stimulus strength increases.

Given similarities in the timing of long-latency stretch reflex and startReact expression in many muscles (long latency stretch reflex onset ∼57 ms, Lewis et al., 2005 and startReact onset ∼73 ms, Ravichandran et al., 2013), temporal overlap of the two reflexes could explain the wide variety of conditions under which the magnitude of "involuntary" postural responses is observed to change. While the evidence for temporal overlap of two "involuntary" responses is now strong following auditory, somatosensory and vestibular stimuli (Alibiglou and MacKinnon, 2012; Nonnekes et al., 2014), the neural basis for this type of superposition remains a source of debate. A number of investigators have suggested that cortically-initiated preparation for action alters the state of the startle circuit in a manner that results in the full expression of a planned action when the startle circuit is subsequently activated (Rothwell et al., 2002; Shemmell et al., 2009). An anatomical substrate for this type of cortical regulation of startle circuits exists in the form of dense disynaptic connections from

the primary motor cortex to the reticularis pontis caudalis via the zona incerta (Shammah-Lagnado et al., 1987). Tanji and Evarts have also provided evidence that pyramidal tract neurons within the primary motor cortex change their firing rate during movement preparation as soon as an upcoming movement is identified (Tanji and Evarts, 1976), providing a signal capable of altering startle circuit excitability. Unfortunately, a definitive investigation of links between motor cortex activity and that of cells in areas of the reticular formation that have been implicated in the startle circuit has not yet been carried out during movement preparation. The effects of transient primary motor cortex inhibition however, have provided some interesting insights into interactions between cortical and brainstem centers involved in startle and startReact responses.

Inhibiting the primary motor cortex with transcranial magnetic stimulation (TMS) during the period in which a startReact response would be observed has produced varying effects on muscle activity. In some studies, startReact responses are clearly delayed by the cortical stimulus (Alibiglou and MacKinnon, 2012; Stevenson et al., 2014), suggesting a critical involvement of the motor cortex in the generation of the startReact response. Several researchers have proposed models for the circuits underlying startle and startReact responses (Carlsen et al., 2011, 2012; Alibiglou and MacKinnon, 2012) in which startling auditory stimuli are transmitted to the primary motor cortex where they trigger the activation of cells that are biased toward producing a prepared movement. The proposed model describes separate pathways for startle and startReact responses, with the latter being dependent upon the same cortical output neurons as voluntary commands. This model fits previous accounts of preparation-dependent activity of motor cortical output neurons (Tanji and Evarts, 1976) and accounts for similarities in preparation-dependent modulation of long latency stretch reflexes and startReact responses (Kimura et al., 2006; Pruszynski et al., 2011; Spieser et al., 2013; Stevenson et al., 2014). The reliance of startReact responses on a transcortical pathway may also explain observations that prepared actions can be triggered early by non-startling stimuli (Delval et al., 2012). There have been at least two observations, however, of prepared actions being released within a period of cortical inhibition sufficiently powerful to suppress all voluntary activity in a target muscle (Shemmell et al., 2009; Spieser et al., 2013), a combination of events that would not be possible if startReact responses and voluntary motor actions were dependent on the same set of corticospinal tract neurons. These observations are more consistent with models of startReact that emphasize the contribution of subcortical structures (Valls-Solé et al., 2008).

It may be possible to account for the release of prepared actions within a period of cortical inhibition with a model that attributes the release of these actions to startle circuitry in the brainstem (**Figure 1**). The proposed model has the benefit of removing the separation between startle and startReact responses, instead explaining both responses as the result of subcortical "startle" circuits, explaining why cortical inhibition longer than 100 ms (Shemmell et al., 2009; Spieser et al., 2013), stroke (Honeycutt et al., 2015) or pathological degeneration of the corticospinal tract (Nonnekes et al., 2014) do not eliminate startReact expression. This model includes well-described transcortical sensorimotor pathways that provide the capacity for transcortical reflex transmission and the generation of longer latency task-specific actions. Factors such as the magnitude of the sensory stimulus and the predictability of the required response may determine the likelihood of motor actions being initiated within the reticular formation.

The delaying effect of TMS on startReact responses is accounted for in the model with evidence that TMS of motor cortical cells also has inhibiting effects on cells within the reticular formation. A period of prolonged inhibition (up to ∼90 ms following a stimulus) of reticular formation neurons has been described by Fisher et al. (2012) following TMS of the primary motor cortex in monkeys. Interestingly, experiments in which startReact responses are preceded by TMS (Shemmell et al., 2009; Alibiglou and MacKinnon, 2012; Spieser et al., 2013; Stevenson et al., 2014) show the startReact response initiated ∼100 ms after the TMS pulse, shortly after the putative release of inhibition within the reticular formation. The TMS-induced inhibition within the reticular formation would presumably be limited to neurons influencing the same muscles as the stimulated cortical neurons, explaining why activation of muscles innervated by facial nerves (SCM and OO) is not delayed by stimulation within the motor cortex representation of the upper limb (Stevenson et al., 2014). Further support for the idea that startReact responses are released through reticulospinal projections is offered by evidence that these responses are absent in individuated finger movements despite being present in more proximal muscles (Carlsen et al., 2008; Honeycutt et al., 2013). This may relate to the paucity of reticulospinal projections to distal muscles of the upper limb (Riddle and Baker, 2010). Finally, evidence that startReact responses are not amenable to pre-pulse inhibition, as startle responses are, may still suggest separate pathways for these responses (Valls-Solé et al., 2005, 2008), but this difference may also be explained by the higher attentional demands of task-specific preparation compared to a resting situation (Maslovat et al., 2012). The proposed model for these responses relies on the latter explanation but in doing so, describes a relatively simple system that is consistent with the sustained reliance upon giant brainstem neurons for rapid adaptive responses of a wide range of animal species.

CONCLUSION

Despite being two of the most primitive and fundamental mechanisms for movement initiation, the purpose of the stretch reflex and startle response remains unclear in humans. Behavioral advantages provided by the ability to release prepared movements rapidly appear to have led to a control system in humans in which voluntary and involuntary response mechanisms overlap substantially. I suggest a number of modifications to a previous model of startle-induced movement release (startReact) involving both transcortical and subcortical pathways for sensory processing, with the transcortical pathway sharing output neurons with the transcortical stretch reflex and voluntary motor system. I suggest that transcortical pathways have evolved to provide enormous flexibility of control, complementing less flexible but faster subcortical motor pathways. Together, these motor pathways blur

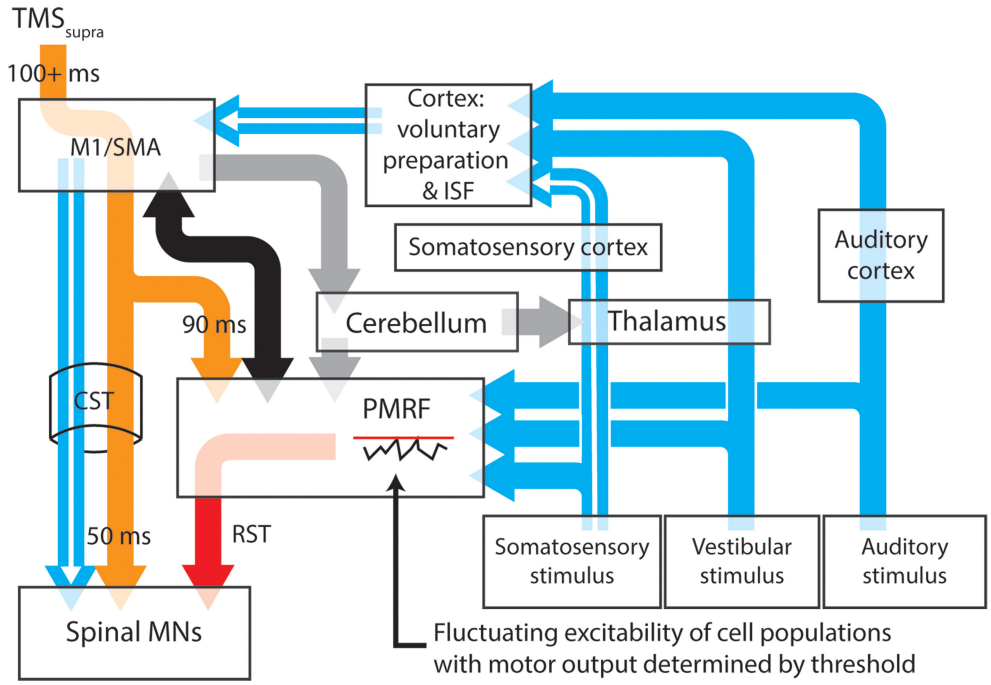

FIGURE 1 | A proposed model for the neural pathways subserving the expression of long latency stretch reflexes, startle and startReact responses. Transcortical contributions to long latency stretch reflexes are enabled by a pathway that involves the primary somatosensory and motor cortices before descending to muscles through the corticospinal tract (white arrows). Stimulation of somatosensory, vestibular or auditory systems results in transmission of these signals to the cortex and the pontomedullary reticular formation (blue arrows), each of which have thresholds for activating output cells. Inhibition of the primary motor cortex (or areas involved in movement preparation) by application of suprathreshold TMS (orange arrows) results in almost simultaneous inhibition of cells within the spinal cord and PMRF, although for different periods of time. Spinal motoneurons appear to be inhibitied for ~50 ms after TMS, while cells within the PMRF are inhibited for ~90 ms in non-human primates. Output cells within the motor cortex however, can be inhibited for up to 200 ms (Strick, 1983). During periods of cortical inhibition, activation of the corticospinal tract is not possible, although a combination of cortico-reticulospinal input (black arrows) and sufficiently large sensory input can still activate reticulospinal tract cells (red arrow) after any TMS-induced inhibition of PMRF ceases. The likelihood of PMRF output (startle or startReact responses) is determined in this model by the magnitude of the sensory input and the instantaneous excitability of PMRF cells. A similar situation is likely to exist at the cortical level (see Alibiglou and MacKinnon, 2012). Task, posture and stability-dependent regulation of stretch reflex and startReact responses likely involves input from the cerebellum to both the primary motor cortex and reticular formation (gray arrows). In this figure thalamocortical projections to regions responsible for voluntary motor preparation, but projections directly to M1 may also play an important role in modulating rapid responses. Output nuclei and detailed information about synapse locations for each pathway have been omitted from this figure. M1, Primary motor cortex; SMA, supplementary motor area; PMRF, pontomedullary reticular formation; ISF, intersensory facilitation; MN, motoneuron.

the boundaries between involuntary and voluntary motor control and provide us with the capacity to respond rapidly to environmental stimuli in a highly flexible and context-dependent manner.

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Primary motor cortex and fast feedback responses to mechanical perturbations: a primer on what we know now and some suggestions on what we should find out next

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Many researchers have drawn a clear distinction between fast feedback responses to mechanical perturbations (e.g., stretch responses) and voluntary control processes. But this simple distinction is difficult to reconcile with growing evidence that long-latency stretch responses share most of the defining capabilities of voluntary control. My general view—and I believe a growing consensus—is that the functional similarities between long-latency stretch responses and voluntary control processes can be readily understood based on their shared neural circuitry, especially a transcortical pathway through primary motor cortex. Here I provide a very brief and selective account of the human and monkey studies linking a transcortical pathway through primary motor cortex to the generation and functional sophistication of the long-latency stretch response. I then lay out some of the notable issues that are ready to be answered.

Keywords: reflex, long-latency, upper-limb, primary motor cortex, transcortical pathway

INTRODUCTION

The nervous system responds to unexpected mechanical perturbations with a stereotypical sequence of muscle activity. The fastest and crudest response is the short-latency stretch response, which occurs so quickly that is must reflect spinal processing (Pierrot-Deseilligny and Burke, 2005). The slowest and most sophisticated response is labeled "voluntary", often because it occurs at latencies greater than typical measures of voluntary reaction time (Prochazka et al., 2000). At intermediate latencies is the long-latency stretch response, which occurs faster than typical measures of voluntary reaction time yet produces a wide range of sophisticated responses often reserved for voluntary control processes (for reviews, see Scott, 2004, 2012; Shemmell et al., 2010; Pruszynski and Scott, 2012): modulation by subject intent (Hammond, 1956; Hagbarth, 1967; Crago et al., 1976; Evarts and Granit, 1976; Colebatch et al., 1979; Rothwell et al., 1980; Pruszynski et al., 2008; Shemmell et al., 2009; Manning et al., 2012; Ravichandran et al., 2013), sensitivity to task goals (Marsden et al., 1981; Doemges and Rack, 1992a,b; Dietz et al., 1994; Häger-Ross et al., 1996; Nashed et al., 2012), engagement during decisional processes (Yang et al., 2011; Selen et al., 2012; Nashed et al., 2014), flexible routing of sensory information across the musculature (Cole et al., 1984; Ohki and Johansson, 1999; Mutha and Sainburg, 2009; Dimitriou et al., 2011; Omrani et al., 2013), and knowledge of the physical properties of the arm (Gielen et al., 1988; Soechting and Lacquaniti, 1988; Koshland et al., 1991; Kurtzer et al., 2008, 2009, 2013, 2014; Crevecoeur et al., 2012; Crevecoeur and Scott, 2013) and environment (Akazawa et al., 1983; Bedingham and Tatton, 1984; Dietz et al., 1994; Kimura et al., 2006; Perreault et al., 2008; Pruszynski et al., 2009; Shemmell et al., 2009; Krutky et al., 2010; Ahmadi-Pajouh et al., 2012; Cluff and Scott, 2013).

Here, I provide a brief review of the monkey and human studies linking the long-latency response of the arm, and its functional sophistication, to a transcortical pathway centered on primary motor cortex (M1). Understanding these neural links is motivated by recent theories of motor control—based on optimal feedback control (Todorov and Jordan, 2002)—which suggest that voluntary motor behavior reflects sophisticated manipulation sensory feedback (Scott, 2004). My intention is not to be exhaustive (for that, see Pruszynski and Scott, 2012), but rather to highlight a few particularly notable studies to summarize what we know now and motivate a few things that we should do next.

TRANSCORTICAL CONTRIBUTION TO THE LONG-LATENCY STRETCH RESPONSE

There are essentially three independent lines of evidence—in monkeys and humans–that a transcortical pathway though M1 contributes to the long-latency stretch response. The first and strongest evidence comes from monkey work showing that corticomotoneurons, which project directly from M1 to motoneurons, produce post-spike facilitation in their target muscles at such short latencies (**Figure 1A**) that they can contribute to the long-latency stretch response even when accounting for

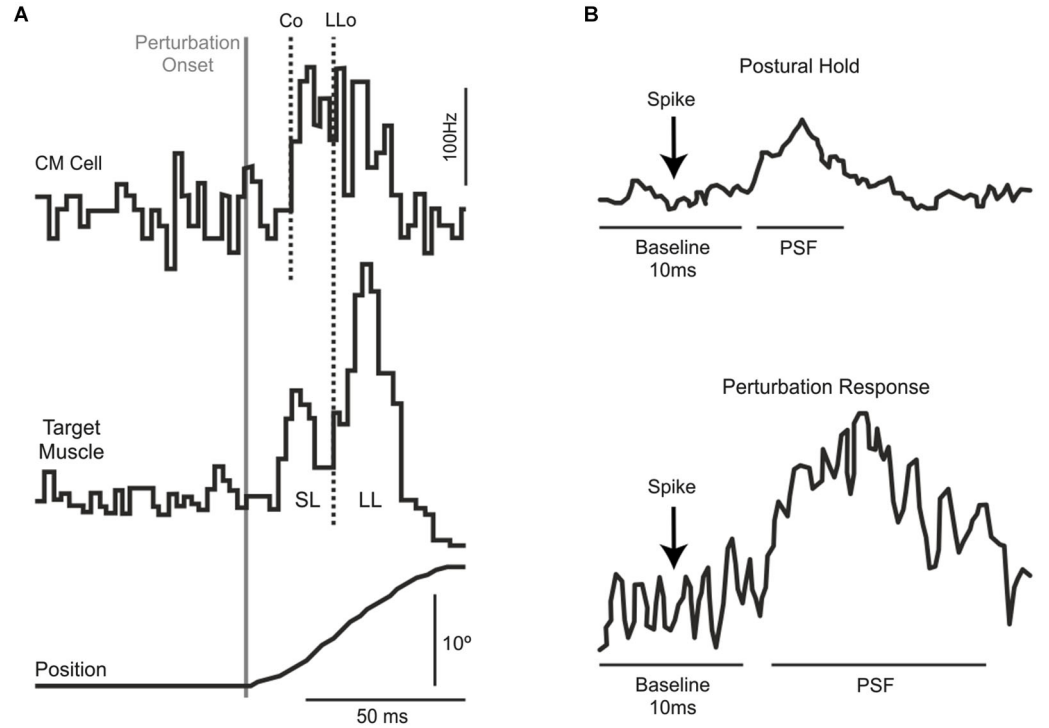

FIGURE 1 | (A) Extracellular recordings from a single corticomotoneuronal neuron in primary motor cortex (top) and muscle activity from its target muscle (middle) in response to excitatory torque perturbations that causes wrist displacement (bottom). Traces are aligned on perturbation onset. The vertical lines represent the onset of the CM activity (Co) and the onset of the long-latency response in the target muscle (LLo). **(B)** Spike-triggered averages in the target muscle during postural maintenance (top) and after mechanical perturbation onset (bottom). Note the increased post-spike facilitation during the perturbation epoch. Panels **(A)** and **(B)** modified with permission from Cheney and Fetz (1984).

sensory delays (Cheney and Fetz, 1984). Moreover, the observed post-spike facilitation is stronger for spikes occurring during a mechanical perturbation than for spikes occurring during a static hold period (**Figure 1B**), indicating that the causal effect of action potentials from corticomotoneurons in M1 is particularly potent during the long-latency response to mechanical perturbations. These findings are supported by a range of studies in both humans (Abbruzzese et al., 1985; MacKinnon et al., 2000; Spieser et al., 2010) and monkeys (Evarts and Tanji, 1976; Fromm and Evarts, 1977; Wolpaw, 1980; Picard and Smith, 1992; Pruszynski et al., 2011a, 2014) showing changes in M1 activity following perturbation onset that precede the long-latency stretch response.

The second line of evidence comes from clinical studies of people who suffer from Kippel-Fiel syndrome, which causes undesired bilateral movements because of a bilateral bifurcation of descending projections from M1 to the spinal cord. When these participants are presented with mechanical perturbations applied to the finger, they demonstrate unilateral short-latency stretch responses but bilateral long-latency responses (Matthews et al., 1990; Capaday et al., 1991). Specifically, a mechanical perturbation that stretches finger muscles on one hand yields short-latency stretch responses only in the stretched finger muscles but yields long-latency stretch responses in both the stretched finger muscles on that hand and the same (unstretched) finger muscles on the other hand. Because the motor pathway in this patient group bifurcates at the level of M1 output, the mapping from stretched muscle inputs to unstretched muscle outputs must have occurred at that level of M1 or above.

The third line of evidence comes from brain stimulation studies. A wide range of work has shown a supra-linear interaction between the long-latency stretch response elicited by a mechanical perturbation and transcranial magnetic stimulation applied over M1 (Day et al., 1991; Palmer and Ashby, 1992). The most likely explanation for this interaction, which does not occur for the short-latency response, is that the neural mechanisms generating the long-latency stretch response and magnetic stimulation are physically co-localized at the site of stimulation, that is, M1.

FUNCTIONAL MODULATION IN PRIMARY MOTOR CORTEX

Several studies have observed flexible responses in M1 neurons to mechanical perturbations applied to the limb (Evarts and Tanji, 1976; Fromm and Evarts, 1977; Wolpaw, 1980; Picard and Smith, 1992; Pruszynski et al., 2011a, 2014). The most notable of these is the seminal work of Evarts and Tanji (1976) who trained monkeys to respond to a mechanical perturbation by either pulling or pushing the perturbing handle to its limits. They found that M1

neurons signaled the instructed action (Tanji and Evarts, 1976) and then subsequently responded to the same perturbation with two distinct components (Evarts and Tanji, 1976). First, there was a relatively short-latency response starting ∼20 ms after perturbation onset that showed little or no modulation according to the instructed action and a second component starting ∼40 ms post-perturbation which was sensitive to the prior instruction. This timing appeared early enough to account for a clear goal-dependent response in arm muscles starting about 70 ms following perturbation onset.

We recently extended this study to show that such modulation holds when the monkey is performing a task that more closely mirrors previous human work (Pruszynski et al., 2014). Most notably, our task used spatial goals that yielded behavioral responses analogous to the typical "resist" and "do not intervene" verbal instructions and we ensured that the muscles stretched by the mechanical perturbation were pre-activated by a tonic load (Pruszynski et al., 2008). The latter control is particularly critical as it ensures that any change in muscles activity—known to modulate the long-latency stretch response—would be above threshold and thus could be observed (Bedingham and Tatton, 1984; Matthews, 1986; Pruszynski et al., 2009). Our findings were largely consistent with Evarts and Tanji (1976). We found that monkey muscles, like human muscles, showed a multiphasic response with goal-dependent starting about 70 ms after perturbation onset. And we also noted that the initial response of M1 neurons—which began around 20 ms post-perturbation—was not sensitive target position and that goal-dependent activity in M1 neurons emerged about 40 ms after perturbation onset. However, our paradigm revealed a great deal of additional complexity, including the striking observation that many neurons changed their preference from one goal target to another over time following the perturbation.

We have also recently investigated whether the transcortical feedback pathway allows the long-latency stretch response to account for the mechanical properties of the limb (Pruszynski et al., 2011a). In this study, we applied mechanical perturbations at the shoulder and/or elbow joints (Kurtzer et al., 2008, 2009, 2014) to examine whether and when neurons in monkey M1 responded to the underlying torque as opposed to the resulting motion, factors which are decoupled because of the intersegmental dynamics of the limb (**Figure 2A**). Strikingly, the earliest response did not distinguish between the various loading conditions and such discrimination began 40–50 ms after perturbation onset (**Figure 2B**), still about 20 ms before arm muscles appropriately responded to the applied shoulder load. Since local joint motion itself provides ambiguous information about the underlying shoulder torque and since the only other piece of available information arises at the other joint, these findings indicate that M1 neurons eventually integrate elbow and shoulder motion to identify and counter the applied torque, which must be done to stabilize the limb. Notably, we also established a causal role for M1 by applying TMS over human M1 and showing that the long-latency stretch response in shoulder muscles was potentiated even when the shoulder joint was not displaced by the mechanical perturbation. As described above, such potentiation (Day et al., 1991; Palmer and Ashby, 1992; Lewis et al., 2004) must reflect the impact of elbow afferent information onto a cortical circuit controlling shoulder muscles since local shoulder afferents are not physically affected by the perturbation.

Indeed, several studies have used TMS to link M1 to specific functional capabilities of the long-latency response (Kimura et al., 2006; Shemmell et al., 2009; Spieser et al., 2010). In a very elegant study, Kimura et al. (2006) showed that disrupting sensorimotor cortex did not completely abolish the long-latency response; rather, the stimulation specifically impaired the ability of the long-latency response to predictively compensate for external force fields during reaching. The same approach has been used by Shemmell et al. (2009) to show that interfering with M1 does not change long-latency activity associated with the verbal instructions given to the subject but does affect long-latency activity associated with the stability of the environment, suggesting that only the latter functionality relies on a circuit that includes M1.

WHAT WE SHOULD FIND OUT SOON

As a basis for motivating future work, it is worth quickly reemphasizing what we know today. We know there exists a phasic epoch of muscle activity—termed the long-latency stretch response—that occurs prior to standard measure of voluntary reaction time (Hammond, 1955; Pruszynski et al., 2008). We know that M1 contributes to the long-latency response under normal circumstances (Cheney and Fetz, 1984; Matthews et al., 1990; Capaday et al., 1991; Day et al., 1991; Palmer and Ashby, 1992) but that M1 is not required for observing activity in the long-latency epoch (Tracey et al., 1980; Miller and Brooks, 1981). We know that the long-latency stretch response exhibits a host of sophisticated capabilities during both posture and movement (for detailed review, see Pruszynski and Scott, 2012). And we know that some of these sophisticated responses are apparent in M1 (Evarts and Tanji, 1976; Fromm and Evarts, 1977; Wolpaw, 1980; Picard and Smith, 1992; Kimura et al., 2006; Shemmell et al., 2009; Spieser et al., 2010; Pruszynski et al., 2011a, 2014).

We don't know the limits of the sophistication of the long-latency stretch response relative to voluntary control. Given recent work, however, it is tempting to speculate that the long-latency response exhibits all the capabilities of voluntary motor control within the constraints imposed by processing time. For example, recent work shows that the long-latency stretch response is modified as subjects learn novel force environments (Ahmadi-Pajouh et al., 2012; Cluff and Scott, 2013) and that those subjects who learn more show more substantial modulation of the long-latency stretch response (Cluff and Scott, 2013). Thus, adapting motor commands to compensate for changes in the environment—often considered a hallmark of voluntary motor control (Shadmehr and Wise, 2005)—at least partly rely on changes in feedback control processes such as the long-latency stretch response. Similarly, we now know that the long-latency stretch response includes predictions about the future state of the limb based on priors about the load environment (Crevecoeur and Scott, 2013). Such a predictive scheme—akin to a forward model (Kawato and Wolpert, 1998)—seems critical for ensuring stable feedback control with noisy and delayed inputs.

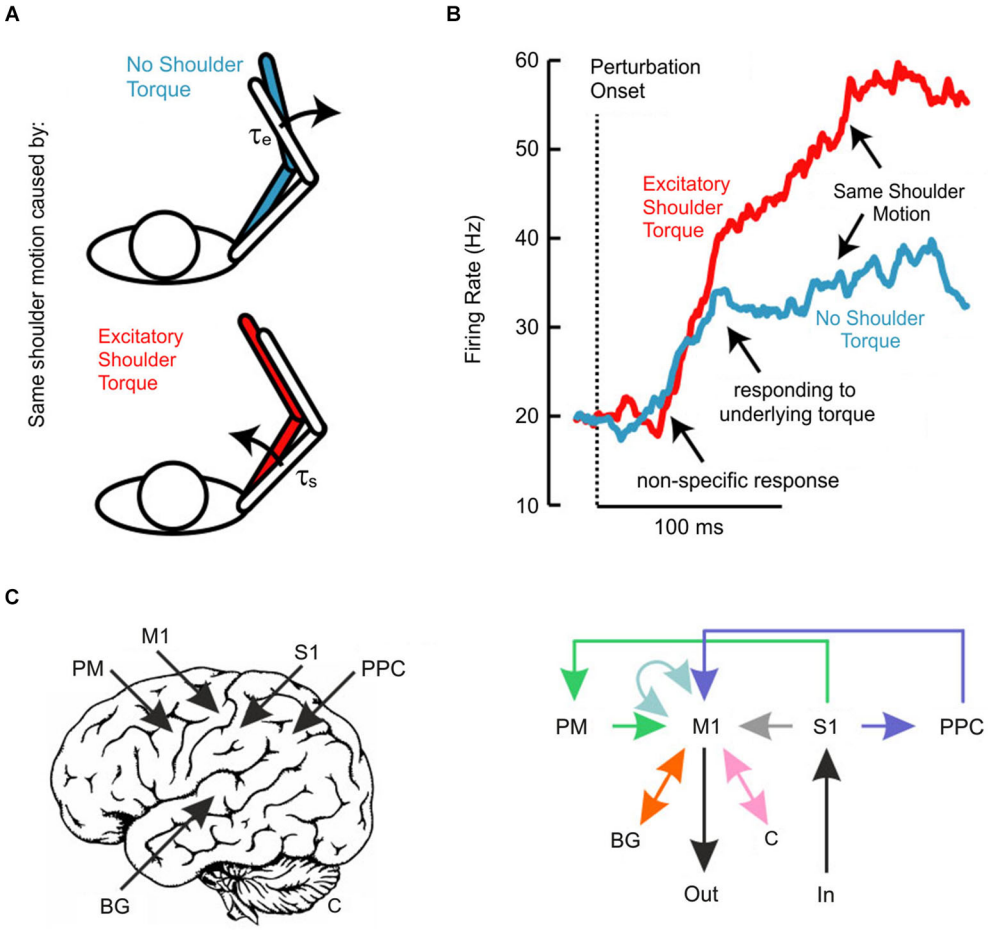

FIGURE 2 | (A) Schematic of experiment investigating whether long-latency responses account for limb dynamics. Perturbations were chosen so that the same shoulder motion arose because of either a pure shoulder or pure elbow torque. **(B)** Traces depict the average population response of neurons in primary motor cortex aligned on perturbation onset. Note that the two conditions evoke the same initial response and that appropriate differentiation does not emerge until ~50 ms post-perturbation. **(C)** Schematic representation of the neural pathways that likely contribute to the long-latency response in primary motor cortex. Deciphering which of these circuits contributes under which circumstances is an important outstanding question. Panels **(A)** and **(B)** modified with permission from Pruszynski et al. (2011a).

One important capacity that has yet to be explored in detail is whether and how the long-latency stretch response accounts for the kinematic redundancy of the limb. That is, if a given motor task can be accomplished in many ways, as it almost always can, does the neural machinery that generates the long-latency response tend to choose solutions that optimize task success? This type of adaptive control has been shown in various contexts for voluntary motor control (Latash et al., 2002; Todorov, 2004) but, so far has only been suggested with respect to the long-latency stretch response (Scott, 2004). We also know little about whether and how the long-latency stretch response integrates multiple pieces of sensory information such as that arising from tactile mechanoreceptors, muscle spindles and Golgi tendon organs. Take, for example, our own result showing that the long-latency stretch response accounts for the dynamics of the limb when generating a shoulder response by integrating motion information across both the elbow and shoulder (Kurtzer et al., 2008; Pruszynski et al., 2011a). The plainest explanation is that this integration is based on sensory information arising from the muscles themselves but it may well be tactile inputs from the stretching skin, which travel as slightly slower transmission speeds, are critical in this respect. Furthermore, the long-latency stretch response is only one of many fast feedback responses that can potentially contribute to muscle activity in the long-latency epoch (Goodale et al., 1986; Pélisson et al., 1986; Pisella et al., 2000; Franklin and Wolpert, 2008; Pruszynski et al., 2010; White and Diedrichsen, 2010; Knill et al., 2011). Understanding the role of these different modalities and, specifically, how they interact and how they are integrated in naturalistic motor behavior (for topical reviews, see Hatsopoulos and Suminski, 2011; Cluff et al., 2014) is critical for our broader understanding of limb motor control.

Functional questions notwithstanding, I believe that most critical outstanding issues relate to how the various neural pathways and circuits help form and sculpt the long-latency stretch response. I have emphasized so far the notion that the

sophistication of the long-latency stretch response arises because of a transcortical feedback pathway centered on M1. It is critical to emphasize however, that M1 does not act alone and the transcortical feedback pathway includes potential contributions from many other structures both cortical (e.g., premotor cortex, posterior parietal cortex) and subcortical (cerebellum, basal ganglia) (Scott, 2004). Although less is known about these areas and how they contribute to fast feedback responses as compared to M1, there is plenty to suggest that they do contribute and a key challenge for future studies is to unravel when and how this occurs.

A potential window into this problem may be the repeated observation that the initial phase of M1 activity—starting about 20 ms post-perturbation—appears to be relatively fixed and that sophisticated responses do not arise until about 40 ms post-perturbation (Evarts and Tanji, 1976; Pruszynski et al., 2011a, 2014), even when the required response is known well in advance of the perturbation. Such a non-specific response is similar to neurons in primary visual cortex, which respond quickly to objects in their receptive field but do not signal motion direction for another 20–30 ms, a delay attributed to processing among neurons within primary visual cortex (Knierim and van Essen, 1992). The temporal evolution of the long-latency response may also reflect intrinsic processing in M1 or, perhaps more likely, it may reflect the additional influence of other neural structures (**Figure 2C**).

One candidate is cerebellum. It is well established that there exist neurons in the dentate and interpositus nuclei of the cerebellum that respond to mechanical perturbations (Strick, 1983) and, indeed, the long-latency stretch response is reduced in humans who suffer cerebellar dysfunction (Hore and Vilis, 1984; Kurtzer et al., 2013). Those neurons in interpositus respond quickly to the perturbation (∼20 ms) but have little or no goal-dependent modulation whereas neurons in dentate tend to respond at longer-latencies and are strongly influenced by the goal of the task. It is tempting to suggest that the two distinct components of the long-latency response in M1 reflect inputs from the interpositus and dentate nuclei, respectively. However, this cannot be the full story, as cooling the entire cerebellum leads to little change in the initial response and only partially reduces the second response (Meyer-Lohmann et al., 1975; Vilis et al., 1976). On the other hand, one reasonable hypothesis, as yet untested, is that dentate neurons modulate rather than generate the later M1 response.

There exist other candidate contributors. For example, previous studies have reported that pre-motor cortical neurons quickly respond to mechanical perturbations (Picard and Strick, 1996; Boudreau et al., 2001) and this area, which projects directly to M1, is known to be remarkably sensitive to motor planning and task goals (Picard and Strick, 1996; Wise et al., 1997; Cisek and Kalaska, 2005). Similarly, posterior parietal cortex is involved in attentional mechanisms and motor control (Andersen and Buneo, 2002), receives inputs from somatosensory cortex and projects to the frontal cortex including M1 (Petrides and Pandya, 1984). Diseases of the basal ganglia typically lead to markedly exaggerated long-latency stretch responses (Tatton and Lee, 1975; Rothwell et al., 1983), which may reflect changes in the transcortical pathway (DeLong and Wichmann, 2007), though recent studies with Parkinsonian monkeys suggest that such effects are more complicated than mere changes in the sensitivity of M1 neurons to sensory input (Pasquereau and Turner, 2013). And recently, a compelling argument has been made that startle-like brain stem processes contribute to the long-latency stretch response in various contexts (Shemmell et al., 2010) and, indeed, neurons in the reticular formation that project to the distal arm muscles also respond to mechanical perturbations at such short latencies that they likely contribute to muscle activity in the long-latency epoch (Soteropoulos et al., 2012).

In sum, the long-latency stretch response is strikingly sophisticated and, though most effort has been centered on its generation and modulation via the transcortical pathway through primary motor cortex, it likely involves many neural circuits with their own complex interactions (Kimura et al., 2006; Lourenço et al., 2006; Shemmell et al., 2009; Pruszynski et al., 2011b). Experiments with modern techniques are needed to revolve which of these circuits contribute to which functional capacity under what circumstances, how each pathway accounts for the actions of the others, and how processing for feedback responses relates to the circuitry typically associated with voluntary motor control.

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Long-latency reflexes account for limb biomechanics through several supraspinal pathways

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Accurate control of body posture is enforced by a multitude of corrective actions operating over a range of time scales. The earliest correction is the short-latency reflex (SLR) which occurs between 20–45 ms following a sudden displacement of the limb and is generated entirely by spinal circuits. In contrast, voluntary reactions are generated by a highly distributed network but at a significantly longer delay after stimulus onset (greater than 100 ms). Between these two epochs is the long-latency reflex (LLR) (around 50–100 ms) which acts more rapidly than voluntary reactions but shares some supraspinal pathways and functional capabilities. In particular, the LLR accounts for the arm's biomechanical properties rather than only responding to local muscle stretch like the SLR. This paper will review how the LLR accounts for the arm's biomechanical properties and the supraspinal pathways supporting this ability. Relevant experimental paradigms include clinical studies, non-invasive brain stimulation, neural recordings in monkeys, and human behavioral studies. The sum of this effort indicates that primary motor cortex and reticular formation (RF) contribute to the LLR either by generating or scaling its structured response appropriate for the arm's biomechanics whereas the cerebellum scales the magnitude of the feedback response. Additional putative pathways are discussed as well as potential research lines.

Keywords: feedback, posture, internal model, primary motor cortex, cerebellum, reticular formation

INTRODUCTION

Barring a neurological disorder or physical impediment, human subjects can accurately position their upper limbs in the presence of unpredictable loads. Consider how one routinely lifts household objects of different weight or can gently secure the wriggling of an anxious newborn. In both the drab and dear situations mechanical perturbations are applied to the arm and require the nervous system to exert compensatory action to ensure task success; the alternative is dropping a cup or child. An important component of our compensation to external loads is the "long-latency reflex" (LLR). First identified over 50 years ago, the LLR is evident as a burst of muscle activity occurring 50–100 ms following an imposed limb displacement. These pre-voluntary responses display an impressive range of capabilities such as integrating sensory information across multiple muscles appropriate for the dynamical interactions between the arm's linked segments; in this paper I describe this general ability as "knowledge of limb dynamics". Over two decades of research has demonstrated that LLRs utilize knowledge of limb dynamics and an even more extensive body of research has examined spinal and supraspinal substrates for the LLR. Yet, only recently have these efforts intersected to identify the neural substrates of this capability. Here I review the general features of the LLR, evidence that it utilizes knowledge of limb dynamics, and the relatively small (but growing) research on its neural basis.

WHAT IS THE LONG-LATENCY REFLEX?

This section briefly describes the general characteristics of the LLR. For an extensive treatment see the following reviews (Marsden et al., 1983; Shemmell et al., 2010; Pruszynski and Scott, 2012). The LLR of the upper limb denotes the burst of muscle activity occurring 50–100 ms following a limb displacement. Accordingly, the event is situated between the fastest response by the nervous system termed the short-latency reflex (SLR 20–45 ms) and the more delayed voluntary reaction (100 ms is the earliest onset of a wide distribution) (**Figure 1A**). The SLR is exclusively generated by spinal networks using group I afferent input as this is only pathway short and fast enough to responsible. The LLR reflects processing of group I afferents through spinal circuits (Hagbarth et al., 1981; Lee and Tatton, 1982; Lewis et al., 2005; Schuurmans et al., 2009; Kurtzer et al., 2010) and supraspinal circuits (including primary motor cortex and reticular formation) (for review Pruszynski and Scott, 2012) along with spinal processing of group II afferents (Hendrie and Lee, 1978; Lourenço et al., 2006; Meskers et al., 2010). Voluntary reactions involve a more distributed circuitry including premotor cortex and basal ganglia as well as the continued impact of faster circuits (Suminski et al., 2007; Shadmehr and Krakauer, 2008). Accordingly, the LLR should not be considered a singular event reflecting a singular neural process, but rather the net impact of spinal and supraspinal circuits contributing within the 50–100 ms time-scale (**Figure 1B**). Note that all these responses

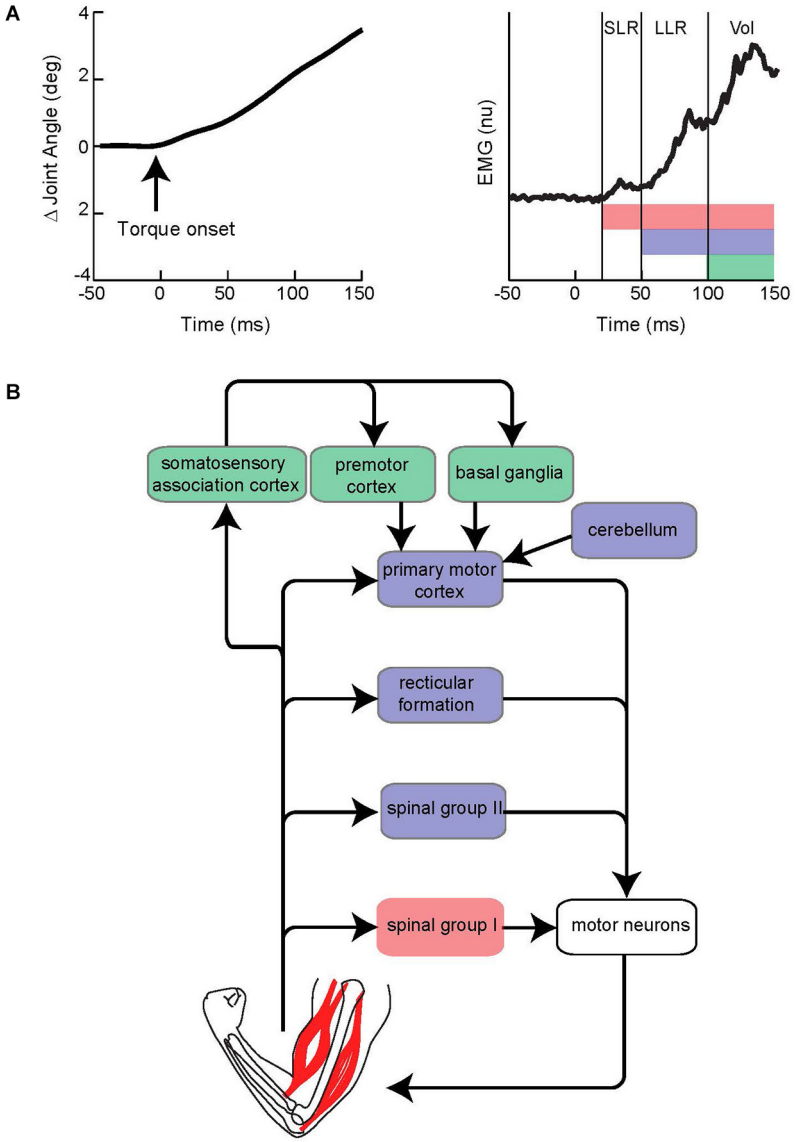

FIGURE 1 | Evoked muscle activity to limb displacement and proposed neural circuitry. **(A)** The left panel depicts an example of joint angle displacement following an applied step torque. The right panel depicts an example of muscle activity evoked by joint displacement. Vertical lines bracket the short-latency reflex (SLR), long-latency reflex (LLR), and Voluntary reaction (Vol) epochs. Pink, purple, and green horizontal bars depict the neural process that contribute to the different epochs. Note the neural contributions continue throughout the perturbation and overlap in time. **(B)** Simplified diagram of neural contributors to the different epochs of evoked activity. Colored boxes correspond to colored bars in panel above. Note that several pathways may be involved for a particular epoch.

can be observed throughout the muscles of the arm (and the leg) although they vary in relative size according to protocol and possibly intrinsic differences in their neural control. The LLR shares features with both the SLR and voluntary reaction. However, it is not identical to either nor can it be considered a simple mix of the SLR and voluntary reaction due to their temporal overlap. One important difference between the responses is that the SLR and LLR rely mostly on information from muscle afferents whereas voluntary reactions can be engaged by a broader range of somatosensory inputs. Anesthetizing the skin or joint afferents has little affect on the SLR and LLR (Bawa and McKenzie, 1981; Cody and Plant, 1989) whereas non-noxious cutaneous stimulation can evoke a voluntary reaction but not earlier responses (Rothwell et al., 1980); some exceptions have been observed with the fingers appropriate for their specialized role in handling objects (Loo and McCloskey, 1985). Differences between the SLR and LLR are also evident with protocols that selectively attenuate one response but not the other. The tendon tap commonly used during a physical exam will powerfully recruit the SLR but not the LLR (Jaeger et al., 1982; Lee and Tatton, 1982). Conversely, a slow sustained displacement of the limb segment will evoke a substantially larger LLR

than SLR (Lee and Tatton, 1982). This period-specific pattern likely reflects differences in their peripheral afferents and central circuits.

An important functional difference between the three epochs is their automaticity (see Pruszynski et al., 2008 for review). Voluntary reactions can be completed suppressed at the whim of the subject whereas SLRs occur in the absence of any voluntary effort and do not change with the intention to react more or less vigorously. LLRs are neither strictly automatic nor strictly voluntary. Subjects attempting to "yield" to a limb displacement will continue to exhibit a LLR, yet they also exhibit larger LLRs when they attempt to "resist" the limb perturbation. We discuss the likely underpinnings of this modifiability in a subsequent section ("Contributions by the reticular formation"). In addition, and central to this review, the the SLR, LLR, and voluntary reaction differ in their ability to integrate sensory information. Voluntary reactions can involve virtually arbitrary couplings of controllable body parts so we can easily flick a finger in response to a tap of the foot. At the other end, SLRs have the least flexible relation to sensory input; they are only evoked in a particular muscle by joint displacements which stretch that muscle. LLRs have a degree of flexibility between the SLR and voluntary reaction as they are evoked by either local muscle stretch or stretch of remote muscles and this mapping accounts for the arm's biomechanics, in contrast to the near-arbitrary mapping of voluntary reactions.

In sum, the SLR, LLR, and Voluntary responses have a complex partially overlapping character which transitions from the simplest and most rapid to the most complex and most delayed. As a general heuristic we can view these responses as an evolving approximation to the ideal or optimal response with a trade-off between speed and accuracy (Todorov and Jordan, 2002; Scott, 2004). The LLR is a key link in this sequence as it occurs at $\geq$2X the rate of voluntary reactions and displays a wide range of abilities including knowledge of limb dynamics.

WHY IS KNOWLEDGE OF LIMB DYNAMICS IMPORTANT?

Our bodies are mechanically complex. Movements of one body part depends on applied loads at different body parts due to their physically linkage. Furthermore, this relation is non-linear, position-dependent due to gravity, and context-dependent (e.g., reaching with or without a hand-held object). Actions performed without anticipating this complexity would be inefficient and potentially destabilizing by inducing a series of unwanted and unexpected consequences. Hence, researchers have been highly motivated to understand whether subjects anticipate this complexity and how so. For self-selected actions,the answer is a resounding "yes";for an extensive treatment see the following reviews (Kawato and Wolpert, 1998; Sabes, 2000; Tin and Poon, 2005). One demonstration (of many) is that healthy subjects can easily acquire an object that is placed on the opposite side of their body by simultaneously turning their trunk and reaching to the object (Pigeon et al., 2003). The twisting trunk movement creates a rotating platform for their arm movements that acts to perturb the path of the hand as it travels to the target. Without the properly counteracting arm torques the hand path would bow outward from the body as the trunk rotated away from it. Instead, our hand movements follow a straight course in external space as if the trunk had not rotated at all. The nervous system achieves this fast and accurate pattern of movement by predictively generating the appropriate counteracting torque since arm movements are significantly disturbed by much smaller perturbations introduced by passively rotating the body while reaching (Lackner and Dizio, 1994) or applying rotary-like forces by a robot (Shadmehr and Mussa-Ivaldi, 1994). Moreover, subjects quickly adapt to such novel forces patterns and then exhibit an opposing pattern of movement errors when the novel forces are removed. The presence of adaptation "aftereffects" indicate an updating of the neural representation of arm dynamics and are a powerful window into the structure of this knowledge.

An two-decade effort has examined how neural representations of limb dynamics are used during self-initiated/planned actions. A number of control schemes have been proposed such as rule-based coordinative patterns (Almeida et al., 1995; Gottlieb et al., 1997), forward models which predict how motor commands create body motion (Flanagan and Wing, 1997), inverse models that transform intended body motions to motor commands (Shidara et al., 1993), paired inverse and forward models (Wolpert and Kawato, 1998), controllers that are collections of local tuning functions (Thoroughman and Shadmehr, 2000) or that identify the underlying physical laws and contexts (Braun et al., 2009). All of these schemes fall under the broad banner of "knowledge of limb dynamics" insofar as they encapsulate (in various degrees) the mechanical properties of the body and environment.

In recent years, researchers have increasingly asked whether our corrective actions also depends on a knowledge of limb dynamics (Diedrichsen, 2007; Wagner and Smith, 2008) in contrast to earlier theories positing that feedback corrections were either simple local corrections or dominated by passive muscle properties (St-Onge et al., 1997; Gribble et al., 1998). Among the accumulating evidence is that fast manual adjustments to a visual target jump ($\approx$125 ms delay in hand position) account for the arm's complex mechanics and feedback delays (Gritsenko et al., 2009), without this knowledge the hand's path would be dramatically more curved and irregular than observed. Accordingly, the field of human sensori-motor control is undergoing a significant shift in understanding the relative capabilities of anticipatory/feedforward control vs. corrective/feedback control. Research on the LLR makes an important contribution to this work-in-progress as it is the fastest response by the nervous system (50 ms delay in muscle activity) which utilizes knowledge of limb dynamics.

EVIDENCE THAT THE LONG-LATENCY REFLEX UTILIZES KNOWLEDGE OF LIMB DYNAMICS

Studies over the past 30 years have demonstrated that LLRs utilize knowledge of limb dynamics. Here we review some of that evidence. A clear example is the evoked activity of elbow muscles upon forcibly pronating the wrist (Gielen et al., 1988). This perturbation evokes a SLR in the biceps brachii but not brachialis. Biceps brachii is both an elbow flexor and wrist supinator so it is stretched by wrist pronation whereas brachialis is a pure

elbow flexor which is neither stretched nor shortened by wrist pronation. Importantly, the perturbation evokes an excitatory LLR in biceps brachii and an inhibitory LLR in brachialis. A decrease in brachialis activation is functionally meaningful since it helps balance the elbow flexion produced by biceps brachii as it counters the applied pronation. If the activity of brachialis was not appropriately decreased, then the arm would generate excessive elbow flexion to a pronating perturbation. Hence, the LLR incorporates information across different muscles appropriate to their mechanical linkage and exemplifies knowledge of this relation.

Serial connection between different segments enables their mechanical interaction so that torque applied at one joint will create motion at that joint and at neighboring joints. A well-studied example is arm movement restricted to elbow and shoulder motion in a single plane (Hollerbach and Flash, 1982; Graham et al., 2003). Applying flexion torque to the shoulder will induce flexion motion of the shoulder along with extension motion of the elbow. Similarly, extension torque applied to the elbow will induce extension motion of the elbow along with flexion motion of the shoulder. Because of these mechanical interactions between the two joints, there is no unique relation between shoulder-elbow torque and motion of a particular joint. Different elbow-shoulder torques can induce the same pattern of motion in a particular joint and the same stretch pattern in a particular muscle. If the arm's LLRs accounted for these interactions, then the neural networks would integrate information across different muscles appropriate to counter the underlying torque perturbation. Alternatively, if the LLRs did not account for these interactions, then each muscle would exclusively respond to its own stretch.

In a seminal paper, Soechting and Lacquaniti (1988) tested between these possibilities by displacing the shoulder and elbow in various directions via force pulses applied to the hand. They then compared the evoked activity of several arm muscles to the induced shoulder-elbow motion and the derived shoulder-elbow torque. Overall, the LLRs showed a better match to the joint torque opposite the muscle's action whereas SLRs better matched the joint motion stretching that muscle. Unfortunately, the stream of force pulses induced complex time-varying patterns of joint motion, torque, and background muscle activity which prevented a simple test whether the reflexes responded to local muscle stretch or incorporated stretch information across multiple muscles appropriate for the arm's biomechanics.

Twenty years later Kurtzer et al. (2008) built on this earlier work. Instead of continuous force pulses to the hand, they employed a joint-based robot so that torque could be selectively applied to the shoulder and/or elbow joint (Scott, 1999; Singh and Scott, 2003). The paradigm was focused on posture-related activity of shoulder muscles and contrasted simple patterns of joint motion. In the first set of comparisons, a step torque was applied at just the shoulder or just the elbow (**Figure 2A**). The relative magnitude of these torque perturbations was chosen to induce the same pattern of shoulder flexion (**Figure 2B**). That is, because the mechanical interactions between the two joints, the shoulder could be displaced with an elbow torque or a shoulder torque. Inducing the same amount of shoulder flexion (and stretch of the shoulder extensor) allowed a simple model-free comparison between conditions: similar magnitudes of evoked activity indicates processing of only local muscle stretch (**Figure 2C**) whereas greater evoked activity for the shoulder torque condition indicates compensation of the underlying shoulder torque (**Figure 2D**). Consistent with the earlier studies, the shoulder displacement evoked an identical SLR in the two conditions but greater LLR following the shoulder torque than elbow torque this pattern was observed for both posture and movement tasks (**Figures 3A,B**).

In the second set of comparisons, a torque step was applied to both the shoulder and elbow with relative magnitudes (countering the interaction of elbow torque onto shoulder motion) so that only the elbow was displaced (**Figure 2E**). Shoulder extensor activity that is based on local muscle stretch will not respond to this perturbation since that muscle was neither stretched nor shortened (**Figure 2F**). Alternatively, shoulder extensor activity that accounted for the mechanical interactions across joints would respond to pure elbow motion to counter the underlying shoulder torque; opposing directions of elbow motion would lead to opposing patterns of excitatory and inhibitory activity (**Figure 2G**). These perturbations failed to elicit a SLR indicating that it only reflected local muscle stretch, no stretch leading to no response. Reciprocal bursts of activity were present for the shoulder extensor's LLR which was appropriate for the underlying shoulder torque, an excitatory burst to elbow flexion and inhibitory burst to elbow extension; again, this pattern was observed for both posture and movement tasks (**Figures 3C,D**). The two sets of comparisons (Same shoulder motion/different underlying torque and No shoulder motion/underlying shoulder torque) provide clear evidence that the LLR, but not the SLR, of shoulder muscles have knowledge of the inertial coupling between the elbow and shoulder.

Subsequent studies tested the generality of this knowledge of limb dynamics. The described pattern was consistently observed across different behavioral contexts including postural maintenance (Kurtzer et al., 2008), movement initiation, and movement deceleration (Kurtzer et al., 2009). It was also expressed throughout the adult age range (20–70 yrs) (Kurtzer et al., 2013) and with displacements so small that they approached the natural variability of behavior (Crevecoeur et al., 2012). Hence, knowledge of elbow-shoulder dynamics is a general capability of the shoulder muscle's LLRs. See the following papers for examples of wrist muscle LLRs linked to elbow motion (Koshland et al., 1991; Latash, 2000). Also, note that LLRs of leg muscles indicate that they are not slavishly linked to local stretch. A classic example is the differential activation of ankle muscle LLRs to a translating or tilting platform (Nashner, 1976). The two perturbations induce a similar pattern of ankle displacement but responding to local stretch helps stabilize body posture during translation and destabilizes it during platform rotation by moving the body's center of mass outside the base of support. Recent studies in this vein, supplemented by computational modeling, have further demonstrated that multi-joint integration of body posture utilize a neural representation of the body's center of mass (Safavynia and Ting, 2013).

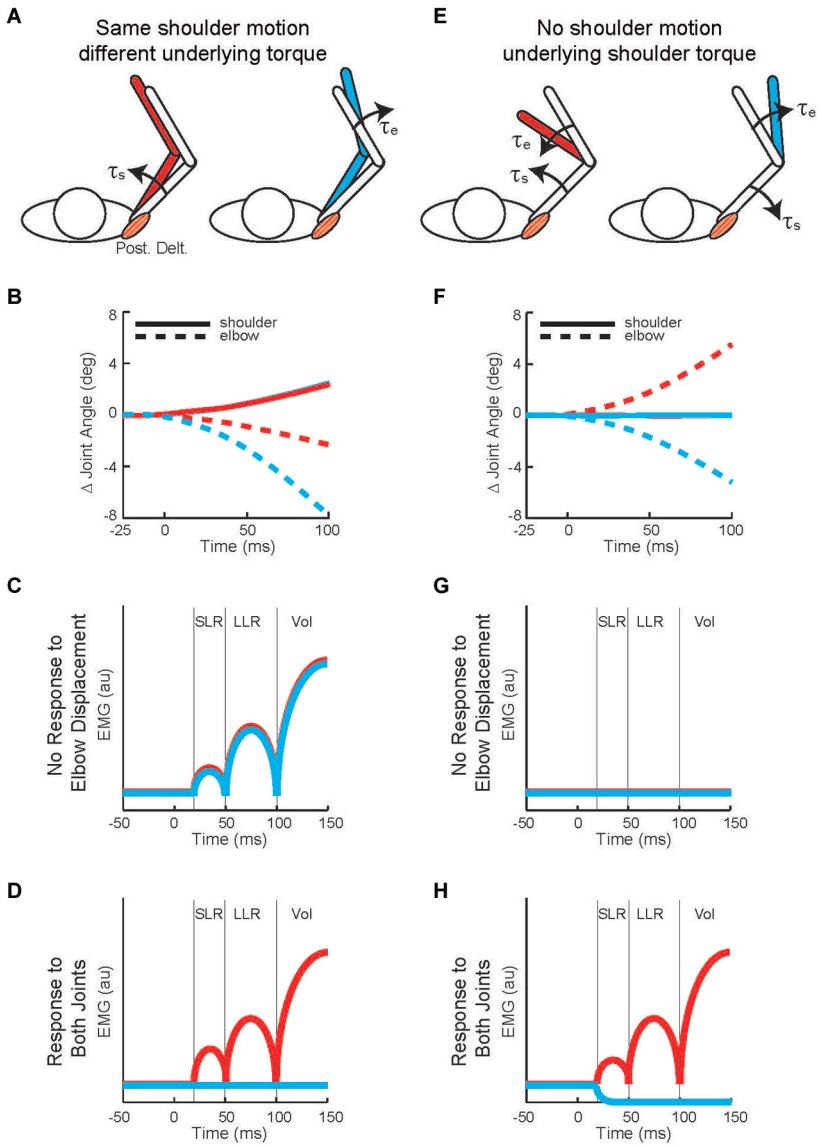

FIGURE 2 | Testing whether shoulder responses are linked to local muscle stretch or multi-muscle stretch. **(A)** Torque perturbations applied to the arm, a shoulder flexor torque (see the red arm) and an elbow extensor torque (see the blue arm). **(B)** Change in joint angle from the starting posture. Solid and dashed lines denote the change in shoulder and elbow angle, respectively. Red and blue indicate motion resulting from shoulder flexor torque and elbow extensor torque, respectively. 0 ms is perturbation onset. Shoulder motion is nearly identical for the two conditions, flexion is positive. **(C)** Predicted shoulder muscle response to the shoulder torque and elbow torque perturbations if the neural processes only utilized local muscle stretch. **(D)** Predicted shoulder muscle responses if the neural processes integrated stretch from shoulder and elbow muscles appropriate to counter the underlying torque. **(E)** Torque perturbations applied to the arm, a shoulder-elbow flexor torque (see the red arm) and a shoulder-elbow extensor torque (see the blue arm). **(F)** Change in joint angle from the starting posture. Same format as **(B)**. The initial joint motion is almost entirely restricted to the elbow. **(G)** Predicted shoulder muscle response to the shoulder torque and elbow torque perturbations if the neural processes only utilized local muscle stretch. **(H)** Predicted shoulder muscle responses if the neural processes integrated stretch from shoulder and elbow muscles appropriate to counter the underlying torque. **(A,B)**, **(E,F)** modified with permission from Kurtzer et al. (2008).

LLRs account for the environment's mechanical stability in addition to the body's intrinsic musculoskeletal properties. A car's brake pedal is mechanically stable since greater forces are required to further depress the pedal and its position restores when the foot steps away. In contrast, a screwdriver is mechanically unstable tool since a misaligned force directed parallel to the screw slot can lead to unrecoverable slippage. Considerable research has established that the nervous system addresses such instabilities by changing how the arm responds to displacements (Mussa-Ivaldi et al., 1985; Burdet et al., 2001; Franklin et al., 2007). This can be achieved by realigning the arm's orientation (and inertial resistance) to the perturbation direction (Trumbower et al., 2009) as well as co-activating muscles to increase their intrinsic stiffness (Rack and Westbury, 1974) and

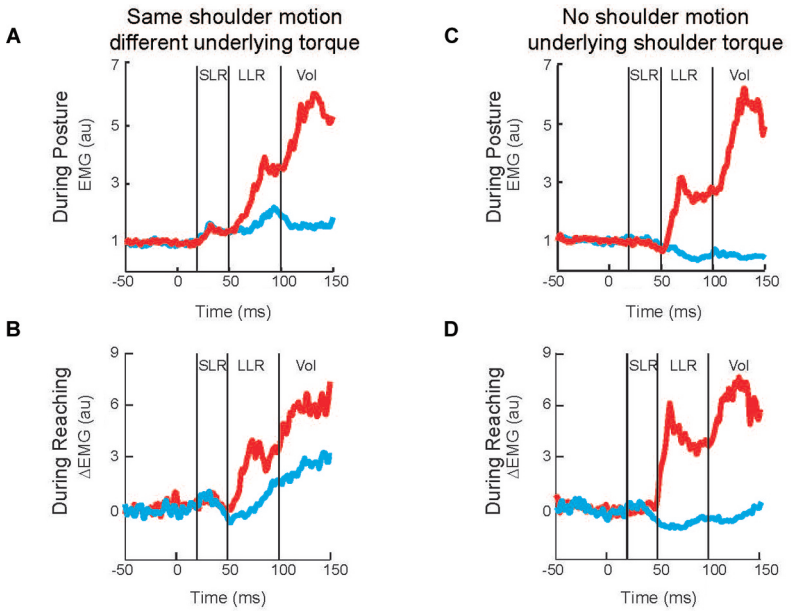

FIGURE 3 | Shoulder muscle responses to perturbations causing selective joint motion. (A) Group average of shoulder extensor muscle activity evoked by two perturbations during postural maintenance. Red and blue traces denote activity during shoulder flexor torque and elbow extensor torque perturbations, respectively (**Figures 2A,B**). **(B)** Group average of shoulder extensor muscle activity evoked by same two perturbations applied during movement initiation; unperturbed pattern of muscle activity has been removed. **(C)** Group average of shoulder extensor muscle activity evoked by two perturbations during postural maintenance. Red and blue traces denote activity during combined flexor and combined extensor torque perturbations which cause elbow flexion and extension, respectively (**Figures 2E,F**). **(D)** Group average of shoulder extensor muscle activity evoked by same two perturbations applied during movement initiation; unperturbed pattern of muscle activity has been removed. **(A,B)** modified with permission from Kurtzer et al. (2008). **(C,D)** modified with permission from Kurtzer et al. (2009).

the automatic scaling of reflexes with background muscle activity (Bedingham and Tatton, 1984; Matthews, 1986; Pruszynski et al., 2009). Even further, LLRs can be modified up and down to the environmental stability for a fixed level of background muscle activity.

Adaptation of LLR sensitivity to environmental stability is evident in a variety of situations. Upper limb LLRs, but not SLRs, are downscaled from normal when subjects behave with a servo-controller that enforces a particular movement independent of the subject's output. Such attenuated responses occur in both single-joint paradigms (Akazawa et al., 1983; Doemges and Rack, 1992) and multi-joint paradigms (Perreault et al., 2008). Conversely, LLRs are upscaled when subjects maintain a steady posture within an unstable environment like a spring with negative stiffness—spring forces that act in the same direction as position deviations and so amplify the positions deviations (Akazawa et al., 1983; Krutky et al., 2010). Upscaled LLRs help provide additional restoring forces to reinforce stable behavior and can be increasingly upscaled for directions of limb motion that have the greatest instability (Krutky et al., 2010). It should be emphasized that adaptation of LLRs to environmental stability is a general capability of the upper limb and is expressed by finger, wrist, elbow, and shoulder muscles. A final example of the arm's LLR scaling to environmental instability are reaching movements towards a force field which located in a fixed region of space and involves a constant force directed right or left of the hand movement (Kimura et al., 2006), like reaching out of a car window and experiencing the sudden lateral gust of wind. When subjects expect the direction of the upcoming force field then they scale their LLRs appropriately. LLRs elicited as the hand approaches the force field are upscaled in those muscles which compensate the upcoming force direction. The shoulder flexor has an upscaled response to an impending force field expected to extend the shoulder, and the shoulder extensor has an upscaled response to an impending force field expected to flex the shoulder.

A highly influential demonstration of the neural representation of limb dynamics is rapid adaptation of reaching movements to a novel force environment (Lackner and Dizio, 1994; Shadmehr and Mussa-Ivaldi, 1994; Sainburg et al., 1999). If LLRs have similar neural representations then we should expect that LLRs can be rapidly retrained to new force environments. Shadmehr et al. (Ahmadi-Pajouh et al., 2012) tested this possibility by having subjects adapt to a "curl field"—force proportional to the hand's speed and orthogonal to its heading—and intermittently perturbed the arm with force pulses. Critically, the perturbations occurred just prior to the cued movement onset since alterations in LLRs evoked during movement could reflect true learning or automatic scaling to the altered muscle activity to compensate the curl field. The results demonstrate that adaptation of LLRs was specific to the structure of the curl force field; LLRs were upscaled to a rightwards force pulse during

training with a rightwards curl force but not a leftwards curl field. Despite its important contribution, LLRs were tested prior to movement and, therefore, could not disambiguate if they support movement adaptation or are more generic direction-specific responses.

A solution to this conundrum—how to test LLR adaptation during movement when movement adaptation leads to changes in the compensatory muscle activity and can automatically scale LLRs—was elegantly provided by Cluff and Scott (2013). Rather than a curl force field, subjects adapted their reaching movements to velocity-dependent resistance of their elbow motion (**Figure 4A**). Successfully moving to targets involving elbow extension and flexion required compensatory activation of elbow extensor and flexor muscles whereas a third target required only shoulder motion so that no compensatory elbow torque was needed. Movement to the targets requiring elbow motion created initial movement errors followed by adaptation (**Figure 4B**) by changing the anticipatory pattern of elbow muscle activity (**Figure 4C**). A third target required only shoulder motion so that no compensatory elbow torque was needed and no change in

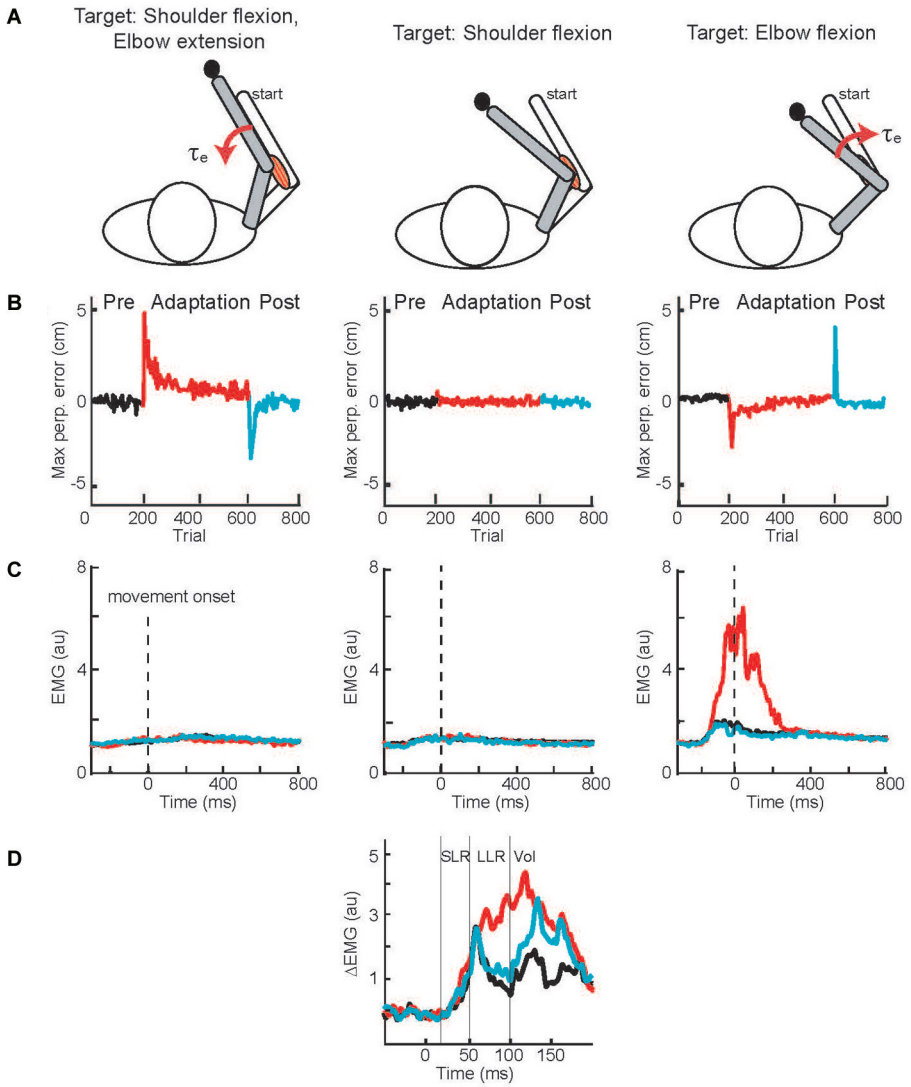

FIGURE 4 | Applied joint torques and joint motion to test adaptation of LLRs. (A) Configuration of the arm at the starting position and at the final position when reaching to three targets. A force field applied loads which resisted elbow motion, torque proportional to elbow velocity. The target on the left required shoulder flexion and elbow extension; a resistive load at the elbow applied a flexion torque. The target in the middle only required shoulder flexion; there was no load applied to the elbow as there was no elbow motion. The target on the right required elbow flexion; a resistive load at the elbow applied an extension torque. **(B)** Deviation of the handpaths from a straight line when reaching to the three targets; black, red, and blue denote the movement errors before, during, and after the application of the elbow resistive load. **(C)** Activity of elbow flexor muscle when reaching to the three targets before, during, and after introducing the resistive loads at the elbow. **(D)** Evoked activity of the elbow flexor muscle when reaching to the target requiring only shoulder motion. Data is shown for before, during, and after introducing the resistive load at the elbow. Figure modified with permission from Cluff and Scott (2013).

elbow muscle activity was observed (**Figures 4B,C**). Yet, during movements to this target an elbow extension perturbation evoked upscaled elbow flexor LLRs appropriate to compensate the novel force field (**Figure 4D**). The link between movement adaptation and LLR adaptation was further strengthened by their similar asymptotic time course along with subject-by-subject correlation in the extent of movement and LLR adaptation.

Taken together, the results indicate that the arm's LLR expresses a wide range of capabilities that reflect knowledge of limb dynamics. Note there are a number of other capabilities reflecting knowledge of limb dynamics which were not discussed at length such as coordinating actions across different effectors (Cole et al., 1984; Dimitriou et al., 2012; Omrani et al., 2013) and predictive responses (Hore and Vilis, 1984; Crevecoeur and Scott, 2013). Unfortunately, the neural basis for these other capabilities is effectively unexplored whereas most of the preceding material has an analogous physiological study. The following sections will describe how primary motor cortex, reticular formation, and cerebellum may contribute to LLR's knowledge of limb dynamics.

CONTRIBUTION BY THE PRIMARY MOTOR CORTEX

Primary motor cortex (M1) is the medio-lateral strip of cerebral cortex immediately rostral to the central sulcus and marks the beginning of frontal cortex (Porter and Lemon, 1993). It is well-known that M1 provides an important contribution to voluntary control. Changes in its activity precedes movement onset, co-evolves with arm muscle activity (Cheney and Fetz, 1980; Morrow and Miller, 2003), and broadly mirrors the arm's biomechanics (Scott and Kalaska, 1997; Scott et al., 2001; Cherian et al., 2013). The tight association of M1 activity and voluntary movement is enabled by M1's substantial descending projection (via the corticospinal track) onto spinal networks that engage the limb's musculature (Cheney and Fetz, 1980; Park et al., 2004). A wealth of information also indicates that M1 contributes to the LLR. M1 receives rich innervation by somatosensory inputs (via the dorsal column pathway) (Asanuma, 1975) and shows fast activation to perturbations of the wrist, elbow, or shoulder (Conrad et al., 1975; Evarts and Tanji, 1976; Suminski et al., 2007; Herter et al., 2009). Furthermore, an unambiguous linkage to LLRs is established for those M1 neurons with a rapid response to limb perturbations and that direct synapse onto spinal motor neurons (Cheney and Fetz, 1984).

Several experimental methods acutely elevate or attenuate the activity of M1 and produce similar effects on the arm's LLRs. Relatively tonic changes in excitability (lasting several minutes) can be induced by repetitive transcranial magnetic stimulation (TMS; Tsuji and Rothwell, 2002). Single pulses of TMS can also be timed to impact LLRs during a particular perturbation trial. The most common paradigm (Day et al., 1991) compares the magnitude of three muscle responses: evoked by muscle stretch (**Figures 5A,B**), evoked by a TMS pulse (**Figure 5C**), and evoked by the two stimuli applied together(**Figures 5D,E**). If the neural circuits which generate the response to muscle stretch are separate from those which generate the response to a TMS pulse then applying the two stimuli together should yield a response equal to the linear sum from the two separate stimuli: (A) + (B) = (A+B). Alternatively, if the two stimuli are processed through a shared

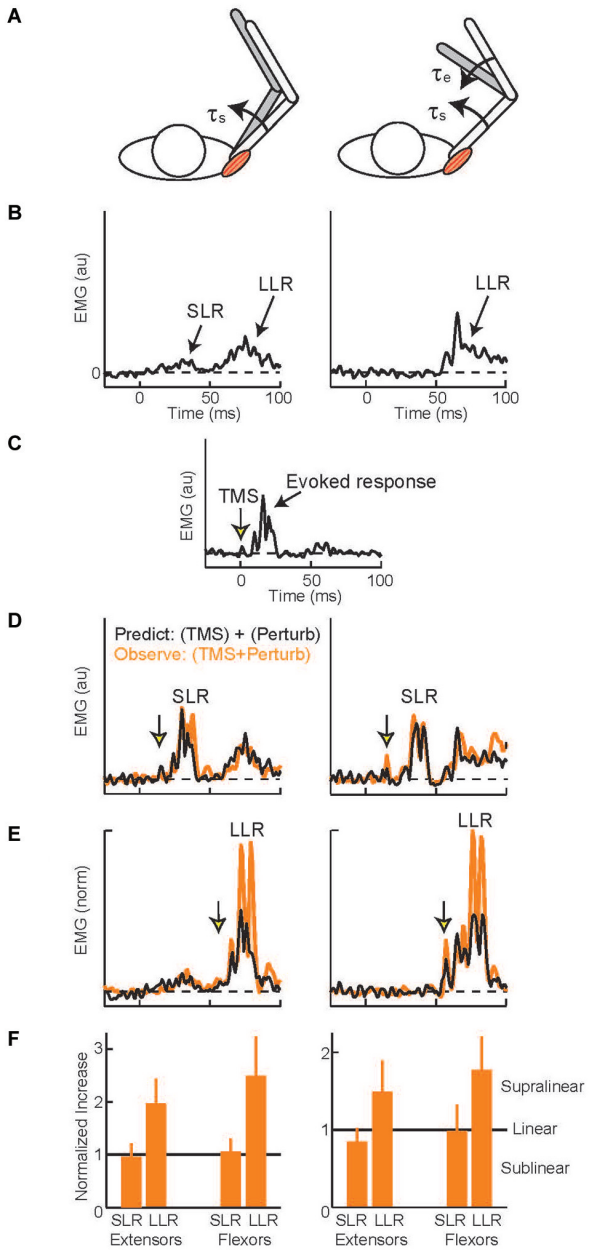

FIGURE 5 | Evoked muscle activity to perturbation torques and transcranial magnetic stimulation. **(A)** Torque perturbations applied to the arm, a shoulder flexion torque which displaced the shoulder joint (left cartoon) and shoulder + elbow flexion torque which only displaced the elbow (right cartoon). **(B)** Evoked activity of the shoulder extensor muscle during shoulder displacement (left panel) and pure elbow displacement (right panel), 0 ms is perturbation onset. Data from a representative subject **(C)** Evoked activity in the shoulder extensor to a single TMS pulse, 0 ms is TMS onset. **(D)** TMS pulse timed to occur during the SLR with shoulder displacement (left panel) and pure elbow displacement (right panel). Orange trace is the observed muscle activity to the combined stimulus; black trace is the predicted response, summed activity to the separate perturbation and TMS stimuli. **(E)** TMS pulse timed to occur during the LLR. Same format as above. **(F)** Group data for the two shoulder muscles. Data normalized to predicted response so values equal to 1 equal linearity whereas values above 1 indicate superlinearity and evidence of a common cortical circuit. Figure modified with permission from Pruszynski et al. (2011a).

cortical circuit then interactions within that circuit should create a net response different from the sum of the separate responses: (A) + (B) ≠ (A+B). Independence of the generative circuits is evident in the shoulder's SLR to shoulder muscle stretch (**Figures 5B,D**, left panels)—no difference from the linear sum—which makes intuitive sense as SLR reflects spinal circuitry and the TMS evoked response depends on cortical circuitry. Evidence of a shared cortical circuit is obtained when the TMS pulse is timed to occur within the shoulder muscle's LLR to shoulder muscle stretch (**Figures 5B,E**, left panels) (Pruszynski et al., 2011a). Here the response is substantially larger than the linear sum. Similar observations have been made for finger, wrist, and elbow muscles indicating that M1 generally contributes the LLRs of the upper limb (Day et al., 1991; Lewis et al., 2004, 2006). TMS likely potentiates the LLR by activating cortical circuitry rather than a subcortical target of M1. This inference is justified by the fact that electrical stimulation applied over the scalp (transcranial electric stimulation, (TES)) preferentially excites the descending cortical axons (not the cortical circuitry activated by TMS) and fails to potentiate LLRs (Day et al., 1991).

Despite extensive research showing that primary motor cortex supports LLRs and that LLRs have knowledge of the arm's biomechanics, there are relatively few studies on M1 contributing this ability to LLRs. Here we discuss the available evidence. One recent study examined multi-joint LLRs of shoulder muscles using the TMS paradigm described above (Pruszynski et al., 2011a). LLRs in shoulder muscles are evoked when displacing only the elbow joint which is appropriate to counter the underlying shoulder-elbow torque that caused elbow motion (see earlier section). These responses must be driven by sensory information from muscles crossing the elbow since the shoulder muscles are not stretched by elbow motion. Accordingly, by timing the TMS pulse to coincide with the shoulder's LLR during elbow displacement one can test whether the "elbow afferent-to-shoulder muscle" circuit involves M1. For both shoulder extensor and flexor muscles the observed response to elbow displacement and TMS was greater than the linear sum to the two separate stimuli (**Figures 5E,F** right panels) whereas activity during the SLR was equal to the linear sum (**Figures 5D,F** right panels). Hence, M1 contributes to multi-joint integration in the LLR appropriate for the arm's dynamics.

A complimentary experiment was conducted on awake behaving monkeys (Pruszynski et al., 2011a). Recordings of individual M1 neurons were obtained as the animal countered torque pulses applied to its elbow and shoulder. From the entire set of neurons responding to the torque perturbations, a subset was selected which had "shoulder-muscle"-like activity during postural maintenance. These "shoulder muscle"-like neurons were analyzed with the torque comparisons previously described for shoulder muscles. Applied shoulder torque and elbow torques caused a similar initial displacement of the shoulder joint and stretch of the shoulder muscle. If the M1 neurons were driven exclusively by shoulder muscle afferents then they would express a similar burst of activity to the two perturbations. Alternatively, if M1 supports the differential activity observed in the shoulder's LLR then the neurons should respond more vigorously to the shoulder torque than elbow torque perturbation. Differential M1 activity was observed. A second set of comparisons applied shoulder + elbow torque to cause an initial displacement of just the elbow joint. If the M1 neurons were driven exclusively by shoulder sensory information then they should not respond differently to different direction of elbow motion. Instead, the resulting bursts of M1 activity was greater for elbow motions that required increased shoulder muscle activity to counter the underlying torque, the same pattern observed in the LLRs of shoulder muscles. So in both sets of comparisons, the M1 neurons expressed patterns of activity consistent with a representation of the arm's mechanical properties. Moreover, M1 neurons expressed this activity pattern 8–20 ms earlier than the same pattern expressed in shoulder muscles consistent with the known conduction delay from motor cortex to the motor periphery.

TMS has been utilized in a different paradigm to test whether M1 contributes to LLR's knowledge of limb dynamics (Kimura et al., 2006). Here researchers use a strong TMS pulse to induce a prolonged "silent period" following the initial burst of muscle activity. The late phase of the silent period is dominated by cortical inactivation (Ziemann et al., 1993; Brasil-Neto et al., 1995) which blunts M1's sensory-to-motor processing, and, consequently, immediate contribution to the LLR. This paradigm was first utilized to study reflex modulation while subjects reached to a target placed within a lateral force field (discussed in the previous section, Kimura et al., 2006). LLRs were occasionally elicited prior to the hand entering the force field and these responses were upscaled to compensate the impending lateral force: flexor LLRs were upscaled prior to an expected lateral force requiring flexor compensation, extensor LLRs were upscaled prior to a expected lateral force requiring extensor compensation. On a random number of trials, the researchers applied the strong TMS pulse just prior to the arm displacement. The perturbation still elicited a LLR from the arm muscles, but they were no longer scaled to the upcoming lateral force. Note that the interference was not a general feature of motor neuron quiescence since scaling of LLRs was not abolished during a silent period induced by electrical stimulation of the brachial plexus. To reiterate, temporary blockage of primary motor cortex abolished the scaling of the LLR but not its presence. From this result, the authors posit that primary motor cortex does not generate the LLR but alters its sensitivity. Although this hypothesis runs somewhat counter to a wealth of information, the basic finding has been replicated. Healthy subjects exhibit upscaled LLRs when maintaining their limb posture in a normal environment compared to postural maintenance in a very stiff environment where their motor effects are clamped. LLR scaling to these two environments is abolished during a TMS-induced silent period (Shemmell et al., 2009). Stability-related modulation of LLRs is also absent following cortical stroke (Trumbower et al., 2010), though these individuals express very small responses, unlike the original study, which complicates a direct comparison.

The few studies described in this section provide strong positive evidence that primary motor cortex contributes to the biomechanical knowledge expressed by the arm's LLRs.

CONTRIBUTION BY THE RETICULAR FORMATION

Reticular formation (RF) is a collection of nuclei spanning the brainstem and which contribute to a wide variety of functions

including sensori-motor control (Kuypers, 1981 and Baker, 2011 for review). RF plays a significant role in upper limb behavior as indicated by its prominent descending tract (Lawrence and Kuypers, 1968), innervation of spinal motor neurons controlling muscles throughout the upper limb (Davidson et al., 2007; Riddle et al., 2009), and active modulation during movement and planning stages of self-initiated reaching (Buford and Davidson, 2004; Schepens and Drew, 2004). Studies of individual RF neurons during postural perturbations are extremely limited. The one study on behaving cats demonstrated rapid bursts of RF activity to a foot drop (Stapley and Drew, 2009). Although this activity had an unclear relation to biomechanics or muscle activity, RF likely enables basic control since decerebrate cats have semi-stable stance and normal force reactions to platform displacement (Honeycutt and Nichols, 2010).

Larger LLRs occur when subjects attempt to "resist" a perturbation than "yield" to the perturbation. Identified in the earliest studies of the LLR (Hammond, 1956) this capability has spawned considerable research as a clear example of reflex modulation to voluntary goals (Crago et al., 1976; Colebatch et al., 1979; Jaeger et al., 1982; Lee and Tatton, 1982; Calancie and Bawa, 1985; Capaday et al., 1994; Lewis et al., 2006; Pruszynski et al., 2008; Nashed et al., 2012). A powerful paradigm for studying this phenomenon involves visual targets whose location and size, rather than verbal instructions, communicates how subjects should respond (**Figure 6A**). A small target centered on the hand would require a vigorous response (analogous to "resist") to adequately counter a perturbation and return to the target area. Conversely, a large target centered on the hand would only require a weak response (analogous to "yield") to adequately counter a perturbation and remain within the target area. Accumulating evidence indicates that the task-dependent change in LLR activity is due to the temporal overlap of two different responses, a task-dependent response and an automatic response (Rothwell et al., 1980; Lewis et al., 2006; Pruszynski et al., 2011b), rather than the scaling of single process. This is evident in the described paradigm by pairing a small or large visual target with a background load that requires either compensation by the stretched muscles or compensation by its antagonist (and minimum activation by the stretched muscle). With high background muscle activity and a large target the muscle displays bursts of activity within the SLR and LLR epochs whereas there is almost no evoked activity with low background activity and the large target (**Figures 6B,C**); such changes in response magnitude with background activity is termed "automatic gain scaling" (Matthews, 1986; Pruszynski et al., 2009). In contrast, a nearly constant increase in LLR activity is observed with the small target relative to the large target regardless of background muscle activity (**Figures 6B,C**). This pattern is consistent with the addition of a task-dependent component to an automatic component (Pruszynski et al., 2011b).

RF is a candidate generator for the task-dependent response. A direct link between RF and LLR's task-dependency is stymied by a complete lack of neural recordings during this behavior, but an indirect link can be made via the "StartReact". StartReact is the ultra-fast initiation of a planned action by a startling stimulus (typically a loud tone, 120 dB) (Valls-Solé et al., 1999; for review see Carlsen et al., 2011). Arm muscle activity during StartReact occurs ≈70 ms after the startling stimulus compared to >100 ms for a non-startling stimulus. This faster than normal reaction likely reflects the engagement of RF since these circuits underlie the protective startle response (Yeomans et al.,

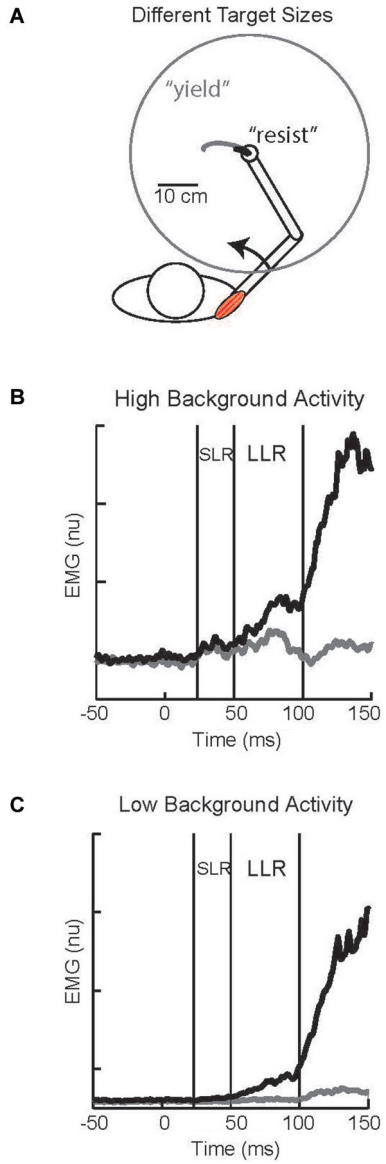

FIGURE 6 | Task-dependent change in LLR. (A) Cartoon of subject responding to an imposed shoulder torque. Maintaining the hand within a small target requires a vigorous response and is analogous to a "resist" instruction; the black trace depicts the small displacement of the hand to the perturbation. Maintaining the hand within a large target requires a weak response and is analogous to a "yield" instruction; the gray trace depicts the large displacement of the hand to the perturbation. **(B)** Evoked shoulder activity while the muscle had a high level of background activity from countering a constant opposing load; black and gray traces correspond to the small and large target conditions, respectively. **(C)** Evoked shoulder activity while the muscle had a low level of background activity as its antagonist countered a constant opposing load. Figure modified with permission from Kurtzer et al. (2014).

2002) and subjects suffering a cortical stroke (Honeycutt and Perreault, 2012) or degenerated corticospinal tracts (Nonnekes et al., 2014) will have delayed voluntary reactions but normal onset of StartReact.

The relation between LLR's task-dependency and StartReact was recently tested (Ravichandran et al., 2013). Subjects were instructed to quickly initiate an elbow movement following an auditory cue. On a random set of trials, their limb was perturbed or a loud sound was presented. The two stimuli caused a similar pattern of activity in the LLR epoch and evoked similar activity of the neck muscle sternocleidomastoid (an indicator of startle). Hence, there is an impressive similarity between the task-dependent response and StartReact.

Before proceeding, it is important to ask whether task-dependency of LLRs could reflect a neural substrate other than RF. Primary motor cortex is a likely candidate for reasons already elaborated. Its perturbation evoked activity also expresses task-dependent changes that parallel the set-dependent changes in upper limb LLRs (Evarts and Tanji, 1976). Recent studies have confirmed that task-dependency is commonly expressed across the population of M1 neurons, though in a more complex manner than earlier supposed, and has the appropriate timing to contribute to the observed muscle responses (Omrani et al., 2014; Pruszynski et al., 2014). However, transient suppression of M1 by a powerful TMS pulse does not diminish the LLR's magnitude during the "resist" instruction (Shemmell et al., 2009). This suggests that the supraspinal generator of LLR's task-dependent component is downstream from M1. RF is the most likely candidate given its general role in posture control and its specific role in StartReact.

With the link between task-dependency of the LLR and RF tentatively established, we now ask whether the task-dependent component, the automatic component, or both possesses knowledge of the arm's dynamics (**Figure 7**). The one study which has examined this important question (Kurtzer et al., 2014) used the 2 × 2 experimental design described above. Subjects were presented with either a small (radius = 2 cm) or large (radius = 30 cm) requiring a vigorous or weak corrective response along with background loads requiring low or high levels of pre-perturbation activity of the examined muscle, a shoulder extensor. The only experimental difference is that two pairs of torque perturbations were utilized: (1) shoulder flexion torque and elbow extension torque to induce similar amounts of initial shoulder flexion (**Figure 8A**); (2) shoulder − elbow flexion torque and shoulder − elbow flexion torque to induce flexion or extension of just the elbow (**Figure 8B**). Differential activity to each pair of perturbations is positive evidence for the LLR's knowledge of limb dynamics (see **Figure 2**). If knowledge of limb dynamics was only expressed by the LLR's automatic component then differential activity should be present with high background activity and absent without background activity, i.e. differential activity would only change with the muscle's background activity (**Figure 7A**). If knowledge of limb dynamics was only expressed by the LLR's task-dependent component then the magnitude of differential activity should be present with the small target and absent with the large target, i.e. differential activity would only change with the target size (**Figure 7B**). Lastly, if knowledge of limb dynamics was expressed by both the automatic and task-dependent component of the LLR then the magnitude of differential activity should increase with high background activity and the small target (**Figure 7C**).

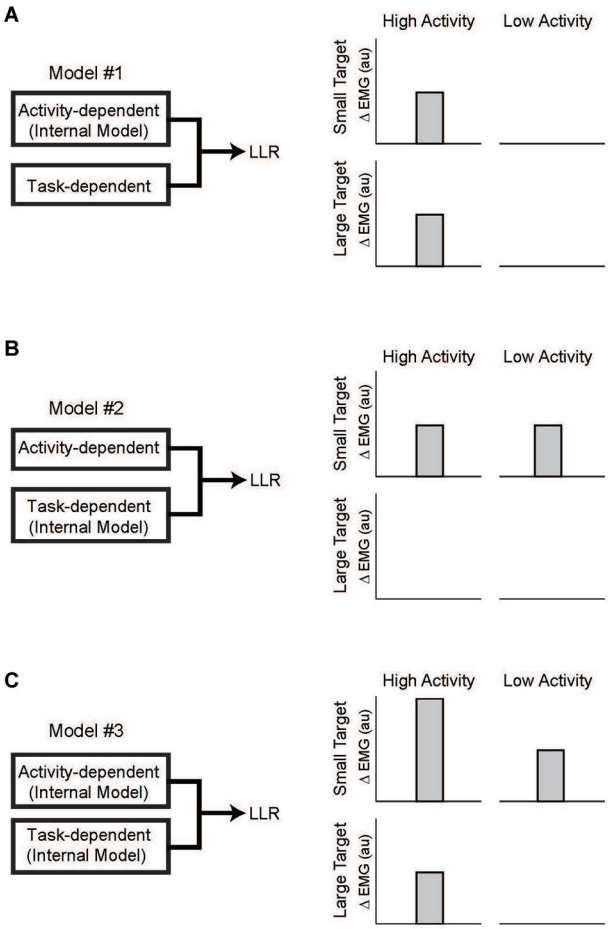

FIGURE 7 | Testing which component of the LLR utilizes knowledge of limb dynamics. (A) Left panel depicts a simple model of LLR comprised of two functional component: an automatic component scaled by background muscle activity and a task-dependent component scaled by target size. Right panel depicts expected pattern of LLR if only the automatic component utilized an internal model of limb dynamics. Expression of that information (i.e., a differential response to the pair of perturbations) would be evident during high background activity of the muscle but would not change with target size. **(B)** If only the task-dependent component utilized an internal model of limb dynamics than expression of that information would be evident with a small target requiring a vigorous response and not change with background activity of the muscle. **(C)** If both the automatic and task-dependent components utilized an internal model of limb dynamics than expression of that information would co-vary with background activity and target size. Figure modified with permission from Kurtzer et al. (2014).

Evoked muscle activity to shoulder displacement (the first pair of perturbations) was highly modulated by target size and background muscle activity (**Figures 8B,E**). Similar to previous studies, the greatest LLRs occurred with the small target and high background combination (top-left panel) which

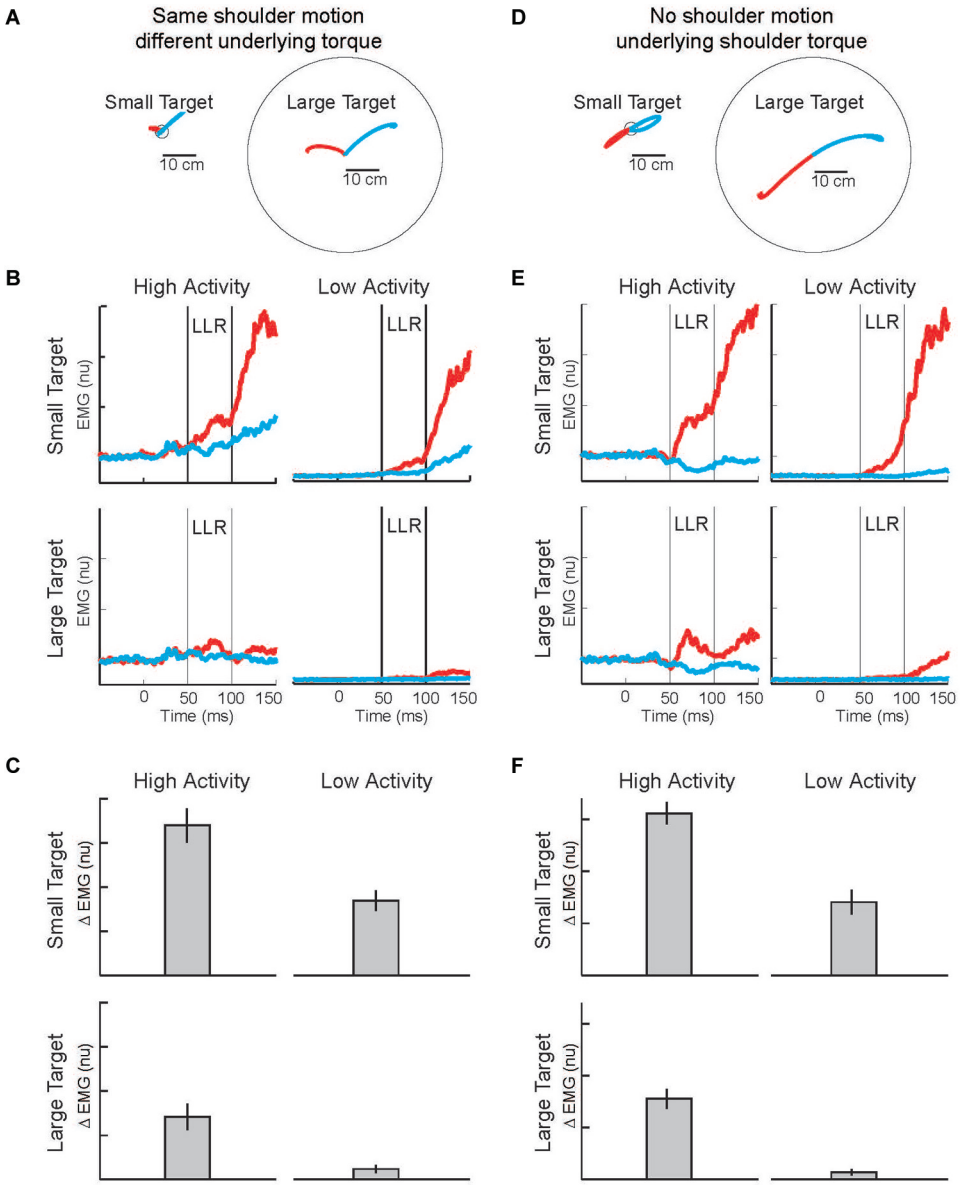

FIGURE 8 | Modulation of LLR to target size and background muscle activity. (A) Torque perturbations applied to the arm, a shoulder flexor torque (red arm) and an elbow extensor torque (blue arm). Red and blue traces show exemplar hand paths resulting from the two torque perturbations during presentation of a small target or large target. **(B)** Group average of shoulder extensor muscle activity evoked by the shoulder flexor torque (red) and elbow extensor torque (bue). The four panels display data during the four combinations of background muscle activity and target size. **(C)** Differential activity of the LLR to the pair of perturbations (shoulder flexor torque and elbow extensor torque) given the four combinations of target size+background muscle activity (compare to predictions in **Figure 7**). **(D)** Torque perturbations applied to the arm, a shoulder + elbow flexor torque (red arm) and a shoulder + elbow extensor torque (blue arm). Red and blue traces show hand paths resulting from the perturbations, same format as above. **(E)** Group average muscle activity evoked by the shoulder + elbow flexor torque (red) and shoulder + elbow extensor torque (bue). **(F)** Differential activity of the LLR to the pair of perturbations (shoulder flexor+elbow flexor torque and shoulder extensor+elbow extensor torque) given the four combinations of target size+background muscle activity (compare to predictions in **Figure 7**). Figure modified with permission from Kurtzer et al. (2014).

presumably recruits both components whereas very weak LLRs occurred with the large target and low background combination (bottom-right panel) which presumably recruits neither component. Response magnitudes between these extremes occurred for the large target/high background combination and the small target/low background combination presumably because the automatic or task-dependent component is selectively recruited, respectively. The critical issue is how the differential activity to the shoulder torque and elbow torque perturbations changes with target size and background activity, the difference between the red and blue traces in each panel. The differential activity clearly changes with target

size and background activity and has the greatest magnitude when both components presumably contribute, compare **Figures 7C**, **8C**.

Complementary results were obtained with the pair of torque perturbations causing motion of just the elbow (**Figure 8D**). Again, the greatest LLRs occurred with the small target and high background combination (top-left panel), the smallest LLRs occurred with the large target and low background combination (bottom-right panel), and response magnitudes between these extremes occurred for the large target/high background combination and the small target/low background combination. As before, the critical issue is how differential activity to the two perturbations (leading to excitatory and inhibitory effects) changes with target size and background activity, the difference between the red and blue traces in each panel. The differential activity is greater during conditions with a small target and conditions with high background activity. The greatest differential magnitude occurs during the small target/high background combination when both the automatic and task-dependent components would contribute, compare **Figures 7C**, **8F**.

Taken together, the results indicate that the task-dependent component and automatic component of the LLR utilize knowledge of limb dynamics. Given the indirect link between task-dependency in the LLR and RF we tentatively conclude that RF contributes to this internal model. A direct test is lacking but would involve neural recordings from this structure. Another possibility is TES as this activates the descending axons of M1 (not its laminar circuitry) and would engage RF though a serial connection or a TMS silence period paradigm that suppresses cortical processing. Clearly, a great deal of work is needed before a definitive conclusion can be made.

CONTRIBUTION BY THE CEREBELLUM

The cerebellum is a massive and highly elaborated subcortical structure which provides a distinct contribution to sensori-motor control (Manto, 2002). In the broadest strokes, the cerebellum is not necessary for either sensation or action, but is critical to motor coordination. It receives somatosensory information from the motor periphery as well as information from motor-related cerebral, brainstem, and spinal networks. Damage to the cerebellum can result in a variety of abnormalities in self-initiated arm movements including improper timing, scaling, and launch direction along with pronounced tremor as the hand nears its target. These problems are present for actions performed at a single joint, like the elbow or wrist (Hallett et al., 1975; Brown et al., 1990; Manto et al., 1994), but are relatively mild compared to the disturbed behavior of the unconstrained arm (Holmes, 1939; Goodkin et al., 1993; Bastian et al., 1996) where limb motion becomes irregular and inconsistent. Cerebellar damage also impairs the ability to actively stabilize the shoulder when attempting fast elbow-only movements (Boose et al., 1999) indicating that subjects inadequately anticipate the arm's multi-joint dynamics, rather than an issue specific to producing multi-joint movement trajectories. Over-compensation and under-compensation also show that inaccuracy is not due to an inability in producing adequate phasic force to counter intersegmental dynamics (Bastian et al., 2000).

The prominent connection between the cerebellum and primary motor cortex (Middleton and Strick, 1998) and the prominent role of primary motor cortex for the LLR (Pruszynski and Scott, 2012) suggests that the cerebellum has an important role for LLRs. (Note that the cerebellum also provides input to the RF and almost certainly modulates its action (Asanuma et al., 1983)). Neurons in the dentate and interposed output nuclei of cerebellum respond to limb perturbations over a range of times (Strick, 1983), the earliest bursts of cerebellar activity could impact M1 activity within the long-latency epoch. Cerebellum does influence M1's processing of somatosensory information since a cooling probe applied to cerebellar output nuclei depresses reflex-related activity of M1 (Meyer-Lohmann et al., 1975). Moreover, cerebellar cooling results in the limb behaving like an underdamped spring with sustained oscillations over the goal target (Vilis and Hore, 1980). Evidence is mixed whether the cerebellum alters the LLR of stretched upper limb muscles. Cerebellar cooling did not alter the LLR in the stretched elbow muscle. Rather the shortened elbow muscle had a delayed and sustained antagonist burst which initiated the oscillatory movement. Researchers have also reported lowered (Marsden et al., 1977) and heightened long-latency responses (Friedemann et al., 1987) in the hand muscles. Note that these studies examined the LLRs when controlling motion at a single joint, a situation known to be less compromised than multi-joint control. To date, only one study has examined if cerebellar damage alters the arm's LLRs during multi-joint control (Kurtzer et al., 2013) and compromised the LLR's knowledge of limb dynamics.

To test if cerebellar damage compromises the knowledge of limb dynamics utilized by the arm's LLR, the authors employ a paradigm described in the previous sections (**Figures 2**, **3**). Subjects maintained their arm in a steady posture while four different torque perturbations were unexpectedly applied. A shoulder flexor torque and elbow extensor torque induced the same amount of initial shoulder flexion whereas a shoulder-elbow flexion torque and shoulder-elbow extension torque induced pure elbow flexion and pure elbow extension, respectively. These torque combinations tested whether the shoulder extensor's LLR was driven by shoulder motion only or by motion of both joints appropriate to counter the underlying torque. The participants in the experiment included individuals who suffered cerebellar damage leading to ataxic arm behavior and healthy matched controls. If the pattern and magnitude of LLRs were entirely independent of the cerebellum, then cerebellar damaged individuals would express normal LLRs (**Figure 9A**). Alternatively, if knowledge of limb dynamics depends entirely on the cerebellum, then their shoulder LLRs would continue to respond to the local shoulder motion but fail to respond to elbow motion (**Figure 9B**); that is, the LLRs would show the same simple pattern of response exhibited by the SLR.

The motor behavior of cerebellar-damaged individuals exhibited the characteristic oscillatory and inaccurate arm motion to limb perturbations. Their LLRs were also altered from normal but in an unexpected way. Both healthy and clinical subjects had greater LLRs in the stretched shoulder extensor when shoulder displacement was induced by shoulder flexor torque vs. elbow extensor torque (**Figures 9C,D**, left panels). Healthy

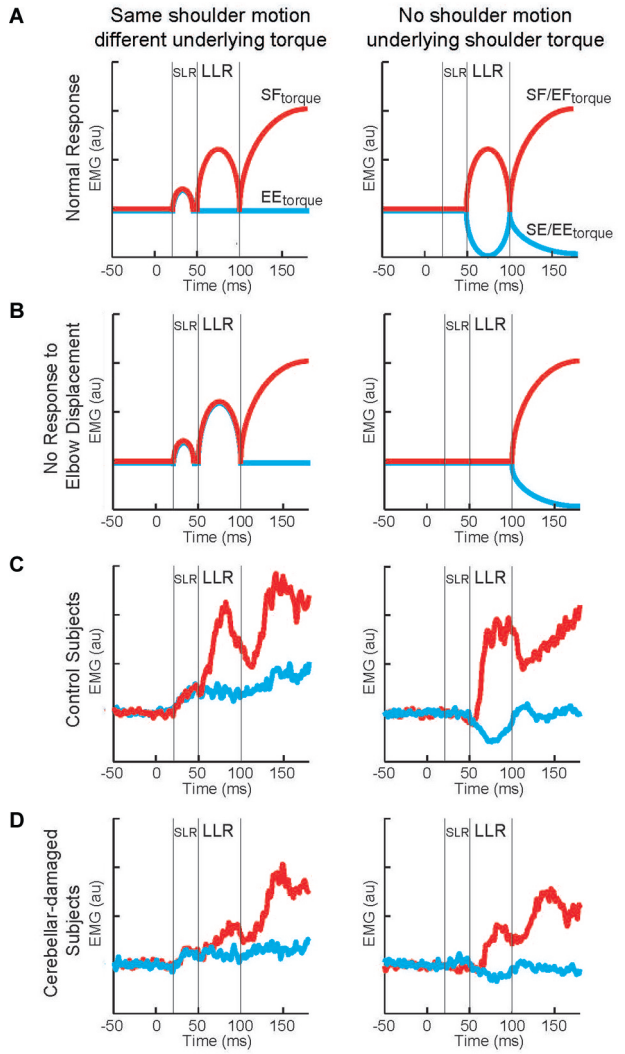

FIGURE 9 | Long-latency reflexes during cerebellar damage. (A) Cartoon of evoked activity from the shoulder extensor by healthy subjects. Panels on the left indicate responses to shoulder displacement caused by a shoulder flexor torque (red) and an elbow extensor torque (blue). Panels on the right indicate responses to elbow displacement caused by a shoulder + elbow flexor torque (red) and an shoulder + elbow extensor torque (blue). **(B)** Cartoon of predicted shoulder muscle activity if cerebellar damage eliminates the ability to integrate multi-joint muscle. **(C)** Group average of shoulder extensor muscle activity by a group of healthy subject. **(D)** Group average of shoulder muscle activity by a group of subjects suffering cerebellar damage. Figure modified with permission from Kurtzer et al. (2013).

and clinical subjects also had excitatory shoulder LLRs when their elbow was displaced into flexion and inhibitory LLRs when their elbow was displaced into extension (**Figures 9C,D**, right panels). Accordingly, cerebellar-damaged individuals expressed a pattern of multi-joint integration appropriate for the arm's intersegmental dynamics.

The main difference from normal was much smaller LLRs. The smaller LLRs in the cerebellar-damaged group did not reflect a general change in reflex excitability as their SLR was not decreased from normal. Nor did smaller LLRs reflect a less vigorous motor set since their voluntary response (>100 ms) was not decreased from normal. Nor was there greater downscaling of LLRs to a subset of perturbations. Rather the cerebellar group had the same relative magnitudes of LLRs to the perturbations as the normal group.

The conserved pattern of LLR activity indicates that the knowledge of limb dynamics used to generate LLRs is housed outside of the cerebellum. The smaller level of activity suggests that its overall sensitivity to limb displacement is modulated by the cerebellum. A similar conclusion has been made by a several researchers (Holmes, 1939; MacKay and Murphy, 1979; Jo and Massaquoi, 2004).

One can make a reasonable *post hoc* explanation for the lowered LLRs with cerebellar damage. Cerebellum enables a broad number of motor abilities that rely on predicting future states of the body based on current sensory information, ongoing motor commands, and a representation of limb mechanics (for review see Bastian, 2006), i.e. a forward model. Recordings of single Purkinje neurons while the monkey moved its arm against different loads demonstrate that cerebellar activity is linked to the predicted state of the arm not the exerted motor commands (Pasalar et al., 2006). Such forward models allow fast feedback control of a system with time-delays, like our body and nervous system. If the predicted sensory states are noisy and inaccurate, like with cerebellar damage, then feedback gains must be decreased in order to ensure stability. This reasoning has accounted for the altered behavior of lift-grip actions made in a low gravity environment (Crevecoeur et al., 2010). A recent study also found that single-joint arm movements by cerebellar damaged subjects were consistent with lowered feedback gain (Bhanpuri et al., 2014). In addition, cerebellar damage has been shown to degrade the predictive ability of fast feedback control including scaling the initial leg muscle response to the amplitude of surface displacement (Horak and Diener, 1994) and cerebellar cooling eliminates the ability to generate early antagonist responses to a pulse perturbation (Hore and Vilis, 1984). Taken together, the cerebellum may use prediction accuracy of its forward models to gain modulate the neural pathways providing knowledge of limb dynamics to the LLR.

POSSIBLE CONTRIBUTION BY OTHER NEURAL SUBSTRATES

The three previous sections discussed how primary motor cortex, RF, and cerebellum enable the LLR's compensation of arm's biomechanics. The focus on these three brain regions was not intended to exclude other possible contributors, but describe the relatively few physiological studies that are directly relevant. Neural pathways which could contribute to this capability but have not been tested include the basal ganglia, red nucleus, additional cortical areas, and spinal cord. Basal ganglia is a likely candidate as it is strongly linked to primary motor cortex and RF (Middleton and Strick, 2000). Moreover, disorders of basal ganglia are linked to alterations in LLRs such as an increased response magnitude paralleling the well-known increase in limb rigidity (Tatton and Lee, 1975; Rothwell et al., 1983) and an inability to alter LLRs to the perturbation context such as platform tilt when standing

with or without a hand-hold (Schieppati and Nardone, 1991, also Horak et al., 1992). Red nucleus likely plays an important role in the LLRs of non-human primates via its substantial descending tract to the spinal cord (Lawrence and Kuypers, 1968) and generally similar activity patterns as M1 neurons (Cheney et al., 1991). However, the rubrospinal tract is quite small in humans (Nathan and Smith, 1982) and is not expected to provide significant direct contributions to motor output including the LLR. Several motor cortical regions, in addition to primary motor cortex, could be involved in the LLR by either projecting to M1, brainstem or spinal targets. This includes supplemental motor area which appears to modulate the automatic component of LLR via its connection with M1 and may engage the RF and its task-dependent component of LLR (Hummelsheim et al., 1986; Dick et al., 1987; Spieser et al., 2013). Lastly, group II-spinal circuits most likely contribute to the LLR (Hendrie and Lee, 1978; Lourenço et al., 2006; Meskers et al., 2010) and electrical stimulation of the peripheral nerves has revealed that group II afferents make multi-muscle connections (Lourenço et al., 2006). Future studies should uncover the efficacy and pattern of these connections during more naturalistic limb displacements. In sum, there are variety of neural pathway which could provide complimentary or distinct functions to the LLR that enable it to account for the arm's biomechanics.

CONCLUSION

A significant body of work has explored the capabilities of the LLR. Knowledge of limb dynamics is a core capability of LLRs and allow a degree of motor sophistication that rivals planned voluntary actions (Scott, 2004; Pruszynski and Scott, 2012). The material reviewed here considers three supraspinal circuits which may support this function: primary motor cortex, RF, and cerebellum.

The most direct and convincing evidence is that primary motor contributes to the LLR's knowledge of limb dynamics. This is consistent with M1's strong link to the motor periphery, LLRs, and motor adaptation. Although there are relatively few studies on this topic, they utilize neural recordings and non-invasive brain stimulation, the data is unambiguous and the logic is straightforward. Taken together, it can be concluded that primary motor cortex provides knowledge of limb dynamics used by the LLR.

The RF is another natural candidate given its sensory and motor pathways. Although there is no direct evidence (given the complete lack of neural recordings) we can make reasonable inferences on the neural basis of StartReact and its association with task-dependency of the LLR. Given this chain of reasoning, the evidence is consistent with a reticular contribution. It can be tentatively concluded that RF provides knowledge of limb dynamics used by the LLR.

The final supraspinal circuit we considered is the cerebellum. This is still another natural candidate given its sensory inflow, efferent connection to primary motor cortex, and critical role in motor coordination. The one study on this topic examined a clinical population. These individuals had the classical signs of ataxia and postural instability yet their LLR had the same pattern of activity as normal. An unaltered motor pattern in a clinical population indicates that the damaged brain area does not directly contribute to that motor pattern. We concluded that the cerebellum scales the gain of neural pathways that provide the structured response of the LLR.

It should be emphasized that the material on this topic is a starting point and not a final chapter. A few outstanding questions in no particular order:

- If multiple supraspinal substrates possess knowledge of limb dynamics, in what ways do they differ?
- Do spinal pathways possess knowledge of limb dynamics?
- What is the neural basis of adapting long-latency reflexes?
- How do the neural circuits represent the different features of the body/environment?
- In what ways does the knowledge of limb dynamics for the long-latency reflex differ from that utilized by self-initiated/voluntary actions?

Answering these questions will greatly enrich our understanding of fast feedback control.

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Task, muscle and frequency dependent vestibular control of posture

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The vestibular system is crucial for postural control; however there are considerable differences in the task dependence and frequency response of vestibular reflexes in appendicular and axial muscles. For example, vestibular reflexes are only evoked in appendicular muscles when vestibular information is relevant to postural control, while in neck muscles they are maintained regardless of the requirement to maintain head on trunk balance. Recent investigations have also shown that the bandwidth of vestibular input on neck muscles is much broader than appendicular muscles (up to a factor of 3). This result challenges the notion that vestibular reflexes only contribute to postural control across the behavioral and physiological frequency range of the vestibular organ (i.e., 0–20 Hz). In this review, we explore and integrate these task-, muscle- and frequency-related differences in the vestibular system's contribution to posture, and propose that the human nervous system has adapted vestibular signals to match the mechanical properties of the system that each group of muscles controls.

Keywords: vestibular reflexes, postural control, task dependent, frequency response, appendicular muscles, axial muscles

INTRODUCTION

The vestibular system senses linear and angular head motion in space. This sensory information is used by the central nervous system to elicit reflexes and control appendicular, axial and extraocular muscles that are crucial for posture and gaze. Vestibular reflexes vary across and within muscle groups and are modulated by spatial and temporal factors related to a muscle's contribution to the system dynamics, the different neural pathways innervating each muscle, and the congruency of sensory signals and motor commands for a given task. Recent findings from our lab indicate that these modulating mechanisms may be related to the frequency content of the vestibular signals impinging on the different muscles. Like many electromechanical systems, the vestibular system's input-output response varies with stimulus frequency, and like many biological systems, the bandwidth of this frequency response has evolved to match the mechanical system being controlled. This review examines the frequency response of the vestibular system's reflexive control of posture. More specifically, it focuses on the differences in the frequency response and task dependence of vestibular reflexes controlling appendicular and spinal muscles in order to better understand the neurophysiological principles governing how humans achieve stable upright posture of the head and body. We argue that the frequency response of vestibular reflexes is governed by the mechanical systems under their control, with the neck system exhibiting a broader bandwidth than the appendicular muscles. The higher frequency response in neck muscles can be modulated but not inhibited, and in contrast to the lower frequency response observed in the appendicular muscles, its contribution to muscle activity does not dependent on a neck muscle's contribution to postural control. Based on this evidence, we propose the higher frequency response of the vestibulocollic reflexes (VCR) is functionally similar to the vestibulo-ocular response for the coordination of eye-head movements as well as head postural control during gaze shifts.

FREQUENCY RESPONSE OF THE VESTIBULAR SYSTEM

The frequency response of the vestibular system is governed by the electromechanical properties of the sensory organs and the various neural structures and pathways that then carry these sensory signals to motor neurons (see **Figure 1**). As described in more detail below, these properties appear to be tuned to generate response characteristics specific to the biomechanical system being controlled by those muscles.

Vestibular signals originate from two types of sensory organs: the otolith organs, which encode linear motion, and the semicircular canals, which encode angular motion. Two otolith organs and three semi-circular canals are contained in each of the two vestibular apparatus. Otolith afferents demonstrate dynamic responses that are in phase with linear acceleration, whereas semi-circular canal afferents demonstrate dynamic

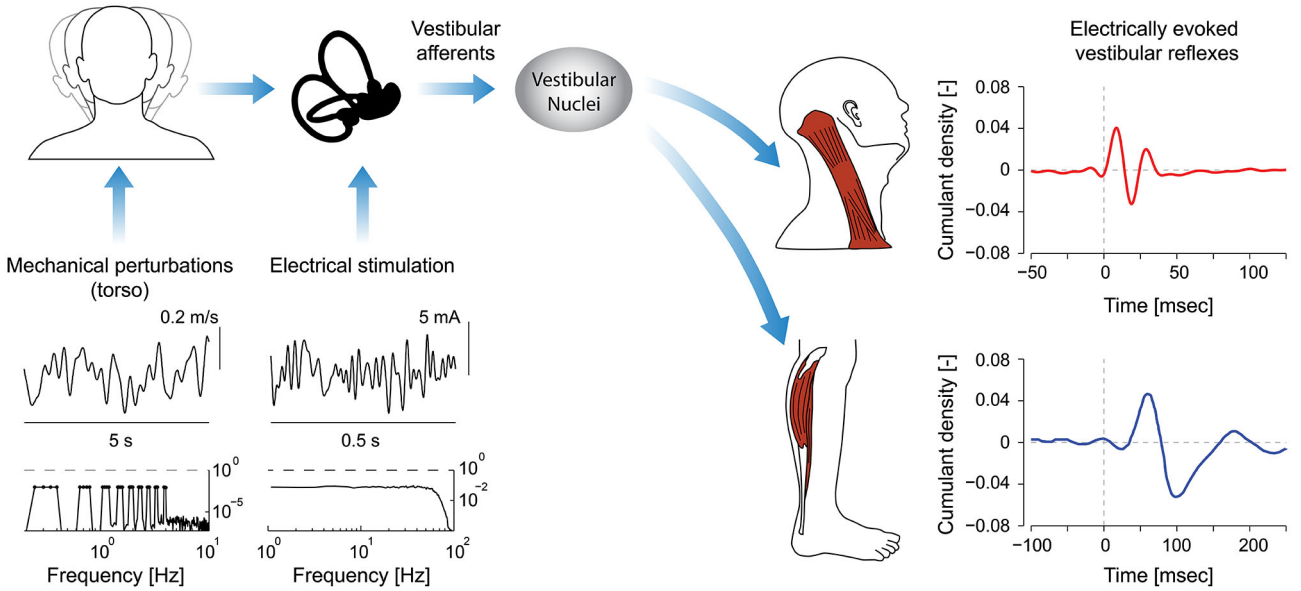

FIGURE 1 | Signal processing pathways and evoked reflex responses as a result of mechanical perturbations and/or electrical stimulation. Input stimuli span specific bandwidths (see spectra, mechanical: 0–4 Hz; electrical stimulation: 0–75 Hz) and when applied to the head generate vestibular afferent activity. Note: the representative mechanical perturbation is applied via the torso and limited to less than 10 Hz on account of the bandwidth of mechanical device applying the perturbation and the biomechanics of the human body. Consequently, the evoked responses in axial and appendicular muscles are presented only in response to electrical stimuli with identical bandwidths (0–75 Hz). Afferent signals descend through the vestibular nuclei (VN) to axial and appendicular muscle motoneurons. The evoked reflexes in axial muscles have much shorter latencies than those in appendicular muscles (8 ms vs. 50 ms). Different time scales were used to illustrate the evoked responses (250 ms vs. 150 ms). (Data for cumulant density plots and perturbation/stimulation signals are adapted from Forbes et al., 2013a,b, 2014).

responses that are in phase with angular velocity at frequencies above about 0.1 Hz and up to 4.0 Hz (Goldberg et al., 2012).

Animal and human studies have reported that normal head motion, and thus the stimulus for the vestibular system, has relatively low frequency content. Animals performing voluntary head movements (with or without gaze redirections) exhibit head rotational velocity profiles containing frequency information approaching 20 Hz (Armand and Minor, 2001; Huterer and Cullen, 2002). Similarly, head rotational velocity in humans performing locomotor tasks exhibit frequency content up to 20 Hz (Grossman et al., 1988; Pozzo et al., 1990). Highly active movements, such as running, playing sports, and jumping, seem to increase this bandwidth to 30 Hz or higher (Carriot et al., 2014).

While the measured frequency bandwidth of head motion has been limited to 0–30 Hz, the vestibular afferents are capable of much higher frequency response dynamics. The frequency response (i.e., gain and phase) of turtle otoliths during inertial stimuli reaches 500 Hz and resembles that of a linear second order system with a natural frequency at ∼400 Hz (Dunlap et al., 2012; Dunlap and Grant, 2014). In the rat, the otolith hair cell and calyceal synapses can generate responses above 100 Hz during mechanical probing of hair bundles (Songer and Eatock, 2013). Similarly, canal afferents of the turtle encode mechanical indentation stimuli of the posterior canal duct up to 100 Hz, where the gain of the afferent response increases with frequency across the tested bandwidth (Rowe and Neiman, 2012). During rotational stimuli, the gain of canal afferents relative to input rotational velocity in monkeys also increases with frequency and phase leads the stimulus over the entire reported bandwidth of 0–20 Hz (Sadeghi et al., 2007; Massot et al., 2011). These increasing gains (measured up to 20 Hz) indicate that the vestibular system can encode kinematic head stimuli above the tested bandwidth and thus above the frequencies that occur during normal movements and tasks.

Vestibular afferents may be tuned to specific frequencies of head movement. For example, mammalian canal afferents are categorized as regular or irregular based on their resting discharge variability (Goldberg, 2000). Regular afferents transmit more information at lower frequencies (<15 Hz) (Sadeghi et al., 2007), which is consistent with regular afferents being the primary contributors to the vestibulo-ocular reflex at frequencies <4 Hz (Minor and Goldberg, 1991; Chen-Huang et al., 1997). In contrast, irregular afferents exhibit a steeper increase in gain with frequency and a more pronounced phase advance than regular afferents (Sadeghi et al., 2007). Thus, irregular afferents are proposed to process high frequency information, which may be especially important when muscles need to respond to high frequency transient perturbations such as direct head impacts (Carriot et al., 2014).

Signals from both afferent types are further processed by the vestibular nuclei (VN). This processing depends on the afferent's intrinsic membrane electrophysiology and can differ within and

across nuclei (see review Straka et al., 2005). In the guinea pig medial vestibular nuclei (MVN), neurons are divided into two subtypes (A and B) that vary in spike shape, sensitivity to input currents and dynamic range (Ris et al., 2001; Beraneck et al., 2003). Type B neurons promote high frequency responses whereas type A neurons act as low-pass filters and are better suited to transmit the resting tonic activity of vestibular afferents (Ris et al., 2001). In contrast to MVN neurons, neurons in the lateral vestibular nucleus (LVN) have a lower sensitivity to input currents. LVN neurons appear to lack the decreasing-gain-with-increasing-frequency pattern observed in MVN neurons, and instead synchronize their firing to the input stimuli at a particular "cutoff" frequency (Uno et al., 2003). In monkey VN neurons, the increasing gain and phase described earlier mimic irregular afferents (Dickman and Angelaki, 2004; Massot et al., 2011). However, VN neurons transmit less information about head motion as compared individual canal afferents (Massot et al., 2011). Thus, it appears the type of processing vestibular afferent signals undergo depends on the nuclei and the specific neurons through which they travel.

Variations in the neural pathways may also contribute to the muscle specific characteristics of vestibular reflexes. Vestibulocollic pathways, which innervate the neck muscles, are mostly comprised of three-neuron-arcs that originate primarily from the MVN, descend via the bilateral medial vestibulospinal tracts, and have short (∼8–10 ms) response latencies (Watson and Colebatch, 1998; Forbes et al., 2014). There are also indirect polysynaptic pathways mediating some vestibulocollic signals (reviewed in Wilson and Schor, 1999; Goldberg and Cullen, 2011). In comparison, vestibulospinal pathways, which innervate upper and lower limb muscles, originate from the LVN, and travel primarily ipsilaterally via the lateral vestibulospinal tract. Direct connections to limb motoneurons are exclusively excitatory while indirect connections via spinal interneurons can be both excitatory and inhibitory (Lund and Pompeiano, 1968; Wilson and Yoshida, 1969; Grillner et al., 1970; Shinoda et al., 1986; Davies and Edgley, 1994). In humans, lower limb muscle responses evoked by a vestibular stimulus exhibit longer latencies (∼50–60 ms) than expected from a direct vestibulospinal connection (Britton et al., 1993; Fitzpatrick et al., 1994; Day et al., 1997; Ali et al., 2003; Lee Son et al., 2008), and this delay argues for additional processing of the evoked vestibular signals by central structures. Indeed, there is evidence that vestibular signals converge onto spinal interneurons, indicating that further processing of vestibular information may occur through local spinal pathways (Iles and Pisini, 1992; Thomas and Bent, 2013). Based on the data presented in this section, it appears that the vestibular organs are capable of sensing a wide range of input frequencies, but that the pathways then modulate and filter this response to suit the frequency required for the muscles to control their mechanical system (Forbes et al., 2013a).

EXTRACTING THE FREQUENCY RESPONSE OF VESTIBULO-MUSCULAR SYSTEMS

The frequency response of vestibular reflexes in muscles can be examined using mechanical perturbation and electrical stimulation techniques (see **Figure 1**). A common mechanical perturbation technique used to study VCR and vestibulo-ocular reflexes (VOR) is whole-body motion. Subjects are typically exposed to continuous sinusoidal or stochastic perturbations (e.g., rotation, tilt or translation) to characterize the transfer function, for instance, between head velocity and eye velocity when studying the VOR (Raphan et al., 1979; Robinson, 1981). Transient velocity steps can also be used to characterize the decay of vestibular reflex responses during otherwise constant velocity movements (Raphan and Cohen, 1985). Whole-body perturbations for the study of vestibular reflexes in axial or appendicular muscles may arguably be less relevant since there is no need to keep the head or body upright. They have nevertheless been used to study the frequency response of the VCR in decerebrate and alert animal preparations (Berthoz and Anderson, 1971; Ezure and Sasaki, 1978; Bilotto et al., 1982; Baker et al., 1985; Dutia and Hunter, 1985; Goldberg and Peterson, 1986; Keshner et al., 1992). These particular studies isolate the descending reflex pathways and provide important insight into the open-loop characteristics of neck vestibular reflexes. Whole-body linear accelerations have also been used in humans to induce vestibular responses in quiescent neck muscles, extra-ocular muscles, and upper and lower limb muscles (Greenwood and Hopkins, 1976; Aoki et al., 2001).

Isolated mechanical perturbations applied to the head, body or feet are perhaps more natural stimuli than whole-body perturbations for probing vestibular reflexes. Because these perturbations also stimulate somatosensory receptors, it can be difficult to isolate the vestibular contribution to postural control. During standing perturbations, afferent signals generated by ankle motion can be minimized by controlling the support surface tilt to match body sway (Nashner and Berthoz, 1978; Nashner et al., 1982). A comparison of these sway-referenced perturbations to natural perturbations, i.e., no sway referencing, allow the relative balance-related contributions of the somatosensory and vestibular systems to be estimated during standing balance and torso control (Fitzpatrick et al., 1996; Peterka, 2002; Goodworth and Peterka, 2009). An alternate approach relies on robotic balance systems to simulate normal stance where body motion is controlled by changes in isometric ankle torque (Luu et al., 2011). Robotic systems such as these not only emphasize vestibular contributions to balance, they allow the system's mechanical properties (i.e., stiffness, damping and inertia) as well as the relationship between motor commands and sensory feedback to be manipulated and thus different aspects of postural control to be explored. While similar robotic techniques have yet to be developed for head, neck or torso postural control, the isolation of somatosensory contributions to gaze shifts has been implemented by counter rotating the body during head movements (Roy and Cullen, 2004).

Electrical stimulation of the vestibular organ is a non-invasive experimental technique used to probe human vestibular function (Fitzpatrick and Day, 2004). The applied current, which is delivered percutaneously using electrodes placed behind the ears, modulates the firing rates of vestibular afferents (Goldberg et al., 1984) and provides an artificial, isolated craniocentric vestibular error signal. The behavioral responses to electrical vestibular stimulation have been modelled (Fitzpatrick and Day, 2004) based on the distribution of vestibular afferents within

the labyrinth and an assumption that all afferents (otoliths and semi-circular canals) are affected by the stimulus (Goldberg et al., 1984; Kim and Curthoys, 2004). The virtual head movement generated by binaural bipolar electrical stimulation (one of several possible electrode configurations) generates a perceived rotation about an axis directed posteriorly and superiorly by 18° relative to the Reid's plane and a small lateral linear acceleration (Fitzpatrick and Day, 2004). In perception studies, this virtual rotation correlates maximally with real rotations when their two axes are co-linear (Day and Fitzpatrick, 2005), i.e., when the head is extended by 18°.

The vestibular error signals evoked by electrical stimulation have a strong effect on motor systems. Vestibular reflexes are evoked in ocular, axial and appendicular muscles, and manifest as changes in gaze and postural control in both humans and animals (Nashner and Wolfson, 1974; Lund and Broberg, 1983; Britton et al., 1993; Fitzpatrick et al., 1996; Watson and Colebatch, 1998; Watson et al., 1998; Ali et al., 2003; MacDougall et al., 2003; Aw et al., 2006; Ehtemam et al., 2012; Hsu et al., 2012; Zelenin et al., 2012; Kim, 2013). When the electrical stimulation is applied as sinusoidal or stochastic signals, the frequency response of vestibular reflexes can be characterized in a manner similar to that used with mechanical stimuli in many VOR and VCR studies (Fitzpatrick et al., 1996; Pavlik et al., 1999; Dakin et al., 2007, 2011; Forbes et al., 2013a). Unlike mechanical stimulation, electrical stimulation is not limited by the bandwidth of the mechanical system applying the perturbation or the neuromuscular system being investigated; thus, the frequency response of vestibular reflexes can be characterized over a larger bandwidth. Since concomitant activation of somatosensory afferents is limited to skin afferents behind the ears (which can be minimized with the application of a local anesthetic), electrical vestibular stimulation represents a powerful tool to examine the frequency response of vestibulo-muscular systems across varying postural task conditions.

Despite these advantages, our understanding of electrical vestibular stimulation remains incomplete. For instance, it remains unclear whether otolith and semicircular canal afferents are stimulated equally. Some authors have suggested that only otolith responses are induced in humans (Cohen et al., 2012), whereas others have argued that semicircular canals are also involved (Curthoys and Macdougall, 2012; Reynolds and Osler, 2012). It is not our objective here to enter this debate; instead, we propose to rely on the consistent nature of the electrical vestibular stimulation to compare the frequency response characteristics of vestibular reflexes across postural conditions (e.g., different combinations of sensory feedback or the necessity to maintain balance) and muscle groups (e.g., appendicular and axial). Therefore, a substantial component of this review will consider observations made using electrical vestibular stimulation.

APPENDICULAR MUSCLES: MODULAR CONTROL AT LOW FREQUENCIES

The primary function of vestibular reflexes in appendicular muscles is to generate muscle activity that maintains upright body posture and that ultimately contributes to stabilizing the head in space. Because the vestibular organs are fixed to the head, vestibular information must be transformed from the head reference frame before being used to generate appendicular muscle responses. For instance, postural sway evoked by electrical vestibular stimulation, which occurs primarily in the frontal plane when facing forwards, rotates with the orientation of the head relative to the feet (Lund and Broberg, 1983; Iles and Pisini, 1992; Britton et al., 1993). Consequently, the vestibular-evoked reflex responses in lower limb muscles are reversed between head-left and head-right postures (Britton et al., 1993; Dakin et al., 2007). This craniocentric response remains intact no matter how the head orientation is achieved, whether it be head only, trunk only or a combination of both (Lund and Broberg, 1983). Although these and other studies demonstrate the coordinate transformation that vestibular information undergoes and highlights its importance to standing balance of the whole body, other evidence suggests that this craniocentric principle may be less rigid than initially thought. When stance width is increased and the body becomes more stable in the frontal plane, the response magnitude to electrical vestibular stimulation becomes biased towards the sagittal plane such that changing head orientation results in a nonlinear relationship between head orientation and response direction (Mian and Day, 2014). These more recent results indicate that the balance system also integrates vestibular inputs with respect to whole-body stability (Mian and Day, 2014).

Vestibular reflexes in appendicular muscles contribute to balance over a bandwidth that, much like the vestibular system itself, extends beyond the assumed physiological range of vestibular signals (Armand and Minor, 2001; Huterer and Cullen, 2002). Vestibular reflexes evoked using stochastic electrical stimulation exhibit frequency components up to 25 Hz in lower limb muscles (see **Figure 2**; Dakin et al., 2007, 2010). The gain and phase of the reflexes resemble a low-pass filter with a cut-off of about 15 Hz and a phase inflection point at about 10 Hz (Dakin et al., 2007; Forbes et al., 2013a). The time domain estimate (i.e., cross-correlation) of the evoked muscle responses are equivalent to those from transient step-like stimulation: a biphasic response comprised of short and medium latency components (see **Figure 1**; Dakin et al., 2007). Frequencies above and below the 10 Hz inflection contribute primarily to the short and medium latency components respectively; however, the total response of the reflex is the linear sum of all frequencies and each frequency contributes to specific attributes of each component (Dakin et al., 2011).

This bandwidth of vestibular input to the appendicular muscles does not completely transfer to the mechanical response of standing balance. Vestibular input undergoes mechanical low-pass filtering when converted from lower-limb muscle activity to forces/moments and again from forces/moments to body sway, and results in forces/moments and body sway that are limited to <5 Hz and <2 Hz respectively (Fitzpatrick et al., 1996; Dakin et al., 2010). From a biomechanical control perspective, the high bandwidth of the vestibular input to the muscles is consistent with the electromechanical design principle that the dynamic range of a sensor (e.g., vestibular organ) must be greater than the dynamic range of the actuator (e.g., muscles), which in turn must be greater than the dynamic range of the underlying mechanical system (e.g., the body) to ensure effective and stable control (Franklin et al., 2009; Forbes et al., 2013a).

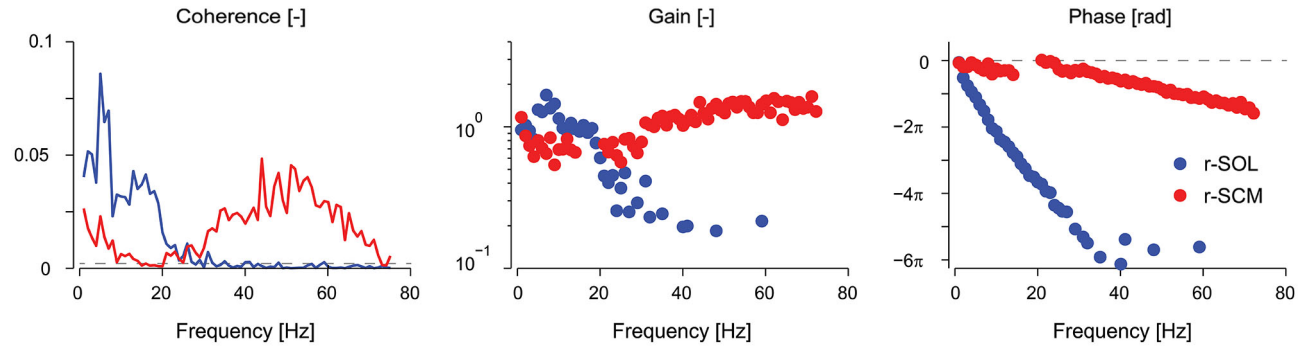

FIGURE 2 | Coherence, gain, and phase frequency estimates of vestibular reflexes for r-SOL and r-SCM muscles elicited by a 0–75 Hz stochastic electrical vestibular stimulus. Vestibular reflexes in the r-SCM span a much wider bandwidth (~0–70 Hz) together with high gains and moderate phase lags relative to the r-SOL. The horizontal, segmented line in the coherence plot represents the level above which the coherence is significant. The horizontal, segmented line in the phase plot represents a phase of zero. r-SCM, right sternocleidomastoid; r-SOL, right soleus. (Data are adapted from Forbes et al., 2013a).

Vestibular reflexes in appendicular muscles also appear to be modulated by both additional sensory feedback and the postural task. For example, response amplitudes to electrical vestibular stimulation increase with altered ankle somatosensory cues and without vision (Nashner and Wolfson, 1974; Britton et al., 1993; Welgampola and Colebatch, 2001), whereas response amplitudes decrease with increasing stance width (Day et al., 1997) and the presence of external support (Britton et al., 1993; Fitzpatrick et al., 1994). Some of these effects however, are not always seen across the observed frequency bandwidth of vestibular reflexes. Fitzpatrick et al. (1996) found that the response gain of electrical vestibular stimulation in leg muscles did not change between 0 and 5 Hz with the eyes open or closed provided subjects stood on a rigid surface. In contrast, response gains increased at all frequencies when subjects stood on a compliant surface and then closed their eyes (Fitzpatrick et al., 1996). In line with this second observation, vestibular reflex gains in leg muscles increase at most frequencies from 0 to 5 Hz when subjects are instructed to minimize sway during electrical vestibular stimulation (Reynolds, 2010). This gain modulation also appears to extend above 5 Hz, where elevation-induced postural threats increase the gain and bandwidth of measured ground reaction forces evoked by electrical vestibular stimulation (Horslen et al., 2014).

Vestibular reflexes in appendicular muscles also vary based on their contribution to balance. For instance, lower limb responses in humans are entirely absent when subjects are seated, and are suppressed when standing subjects contract their leg muscles while being otherwise fully supported by a fixed backboard (see **Figure 3**; Britton et al., 1993; Fitzpatrick et al., 1994; Luu et al., 2012). More notably, vestibular reflexes are also suppressed when subjects balance a body-equivalent inverted pendulum while being externally supported, a task where somatosensory information mimics normal standing but vestibular information is incongruent (Fitzpatrick et al., 1994). The latter observations suggest that in addition to the need for a muscle to contribute to balance, a muscle must remain relevant to balance control for vestibular reflexes to be evoked. More recent work has also shown that this suppression depends on the congruency of the motor and sensory signals (Luu et al., 2012). When standing subjects balanced a robotic platform to which they were rigidly strapped, vestibular input decreased in lower limb muscles in most subjects as the computer imperceptibly took over control of balancing the platform. Based on these results it appears that vestibular input to balance control varies with the congruency of the sensory feedback and the underlying motor behavior (Luu et al., 2012). This principle appears to apply to any appendicular muscle, since vestibular responses can be evoked provided the muscles are directly involved in the task to maintain balance; or in other words, that the force output of the muscle contributes to balancing the body in space (Britton et al., 1993; Luu et al., 2012).

The task dependence of vestibular reflexes in appendicular muscles extends beyond standing balance. During walking in humans, vestibular reflex responses are dynamically modulated in all locomotor muscles about the ankle, knee and hip joints (Iles et al., 2007; Blouin et al., 2011; Dakin et al., 2013). The reflex responses vary with the phase of the gait cycle and also vary between muscles: ankle muscle responses (e.g., soleus and medial gastrocnemius) are typically strongest at heel strike, whereas lateral hip muscle responses (e.g., gluteus medius) are active just before and after heel contact. In addition, the reflex responses do not vary strictly with muscle activation level, which suggests that phase- and muscle-specific responses during walking are organized according to a muscle's functional role in whole-body stabilization (Blouin et al., 2011; Dakin et al., 2013).

The flexible nature of vestibular-evoked responses in appendicular muscles provides a convenient platform to address unanswered questions regarding the human balance system. For example, although it is clear that vestibular information must be congruent with the postural task to evoke vestibular reflexes, the source and relevance of sensory feedback required to engage the vestibular control of standing balance remains to be determined. Similarly, the potential influence of the mechanical properties of standing balance (i.e., stiffness, damping and inertia) on the vestibular—and more generally the sensorimotor—control of standing has yet to be established. For instance, increased

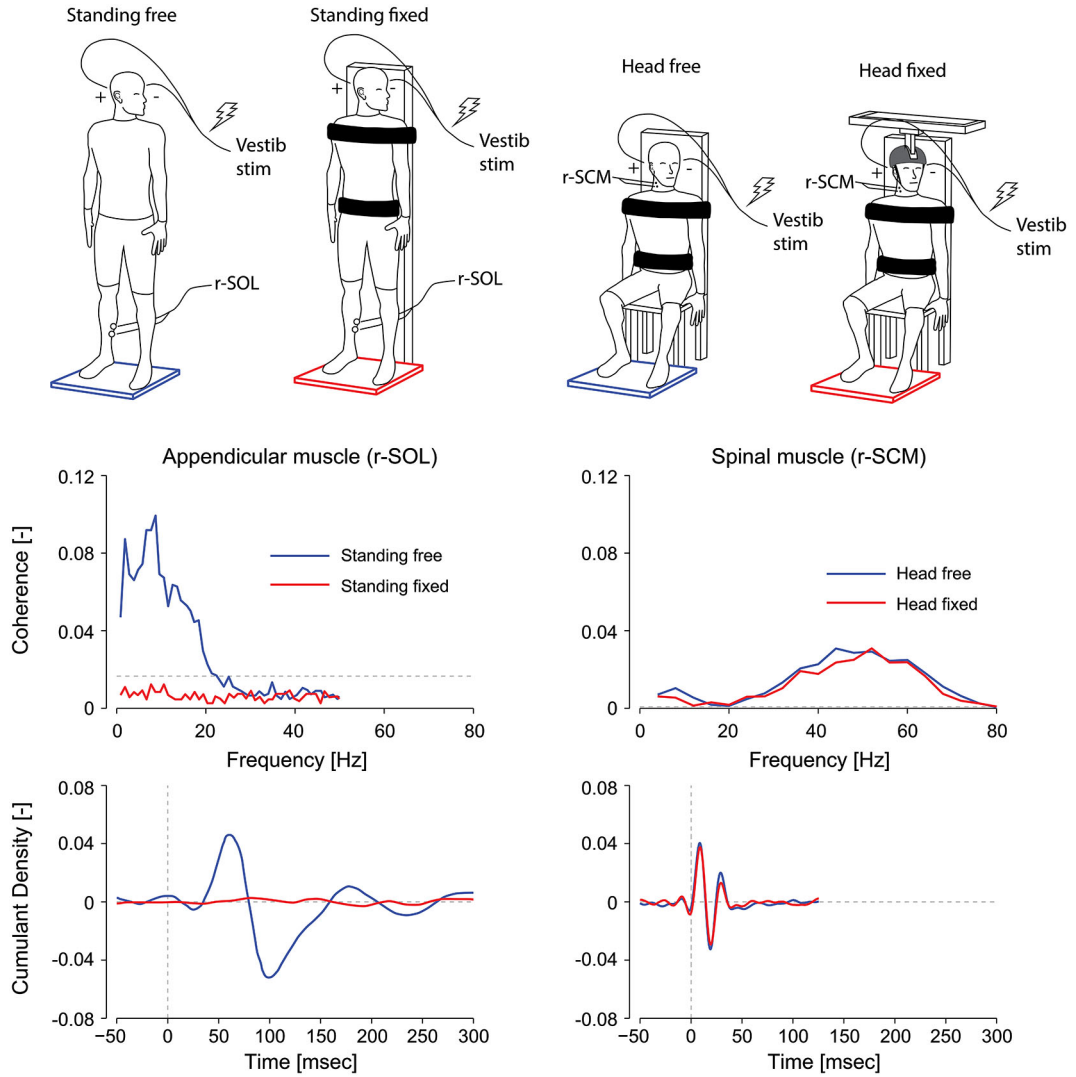

FIGURE 3 | Effect of postural task on appendicular and axial muscles. In appendicular muscles (left plots), vestibular reflex frequency- and time-domain estimates (i.e., coherence and cumulant density respectively) are suppressed when a subject is standing with the torso fixed to a rigid support. In axial muscles (right plots), vestibular reflex responses are maintained when the subject's head is fixed with respect to the torso. Thus, vestibular-evoked responses are present in axial muscles, unlike appendicular muscles, regardless of the postural task. r-SOL, right soleus; r-SCM, right sternocleidomastoid. The horizontal, segmented lines in the coherence plots represent the level above which the coherence is significant. (Data are adapted from Luu et al., 2012; Forbes et al., 2014).

muscle stiffness, as experienced by Parkinson patients, could be simulated in healthy controls in order to understand its effects on sensorimotor processing during standing balance. Robotic balance simulators (i.e., Luu et al., 2011) are viable platforms to explore these questions, and their continued development and application will generate insight into the central processing of vestibular-evoked responses.

AXIAL MUSCLES: ROBUST HIGH FREQUENCY SPINAL STABILIZATION

Most studies of vestibular reflexes in axial muscles have focused on the cervical spine and the VCR. The primary function of the VCR is to stabilize the head in space by generating muscle contractions that oppose the instantaneous head motion. This was first demonstrated by electrically stimulating individual cat semicircular canals and generating stereotyped head movements opposite to those that would activate the canals (Suzuki and Cohen, 1964). Descending vestibular signals innervate neck motor neurons with muscle-specific patterns of inhibitory/excitatory connections (Shinoda et al., 1992, 2006; Perlmutter et al., 1998) that are thought to reflect the function of individual muscles in maintaining the head stable in space (Wilson and Schor, 1999). This is in agreement with the observation that neck muscles generate preferential VCR response vectors during whole-body rotation of the cat (Baker et al., 1985; Keshner et al., 1992).

Although these preferred VCR response vectors evoke highly stereotyped muscle-specific EMG patterns (Peterson et al., 2001), little is known about how these response patterns vary with head posture. In cat dorsal neck muscles, EMG activity varies linearly with changing head yaw orientation during whole-body rotations about the same axis (Banovetz et al., 1995). However, the head must be reoriented up to 25 degrees in order to shift the whole-body-rotation driven muscle activity to a degree greater than the standard error of the population. These results are similar to recent observations in humans showing that electrically evoked VCRs do not vary across head yaw reorientations of up to 60 degrees from neutral (Forbes et al., 2013a, 2014). Considering that the origin and/or insertion points of neck muscles move with the head and neck, it is possible that VCR responses remain close to a muscle's preferred direction in the neutral posture of the head in order to generate a compensatory activity consistent with the craniocentric vestibular error signal.

Dynamical models of the VCR have been created and estimating the open-loop characteristics of these models has been the focus of many studies in animals exposed to whole-body movements (Berthoz and Anderson, 1971; Ezure and Sasaki, 1978; Bilotto et al., 1982; Baker et al., 1985; Dutia and Hunter, 1985). Across most frequencies, VCR responses can be explained by the direct trisynaptic pathways thought to mediate this reflex. At low frequencies (0.01–0.1 Hz), however, muscle responses lag behind input acceleration by up to 150° and lag behind vestibular nucleus neuron responses by up to 90° (Shinoda and Yoshida, 1974; Ezure and Sasaki, 1978). To explain this phenomenon, Ezure and Sasaki (1978) proposed neural integration of the descending vestibular signals, and the existence of indirect polysynaptic neural circuits to accomplish this integration is supported by the absence of response variations during medial longitudinal fasciculus transection in the cat (Miller et al., 1982; Thomson et al., 1995). The exact structures involved in these indirect pathways, however, remain uncertain (see Wilson and Schor, 1999; Goldberg and Cullen, 2011). In humans, the possibility of multiple pathways underlying the VCR is supported by an abrupt gain and phase shift in the frequency response of the sternocleidomastoid and splenius capitis muscles during electrical vestibular stimulation (see **Figure 1**; Forbes et al., 2013a). Although these abrupt changes could be due to destructive interference of two reflex pathways, similar to those observed in mechanically evoked stretch reflexes of the human wrist (Matthews, 1993), additional work is needed to confirm this hypothesis.

In humans, the electrically evoked VCR is a short-latency (∼10 ms) short-duration biphasic waveform (see Rosengren et al., 2010 for review). In the sternocleidomastoid muscle, the peaks of this biphasic waveform occur at about 10–13 ms and 21–23 ms (Rosengren et al., 2010; Forbes et al., 2014) and the frequency content of the response extends up to 70 Hz (see **Figure 2**; Forbes et al., 2013a). As noted for appendicular muscles, this wide bandwidth is thought to facilitate control over the high frequency dynamics (up to 20 Hz) of head-neck stabilization (Viviani and Berthoz, 1975; Grossman et al., 1988; Pozzo et al., 1990). The gain and phase of the VCR varies between muscles, being primarily high frequency in the sternocleidomastoid muscle (30–70 Hz) and primarily low frequency (0–20 Hz) in the splenius capitis muscle (Forbes et al., 2013a, 2014). Regardless of its frequency response, the amplitude of the electrically evoked VCR scales with the amplitude of the background neck muscle activity (Watson and Colebatch, 1998) and is absent when the muscle is not active (Watson and Colebatch, 1998; Forbes et al., 2014).

There is substantial evidence that VCRs are modulated by the concurrent stabilization task, although this modulation appears to be limited primarily to low frequencies. During stabilization of the head-neck during trunk perturbations, the VCRs are thought to dampen oscillations of the otherwise under-damped mechanics of the passive head-neck system (Keshner et al., 1995; Peng et al., 1996). This damping is thought to occur primarily between 1–2 Hz in alert animals and humans (Baker et al., 1985; Goldberg and Peterson, 1986; Keshner et al., 1995; Forbes et al., 2013b). Visual fixation improves head-in-space stabilization in humans (Guitton et al., 1986; Goldberg and Cullen, 2011) and may be driven by increased VCR contributions (Forbes et al., 2013b). During anterior-posterior perturbations, there is a shift from minimization of head-in-space motion to head-on-torso motion as the perturbation exceeds the system's natural frequency (∼2–3 Hz) (Forbes et al., 2013b). At perturbation frequencies above 2–3 Hz, long phase lags caused by reflex time delays would cause the VCR to destabilize the system, and as a result the CNS attenuates (but does not inhibit) these neural contributions (Kearney et al., 1997; van der Helm et al., 2002; Schouten et al., 2008).

In contrast to the VCR's low-frequency response dynamics, the VCR's high-frequency (i.e., short latency) response dynamics in the sternocleidomastoid muscle are insensitive to changes in vision, external support, stance width and posture (Watson and Colebatch, 1998; Welgampola and Colebatch, 2001). These insensitivities led us to question whether the requirement to maintain an upright or elevated head posture—a task that relies on vestibular information—governs the high frequency contribution of the VCR response to muscle activity. To answer this question, we fixed the head and torso of subjects and asked them to generate isometric neck muscle contractions. Although subjects activated their neck muscles, this activity was irrelevant to the maintenance of an upright head posture (see **Figure 3**). This condition is analogous to subjects being seated and contracting lower limb muscles when evaluating vestibular task-dependency in appendicular muscles. Unlike the attenuated vestibular-evoked responses observed in appendicular muscles, the VCR responses remained present even with the head fixed (Forbes et al., 2014). Considering that the VCR forms a closed-loop system wherein its output, i.e., neck muscle driven motion, directly affects the vestibular input, a robust VCR makes sense and ensures a highly effective response to external disturbances. A significant reduction in the VCR, however, was observed in the splenius capitis muscle during head fixation (Forbes et al., 2014). This reduction of the splenius VCR response was detected only for the lower frequency response of the VCR (below 20 Hz), which is very weak for the sternocleidomastoid muscle (see **Figure 2**). We propose the effects of task dependency (i.e., muscle activity being relevant to vestibular afference) reported in the appendicular muscles and splenius capitis are expressed primarily in the low frequencies of the vestibular reflex response.

The amplitude of the VCR response (at both low and high frequencies) also varied little between isometric tasks involving different neck muscle activation patterns with equivalent activation levels. For example, similar VCR responses were observed in the sternocleidomastoid muscle during isometric contractions in flexion and yaw, as well as in the splenius capitis muscle during isometric contractions in extension and yaw. This low sensitivity to the combination of muscles being activated highlights the flexibility in neck muscle control, where the activation of a group of muscles does not have strong reciprocal (inhibitory or excitatory) connections to other muscles (Forbes et al., 2014). One exception to this task insensitivity was observed in the sternocleidomastoid during neck muscle co-contraction. Attenuated VCR responses during co-contraction are nevertheless consistent with the goal of head-on-torso stabilization: the increased neck stiffness caused by co-contraction presumably tightens head-to-torso coupling and an un-attenuated VCR response would oppose this coupling and could be detrimental to head-neck stabilization.

Our knowledge of vestibular reflexes to thoracolumbar muscles is limited in comparison to cervical muscles, although there is evidence that vestibular input plays a role in upper body control. In cats, vestibulospinal spinal neurons also form monosynaptic excitatory and inhibitory connections with thoracic spinal motoneurons (Wilson et al., 1970a,b) and responses appear to originate in particular from otolith input (Brophy et al., 1997). In humans, erector spinae muscle responses to electrical vestibular stimuli appear to be organized together with the lower limb muscle responses during standing balance (Ardic et al., 2000; Ali et al., 2003). The latencies associated with these responses are consistent with a progressively descending vestibular signal, occurring earlier in paraspinal muscles (∼61 ms) than in lower limb muscles (∼85 ms) (Ardic et al., 2000; Ali et al., 2003). However, the frequency response of vestibular reflexes in erector spinae muscles have a reduced bandwidth (0–15 Hz) and lower gain roll off (∼3 Hz) compared to lower-limb muscles (bandwidth: 0–25 Hz, gain roll off: ∼15 Hz) and neck muscles (bandwidth: 0–70 Hz, gain roll off: not observed) (Forbes et al., 2013a). The ability to respond effectively to only low frequency vestibular input suggests that thoracolumbar muscles may have a limited functional contribution to standing balance compared to the contribution of lower limb and neck muscles. If we postulate that lower limb muscles balance the trunk, and neck muscles fine-tune this balance for the head, then low frequency coupling of the thoracolumbar spine may be all that is needed to maintain a stiff enough trunk for the system to function.

The relative insensitivity of the VCR to postural task may provide an opportunity to examine several methodological and fundamental questions regarding vestibular sensorimotor processing in humans. For instance, the possibility of evoking the VCR in active neck muscles while the head is immobilized facilitates the experimental and clinical testing of these responses. It also permits investigating how vestibular inputs to the neck motoneurons interact with sensory or descending motor inputs to these motoneurons under well-controlled conditions. For example, potential modulations of the VCR during whole-body motion can be readily tested with electrical vestibular stimuli while keeping the head fixed with respect to the torso. Furthermore, the influence of neck somatosensory inputs on the electrically-evoked VCR could be assessed while volunteers maintain a constant level of neck muscle activity with the head fixed in space. Resolving these important issues will advance our understanding of the vestibular control of neck muscles and potentially lead to applications for patients suffering from head-neck sensorimotor disorders. Future development of head-neck robotic devices, similar to the standing balance robot developed by Luu et al. (2011), could prove similarly useful in exploring the control of neck posture and gaze.

CONCLUSIONS

Prior studies of the vestibular system's contribution to postural control have been limited to frequency bandwidths below 20 Hz. More recent work, however, suggests that vestibular contributions to postural muscles can be measured up to 25 Hz in appendicular muscles and 70 Hz in neck muscles. We argue that this system dependency (i.e., whole-body postural control vs. head postural control) is related to the bandwidth of the mechanical system under control, which for the head-neck system during voluntary movements and imposed force perturbations is up to 5 times wider compared to the whole body during standing balance (Viviani and Berthoz, 1975; Pozzo et al., 1990). It remains unclear how the central nervous system controls the required bandwidth, although neural filtering, created by variations in the dynamics of the VN or the spinal circuitry mediating the descending vestibular signals, may be involved. Further animal studies are needed to evaluate these and other possibilities.

Recent studies also show a frequency dependent modulation of vestibular signals in both appendicular and axial muscle responses at low frequencies (<25 Hz). Although modulation of higher frequencies (up to 70 Hz) in neck muscles was observed in some conditions (i.e., neck muscle co-contraction), this part of the neck vestibular reflexes frequency response were maintained even in conditions where the muscle did not directly contribute to postural control. The absence of a reduced high-frequency VCR response with the head fixed parallels the response of the electrically evoked VOR, which occurs regardless of the functional or postural state of the head and body (Aw et al., 2006). Similar to the VCR, the VOR in extraocular muscles is short-latency and short-duration (Weber et al., 2012), indicating that the VOR is also driven primarily by high frequencies (likely 30–70 Hz and possibly higher). It is noted however, that the frequency response of the VOR has yet to be characterized above 20 Hz.

Furthermore, the VOR is subject to suppression during gaze shifts and gaze pursuit, where an intact VOR would be counter-productive to the intended change in gaze or ongoing tracking (see review, Cullen and Roy, 2004). Whether a similar suppression of the VCR occurs, for example during self-generated head movements where reafferent vestibular information is substantially reduced, remains unknown (Goldberg and Cullen, 2011; Cullen, 2012). Indeed, it is suggested that an intact VCR during self-generated movements may continue to dampen the

head-neck system (Goldberg and Cullen, 2011), since increased head oscillations are observed during voluntary movement in various animal preparations following canal plugging (Schor, 1974; Baker et al., 1982; Paige, 1983). Comparing the electrically evoked VCR during self-generated and passively-imposed movements should provide a clearer answer regarding potential suppression of the VCR during self-generated head movements. Regardless of the exact suppression mechanisms, given that both neck and oculomotor systems receive similar descending input from several neural structures (Freedman et al., 1996; Corneil et al., 2002; Elsley et al., 2007; Knight and Fuchs, 2007), and are activated in a coordinated manner to generate rapid gaze shifts (Guitton, 1992; Guitton et al., 2003), these two systems may work together to generate effective vestibulo-motor responses for gaze control.

The data reviewed here have important implications for understanding the role of the vestibular system in controlling posture and gaze. Indeed, studying separately individual effectors controlled by the vestibular system would lead to diverging conclusions regarding its role in a specific task. A similar statement could be made for the examined bandwidth of the vestibular reflexes. We instead propose an integrative approach that simultaneously examines the complete frequency response of vestibular reflexes in appendicular, spinal and extraocular muscles. Using combinations of robotic systems and electrical vestibular stimulation, it may be possible to evaluate the relative dependence or independence of vestibular input on axial and appendicular systems. The evaluation of vestibular input expressed in multiple motor systems will provide a more comprehensive understanding of how the vestibular system contributes to the complex behavioral tasks of daily living.

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Why we need to better understand the cortical neurophysiology of impaired postural responses with age, disease, or injury

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INTRODUCTION AND PURPOSE

The ability to maintain standing balance and orientation is crucial to mobility and independence. Standing balance is generally maintained by anticipatory postural adjustments associated with voluntary actions. However, inaccurate judgment or impaired anticipatory processes, as well as extrinsic postural perturbations–external forces not generated intrinsically due to voluntary movement (e.g., due to a slip, trip, push, etc.)–can render the need for reactive postural control to recover orientation and balance (Fasano et al., 2012).

For people with disorders of posture and balance associated with aging, neurodegeneration, or injury, an appropriately timed and coordinated postural response to extrinsically perturbed balance may represent the crucial difference between a harmless balance recovery and an aggravated pain condition or injurious fall. Indeed, postural responses to slips and sudden changes in load are common circumstances for incurring an episode of low back pain (LBP), a worldwide leading cause of disability (Manning et al., 1984; Andersson, 1999). In addition, falls associated with aging or neurological disorders are leading causes of injury, decreased activity participation, morbidity, and mortality (Grimbergen et al., 2004; Finlayson and Peterson, 2010; Batchelor et al., 2012). For these reasons research must detail the neurophysiology responsible for producing both healthy and impaired human postural responses to an extrinsically induced perturbation of standing balance.

A recently proposed neurophysiologic model of extrinsically induced postural responses reviewed initial evidence that the cerebral cortex influences these postural responses by (a) priming the most contextually accurate response during preparation, and (b) modifying late response phases (Jacobs and Horak, 2007). The involvement of the cerebral cortex during early response phases thus appears indirect and limited to priming sub-cortically generated synergies based on contextual features known prior to the perturbation, but the cortex can then directly participate in modifying the late response phases to improve response efficacy. Cortical functions associated with priming contextually appropriate responses are thus represented through pre-perturbation measures of cortical activity such as pre-movement potentials, and cortical functions associated with online modifications to late-phase responses are represented by measures of cortical activity following perturbation onset, such as perturbation evoked potentials (PEPs) (Adkin et al., 2008; Jacobs et al., 2008; Mochizuki et al., 2008, 2010). Further research remains needed, however, due to a paucity of data on neural mechanisms of human postural responses with disease or injury.

Understanding cortical function associated with impaired postural responses is essential given (a) the important role of the cerebral cortex for generating postural responses, (b) the potential that its influence may be enhanced to compensate for impaired automated processes of sub-cortical control, and (c) the accessibility of cortex for neuroplastic change with intervention. Unfortunately, because postural responses to extrinsic perturbations were historically considered reflexive and indicative of sub-cortical processing, the literature regarding cortical influence on extrinsically induced postural responses is not well developed. Whereas a more long-standing and developed literature exists on the role of the cerebral cortex for generating anticipatory postural adjustments with voluntary movement—both in the use of many methods of neurophysiologic recording and in the evaluation of people with health conditions (Gurfinkel and El'ner, 1988; Massion, 1992; Saitou et al., 1996; MacKinnon et al., 2007; Tsao et al., 2008; Jacobs et al., 2009a, 2010; Ng et al., 2012; Lomond et al., 2013; Papegaaij et al., 2014), the literature on postural responses to extrinsically induced perturbations is less extensive.

Therefore, the purpose of this opinion article is to focus on the cortical neurophysiology of impaired human postural responses to extrinsic perturbations of upright stance. This article will highlight the insights provided from rare studies of cortical function in people with impaired standing postural responses in order to demonstrate the need and potential value of future research focused on the cortical neurophysiology of impaired human postural responses to extrinsic perturbations.

WHAT WE CAN LEARN FROM CORTICAL NEUROPHYSIOLOGY DURING IMPAIRED POSTURAL RESPONSES

Table 1 highlights common movement impairments and our knowledge of cortical neurophysiology associated with human postural responses to

Table 1 | Summarized examples of impaired postural responses and associated cortical function.

Condition	Major reported impairments of postural responses	Cortical function during impaired standing postural responses
Stroke involving cortex	Feet-in-place responses: change in the distal-to-proximal muscle pattern and delayed muscle onset as well as delayed and slowed rates of force development in the more severely involved limb (Di Fabio et al., 1986; Ikai et al., 2003) Stepping responses: paretic limb exhibits delayed foot-lift, low clearance, need for multiple steps, or an inability to initiate a step (Lakhani et al., 2011; Martinez et al., 2013). Steps are non-paretic limb dominant, even when obstacles block the limb (Lakhani et al., 2011; Mansfield et al., 2012). Impairments associate with increased fall risk and, in contrast, greater use of the paretic limb associates with better recovery (Mansfield et al., 2012, 2013)	Unaware of studies utilizing measures of cortical neurophysiology during standing postural responses post-stroke
Advanced age	Age associates with delays and antagonistic co-contraction of muscles, as well as greater displacement and instability (Halicka et al., 2012) Dual task costs greater for elderly only in late-phase in-place and stepping responses, more so for stepping and more so if balance impaired elder (Brown et al., 1999; Rankin et al., 2000; Brauer et al., 2001, 2002; Zettel et al., 2008)	Electroencephalographic (EEG) PEP delayed, bifid (double-peaked), and decreased with age—effects larger in balance impaired elders (Duckrow et al., 1999)
Parkinson's disease	Falls, instability, antagonistic co-contraction and lack of modulation based on knowledge of perturbation. Stepping responses may exhibit freezing or have decreased velocity and step length (Jacobs et al., 2005, 2009b; Jacobs and Horak, 2006; Smith et al., 2012) With dual tasking, in-place responses are not modulated, and falls increase during stepping responses, but postural preparation or freezing unchanged (de Lima-Pardini et al., 2012; Jacobs et al., 2014a)	Increased desynchronization of EEG beta signal, and this increase associates with decreased response adaptation to perturbation magnitude (Smith et al., 2012)
Low back pain	Increased pre-perturbation muscle activation, increased activation amplitude at distal muscle, but decreased or delayed trunk muscle activation (Jacobs et al., 2011)	Late positive peak PEP larger with LBP; larger PEP correlates with less postural instability, disability, and fear of activity (Jacobs et al., 2014b)

perturbations of standing balance for selected example conditions of stroke, advanced age, Parkinson's disease (PD), and LBP. To demonstrate the case for this opinion article, these conditions represent samples of a much larger scope of postural disorders related to cortical injury, age- and disease-associated neurodegeneration, as well as chronic pain.

STROKE: INSIGHTS INTO CORTICAL NEUROPHYSIOLOGY OF POSTURAL RESPONSES THROUGH CORTICAL INJURY

Unfortunately, studies that measure cortical neurophysiology during standing postural responses of people with a history of stroke remain untested. Nevertheless, studies on stroke highlight the importance of the cortex for selecting and shaping postural response synergies and also highlight needs for understanding the neural mechanisms of altered postural responses following stroke.

Table 1 reinforces the importance of circuits involving the cortex for selecting an efficient and environmentally appropriate synergy (distal-to-proximal feet-in-place patterns and step selection in constrained conditions). The results also support a role for the cortex in generating the late-phase stepping response. Further, it is clear that mechanisms of both impairment and compensation exist, but such compensations (disuse of paretic limb) may represent increased fall risk and slowed recovery. A preliminary case study (Mansfield et al., 2011) suggests that compensatory step training can be beneficial, but such attempts at physical rehabilitation could be optimized if based in a more thorough understanding of the neural mechanisms responsible for these impairments and compensations. In addition, understanding neural mechanisms of impairment and compensation will better direct neurophysiologic treatments such as stimulation, pharmacology, or surgery. It is also unclear how the location and extent of post-stroke lesions affect different aspects of the postural response; the current literature does not clearly define lesion extent and includes injury of both cortical and subcortical regions. Thus, prognostics would benefit from being able to predict likely impairments from the lesion location and area. Clearly, too little is known about the effects of cortical injury on postural responses, and treatment options could be strongly influenced by a better

understanding of cortical function during postural responses post-stroke.

AGING: A LESSON IN HOW RECORDING NEUROPHYSIOLOGY ENHANCES KNOWLEDGE BEYOND INFERENCE FROM BEHAVIOR

Research on aging and cortical function during postural responses has largely been inferred through dual-task costs on the postural response under the assumption that a second task requires cortical resources and, therefore, any effects on postural responses reflect use of cortical resources during the response (Jacobs and Horak, 2007; Maki and McIlroy, 2007). As identified in **Table 1**, this assumption is compatible with findings that dual-task costs are most evident during the late phase of feet-in-place responses and the swing phase of stepping responses, which are thought to be cortically influenced (Jacobs and Horak, 2007). It remains unclear whether the age-related increase in dual-task costs represents greater compensation by cortical resources when subcortical processes of two tasks compete, or whether the cortex has greater influence on postural responses in any condition, which is revealed by competition for cortical resources when dual tasking. Knowing the difference would strongly influence interventions to target sub-cortical vs. cortical physiology as well as to determine the scope of circumstances in which impaired postural responses are a concern.

Recordings of cortical function during postural responses could provide key insight for identifying the mechanisms and circumstances of impairment, which could subsequently direct more optimized intervention. Unfortunately, only one study has attempted to compare EEG potentials evoked by perturbations of standing balance in young and older adults (Duckrow et al., 1999). Findings suggest that age associates with delayed, diminished and prolonged central sensorymotor processing at the cortex. This diminished and prolonged neural processing might explain the lack of a rapid and contextually optimized response. It remains unclear whether the cortex is the source of impairment or if its altered evoked potentials are subsequent to subcortical impairment, but the prolonged time to process the potentials at the cortex could explain the increased use of cortical resources suggested by dual-task studies and provides better focus for targets of further study and intervention that couldn't have been derived through only behavioral inference. Further study would benefit from high-resolution neurophysiologic recordings under single- vs. dual-task conditions in order to enhance understanding of the source and timing of impairments to ultimately direct more efficacious interventions.

PARKINSON'S DISEASE: A LESSON IN HOW RECORDINGS OF CORTICAL FUNCTION REVEAL UNEXPECTED INSIGHTS

In addition to the instability and falls associated with the impaired postural responses of people with PD, one of the more striking aspects is the lack of response modification based on contextual information about the upcoming perturbation's characteristics (**Table 1**). In addition, dual tasking during stepping responses does not alter early postural preparation, but does induce more falls, which suggests an ineffective step subsequent to the postural preparation (Jacobs et al., 2014a). The inability to optimize postural responses based on knowledge of perturbation characteristics and dual-task costs on only the late swing phase of stepping responses again suggest cortical involvement.

Because PD is often characterized as a disorder of diminished movement and cortical excitation during voluntary action, a contextually unmodified postural response might be predicted to associate with diminished preparatory potentials suggestive of a cortical incapacity to generate such potentials. Insights from EEG recordings of preparatory cortical function (contingent negative variation and event related desynchronization), however, demonstrate that people with PD fail to modulate their postural response by over-responding to small perturbations while concomitantly exhibiting increased desynchronization of upper beta (20–29 Hz) EEG signals prior to small perturbations. Further, larger desynchronization corresponds with less modulation of the postural response between small and large perturbation magnitudes (Smith et al., 2012). Beta desynchronization prior to movement is thought to represent motor preparation, inhibition of tonic activation, and/or anticipation of an impending need for movement within circuits that involve motor regions of the cortex (Jenkinson and Brown, 2011; Smith et al., 2012). Thus, recordings of cortical neurophysiology unexpectedly revealed that people with PD over-modulate their preparatory EEG activity prior to generating an unmodulated *hyper*metric response to small perturbations, rather than exhibiting diminished or unmodulated cortical preparation that coincides with the unmodulated response.

Given that preparatory cortical functions appear intact and over-responsive rather than incapacitated, these insights have significant ramifications for the potential to utilize behavioral and physical rehabilitation in order to train contextual response modulation. In addition, pharmacological or stimulation interventions would be directed differently for an over-responsive vs. under-responsive neurophysiologic condition. Therefore, this example in PD demonstrates the important value of recording cortical function during postural responses, because the neural mechanisms of a response may not be as expected based on behavioral inference alone.

CHRONIC PAIN: DEMONSTRATING THAT CORTICAL POTENTIALS TO POSTURAL PERTURBATIONS ARE FUNCTIONALLY RELEVANT

Chronic pain due to musculoskeletal injury such as LBP can significantly alter the central neural control of postural coordination. Although all phases of a postural response can be altered with LBP, the more consistent and significant findings are an enhanced muscle co-activation prior to perturbations and strongly diminished late-phase trunk muscle responses with concomitant increases in distal muscle responses (**Table 1**) (Jacobs et al., 2011). These pre-perturbation and late-phase alterations again implicate changes in cortical function during the postural response, and recent data demonstrate that late-phase evoked EEG potentials are enhanced with LBP. Interestingly, the enhancement appears compensatory because larger potential amplitudes correspond with less center-of-mass displacement, less disability, and less fear

of physical activity (Jacobs et al., 2014b). Thus, these studies in LBP demonstrate two important lessons: (a) even peripheral musculoskeletal injuries alter the neural control of posture through the highest levels of the neural axis, and (b) cortical neurophysiology of postural responses can be relevant to the efficacy of the response and to clinical measures of disability.

SUMMARY

The examples above demonstrate that cortical neurophysiology during postural responses to extrinsic perturbations of standing balance is critical for individuals with postural impairments such as advanced aging, neurodegeneration, and chronic pain. In addition, the little available literature emphasizes how recordings of cortical neurophysiology during extrinsically induced postural responses can offer crucial insights into mechanisms of impaired balance that are not available or unexpected based on behavioral inference alone. Lastly, cortical neurophysiology is functionally relevant to the stability of postural responses and, perhaps, to clinical disability associated with the health condition.

Despite the importance of understanding the neurophysiologic mechanisms of impaired postural responses to extrinsic perturbations of standing balance, very little neurophysiologic recording beyond the muscle has been attempted during these responses. With technologies such as EEG, near infrared spectroscopy, single photon emission computed tomography, transcranial magnetic or direct-current stimulation, etc., and with improved abilities to overcome technical challenges, the opportunity for expansive research on the neurophysiology of extrinsically induced postural responses exists in order to compliment parallel work on voluntary postural control. For any population with disorders of balance and posture, more research is needed to evaluate multiple measures that reflect unique neurophysiologic systems of both preparatory and evoked neural activation. In addition, these recordings should be undertaken across multiple contexts that vary predictability, perturbation characteristics, dual tasking, etc. to more accurately understand how environmental circumstances affect the neural control of postural responses. In so doing, crucial insights are likely to emerge that could support more efficacious interventions and clinical outcomes for those with balance disorders.

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Preservation of common rhythmic locomotor control despite weakened supraspinal regulation after stroke

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The basic pattern of arm and leg movement during rhythmic locomotor tasks is supported by common central neural control from spinal and supraspinal centers in neurologically intact participants. The purpose of this study was to test the hypothesis that following a cerebrovascular accident, shared systems from interlimb cutaneous networks facilitating arm and leg coordination persist across locomotor tasks. Twelve stroke participants (>6 months post CVA) performed arm and leg (A&L) cycling using a stationary ergometer and walking on a motorized treadmill. In both tasks cutaneous reflexes were evoked via surface stimulation of the nerves innervating the dorsum of the hand (superficial radial; SR) and foot (superficial peroneal; SP) of the less affected limbs. Electromyographic (EMG) activity from the tibialis anterior, soleus, flexor carpi radialis, and posterior deltoid were recorded bilaterally with surface electrodes. Full-wave rectified and filtered EMG data were separated into eight equal parts or phases and aligned to begin with maximum knee extension for both walking and A&L cycling. At each phase of movement, background EMG data were quantified as the peak normalized response for each participant and cutaneous reflexes were quantified as the average cumulative reflex over 150 ms following stimulation. In general, background EMG was similar between walking and A&L cycling, seen especially in the distal leg muscles. Cutaneous reflexes were evident and modified in the less and more affected limbs during walking and A&L cycling and similar modulation patterns were observed suggesting activity in related control networks between tasks. After a stroke common neural patterning from conserved subcortical regulation is seen supporting the notion of a common core in locomotor tasks involving arm and leg movement. This has translational implications for rehabilitation where A&L cycling could be usefully applied to improve walking function.

Keywords: cutaneous reflex, supraspinal input, interlimb, afferent feedback, central pattern generator, rhythmic movements, rehabilitation

INTRODUCTION

Supraspinal input, subcortical mechanisms and sensory feedback interact to coordinate limb movement during rhythmic locomotor tasks (Nielsen, 2003; Zehr and Duysens, 2004). Across different forms of rhythmic movement (e.g., swimming, walking, crawling, cycling etc.) similar coordination exists between these nervous system structures where common features of neural control facilitate the interactions between the arm and the legs (Dietz et al., 2001; Haridas and Zehr, 2003; Zehr, 2005). The relative contribution from various levels of control within the nervous system can be teased out with different experimental designs to determine which parts of the nervous system are important for controlling rhythmic movement. For example, volitional muscle activation (e.g., deliberate knee extension) reveals a shift toward strong supraspinal input whereas the same movement during a rhythmic task (e.g., knee extension during swing phase of walking) reveals a shift toward subcortical mechanisms (Zehr et al., 2007). Although different tasks rely more heavily on varying modes of control, all levels of the nervous system are required to fully support movement and are dynamically regulated.

This common nervous system control across rhythmic tasks can be determined by comparing the strength of connections during rhythmic activities probed during reflex studies. In neurologically intact (NI) participants these interactions can be seen in arm and leg muscles following a brief electrical pulse applied to a nerve in the hand or foot to evoke a reflex lasting at least 150 ms in the ongoing background electromyographic (EMG) activity. For example, cutaneous reflex amplitudes in arm and leg muscles were modulated in a similar way across tasks of level walking, incline walking, and stair climbing (Lamont and Zehr, 2006). Commonalities in control are also seen across walking, arm and leg (A&L) cycling and arm-assisted recumbent stepping, where similar phase-dependent modulation was observed despite differences in movement kinematics (Zehr et al., 2007).

Factor analysis revealed that across these tasks, four principal components explained 93% of variance in background EMG and cutaneous reflex amplitude. Commonalities in cutaneous reflex modulation across different forms of rhythmic arm and leg locomotion reveal common central nervous system control (Zehr et al., 2007).

Given that the arms and the legs are functionally linked during locomotion and are subjected to similar nervous system control across rhythmic tasks, incorporating rhythmic arm movement in the rehabilitation of walking after stroke should be considered (Klimstra et al., 2009). Currently, rehabilitation is commonly provided with body-weight-supported treadmill training. However arm and leg cycling, which is similar to walking in terms of muscle activity, joint ranges of motion, and the neural pathways activated, might potentially strengthen interlimb connections in a similar way to walking (Zehr, 2005; Balter and Zehr, 2007). Therefore it would be useful to examine the extent of differences in neural control between A&L cycling and walking that may arise after stroke interrupts "normal" supraspinal regulation.

Following a stroke, decreased supraspinal input leads to alterations in muscle activation levels and patterns in locomotor tasks. Compared to NI participants, changes in burst durations, extent of co-contraction and amplitude modulations are observed during walking (Dimitrijevic and Nathan, 1970, 1973; Shiavi et al., 1987; Burridge et al., 2001; Zehr and Loadman, 2012). Deficits in the regulation of walking are due to interruption of connectivity between supraspinal and subcortical areas occurring as a result of the stroke lesion.

Despite differences in background EMG activity following stroke compared to NI participants, cutaneous pathways remain accessible and part of the "intact" regulation of sensory input still exits. For example, part of the stumble correction response, where stimulation to the top of the foot during the swing phase causes biceps femoris activation and tibialis anterior inhibition, normally observed in NI participants, was preserved in stroke participants (Zehr et al., 1998a). Interlimb connections have also been identified in stroke participants where cutaneous input can access reflex pathways in all four limbs, including the more affected (MA) limb, during rhythmic movement (Zehr and Loadman, 2012; Zehr et al., 2012). Interlimb reflexes were significantly phase-modulated and the depth of modulation for cutaneous reflexes was similar between stroke and NI participants (Zehr and Loadman, 2012).

The extent to which common neural regulation from supraspinal and spinal centers is conserved between locomotor tasks after stroke however, remains uncertain. Thus, the purpose of this study was to test the hypothesis that with decreased supraspinal input in chronic stroke, shared reflex systems from cutaneous networks remain viable and accessible across locomotor tasks. Since rhythmic arm and leg cycling and walking rely on contribution from subcortical circuits (Carroll et al., 2006), we hypothesized partial preservation of patterns of reflex modulation between the two tasks despite reduced supraspinal input after stroke. Background EMG and reflex modulation serve as proxies for the commonalities in neural function and a difference in these variables between tasks will be determined. The evoked responses for each participant were analyzed for the net reflex effect with the use of the average cumulative reflex EMG after 150 ms. This technique was employed because the major focus in this study is to determine the effect that reduced supraspinal regulation has on spinal cord and brainstem locomotor control centers (Zehr et al., 1998b; Komiyama et al., 2000). To probe arm and leg interactions, combined arm and leg stimulation was used as an index for arm and leg coupling where stimulation likely converges in shared reflex pathways (Nakajima et al., 2013).

MATERIALS AND METHODS

PARTICIPANTS

Twelve chronic stroke participants (≥6 months post infarct), between 58 and 80 years old, participated with written informed consent in a protocol approved by the Human Research Ethics Board at the University of Victoria.

EXPERIMENTAL PROTOCOL

To examine similarities in rhythmic locomotor tasks, participants performed two tasks: (1) level walking on a motorized treadmill belt with 0% body weight support (Woodway Desmo M, Waukesha, WI, USA) and (2) seated arm and leg (A&L) cycling using a coupled arm and leg cycle ergometer (SciFit Pro II, Tulsa, Oklahoma, USA). Participants were instructed to maintain A&L cycling at 1 Hz and maintain waking at their self-selected walking speed.

ELECTROMYOGRAPHY

Electromyographic (EMG) recordings were made from tibialis anterior (TA), soleus (Sol), posterior deltoid (PD), and flexor carpi radialis (FCR) from both the more (contralateral; MA) and less affected (ipsilateral; LA) limbs. Skin was cleaned with alcohol and 1 cm surface EMG electrodes (Thought Technologies Ltd.) were applied in a bipolar configuration using a 2 cm interelectrode distance over the muscles of interest. Grounding electrodes were placed over the patella and medial epicondyle of the elbow. EMG signals were pre-amplified 5000× and bandpass filtered at 100–300 Hz (P511 Grass Instrument, AstroMed, Inc.). Data were sampled at 1000 Hz (A/D converter; National Instrument, Austin, TX), and stored to a computer for off-line analysis.

NERVE STIMULATION

In both tasks cutaneous reflexes were evoked via simultaneous stimulation of the nerves innervating the dorsum of the hand (superficial radial; SR) and foot (superficial peroneal; SP). Electrodes for SR nerve stimulation were placed just proximal to the radial head and for SP nerve stimulation on the ankle of the LA limbs. Appropriate stimulation location was checked by ensuring that radiating paresthesia was evoked into the appropriate cutaneous innervation areas of the SR and SP nerves. Cutaneous reflexes were applied with trains of 5 × 1.0 ms pulses at 300 Hz of isolated constant current stimulation (Grass S88 stimulator with SIU5 stimulus isolation and a CCU1 constant current unit AstroMed-Grass Inc., Canada). Stimulus intensity was set as multiples of the threshold for radiating paraesthesia (RT) at 2.2 × RT for the SR nerve, and 2.0 × RT for the SP nerve. Non-noxious stimulation intensities were found for each participant to

ensure non-nociceptive pathways were stimulated. During both tasks, 120 stimulations were delivered pseudo-randomly with an inter-stimulus interval of 1–5 s.

MOVEMENT TIMING

Timing events for arm and leg cycling were determined with custom-made optical encoders detecting position of the right arm crank throughout the movement cycle. Data were divided into cycles and aligned to begin with right arm top dead center. Walking cycle parameters (i.e., heel contact, toe-off) were obtained with the use of custom-made force sensors, located in the insole, and walking phases were divided to begin with LA heel strike.

For comparison of A&L cycling and walking, data were aligned to begin with maximum knee extension. A schematic diagram relating the phases of arm and leg movements for the tasks are shown in **Figure 1**. Eight equally divided phases are shown at the top and functional locomotor phases are compared below.

DATA ANALYSIS

EMG data were analyzed for background amplitudes and reflexes using custom-written software programs (MATLAB, The Mathworks, Inc., Natick, MA). Background EMG was obtained from steps without stimulation and was determined as the average response within a phase normalized to the peak response for each task for each participant. The average trace from the non-stimulated data was subtracted from the average trace of the stimulated data to produce a subtracted EMG "reflex" trace within each phase. Stimuli were then aligned to delivery within eight phases and within each phase, data were full-wave rectified, filtered, and averaged together. The stimulus artifact was removed from the subtracted reflex trace and data were then low-pass filtered at 30 Hz using a dual-pass, fourth order Butterworth filter.

Cutaneous reflexes were quantified as the average cumulative reflex over 150 ms following stimulation. This value is determined as the integral obtained at 150 ms divided by the time interval of integration to yield the overall reflex effect. If the value is positive, overall facilitation has occurred, if the value is negative, overall inhibition has occurred (Zehr et al., 1998b; Komiyama et al., 2000). This quantification method allows for interpretation of modulation of reflex pathways from spinal, brainstem and supraspinal centers where transcortical pathways have time to access and modify output from motoneurons during rhythmic activities and precedes any significant voluntary activation (Zehr et al., 1997). These values were normalized to the peak background EMG response for each task for each participant.

MATHEMATICAL ANALYSIS

To examine basic patterns in neural control, a principal components analysis (PCA) was performed on background EMG and reflex data separately for all arm and leg muscles, recorded during A&L cycling and walking (Zehr et al., 2007) (MATLAB princomp function). From an 8×8 correlation matrix, showing linear dependence between muscles, eigenvalues were determined first. To increase loading on each principal component, an orthogonal varimax rotation of the eigenvalues was performed which grouped variables with similar activity together (Ivanenko et al.,

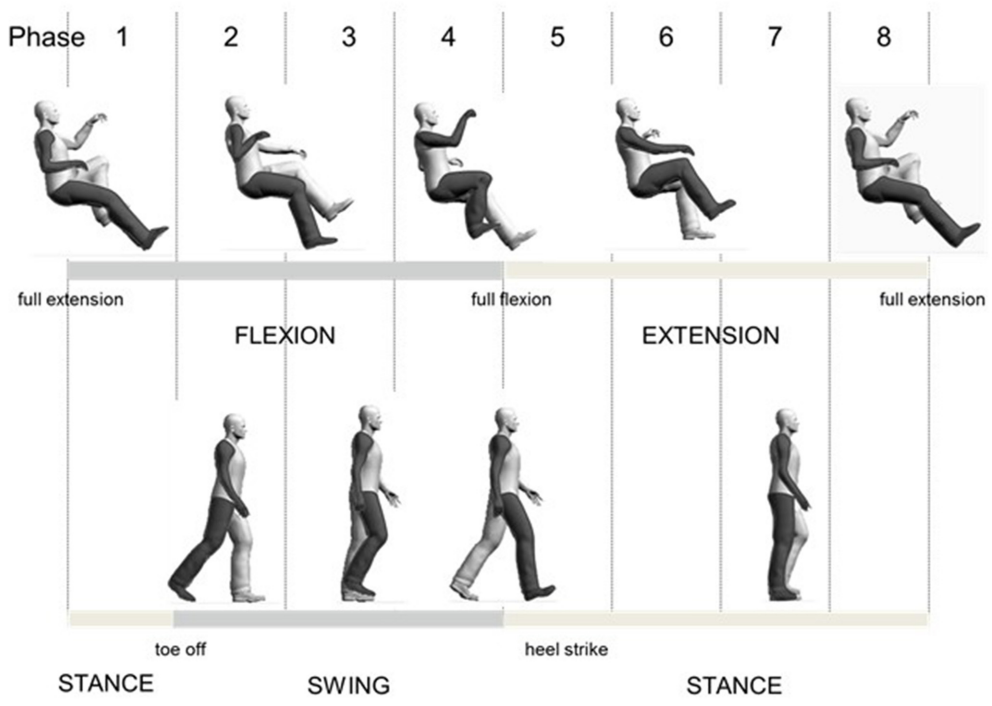

FIGURE 1 | Overall schematic diagram for relating arm and leg cycling to walking.

2004). The percentage of the total variance explained by each principal component was simultaneously calculated (MATLAB pcacov function).

STATISTICS

To compare between tasks, repeated measures analysis of variance (rmANOVA) was preformed separately for the variables of background EMG and net cutaneous reflex was used to determine significant differences (SPSS 18.0, Chicago, IL). The observed effect of each significant difference is also reported as the Cohen's effect size (d) where a small effect is $d = 0.2$, a medium effect is $d = 0.5$ and a large effect is $d = 0.8$ (Cohen, 2013). Cohen's d is useful for determining if any failure to observe significant differences was due to small sample sizes. Analyses were performed using the averaged normalized values for each subject. Using rmANOVA, differences in the pattern of response would be detected as a task-phase interaction indicating a difference in timing of peaks across phases between the two tasks. General amplitude differences in background EMG or net cutaneous reflex between tasks would be detected as a significant main effect of task. Any differences seen across phases, indicating phase dependent modulation of background EMG and net cutaneous reflex, would be seen as a significant main effect of phase. Taking a conservative approach and to examine all possible statistical differences, significant interaction and main effects tests were examined with paired samples *t*-tests to determine phase specific differences between tasks. Statistical significance was set at $p \leq 0.05$.

RESULTS

BACKGROUND EMG

Background EMG patterns for the Sol, TA, FCR, and PD of the MA and LA limbs during SR and SP nerve stimulation for both A&L cycling and walking are shown as bar plots in **Figure 2**. Values for A&L cycling (black bars) and walking (gray bars) are normalized and expressed as percentages of the peak response for each task for each participant. Due to the varying capabilities of each stroke participant walking was maintained at 0.76 Hz and A&L cycling was maintained at 0.89 Hz and no significant differences ($p = 0.549$) in frequency were found between tasks. This allows for comparisons between tasks without the confounding effects of movement frequency and to match movement parameters in Zehr et al. (2007).

In the legs, there were differences in the pattern of background amplitude as differences in timing of the peaks, as indicated by a task-phase interaction for the LA Sol and LA TA [$F_{(7, 70)} = 4.951$, $p < 0.000$, $d = 0.994$ and $F_{(7, 70)} = 9.211$, $p < 0.000$, $d = 0.999$ respectively]. There was significant phase-dependent modulation for both tasks in LA TA {main effect of phase [$F_{(7, 70)} = 7.519$, $p < 0.000$, $d = 0.997$]}. In LA Sol and LA TA there was also a main effect of task [$F_{(1, 10)} = 5.779$, $p = 0.037$, $d = 0.583$ and $F_{(1, 10)} = 15.456$, $p = 0.003$, $d = 0.942$ respectively]. Some significant *post-hoc* differences, between A&L cycling and walking, were observed for LA Sol and LA TA and there were no significant differences for MA Sol and MA TA (see * in **Figure 2**). The small number of differences can be better appreciated by considering the number of phases in which significant differences could have been observed, which is 32 [equal to the number of phases (8) × number of muscle recorded (4)]. In this context, there were 9 differences out of 32 for SR+SP stimulation trials. These few statistically significant differences between tasks indicate that the extent of background EMG amplitude modulation was similar across tasks.

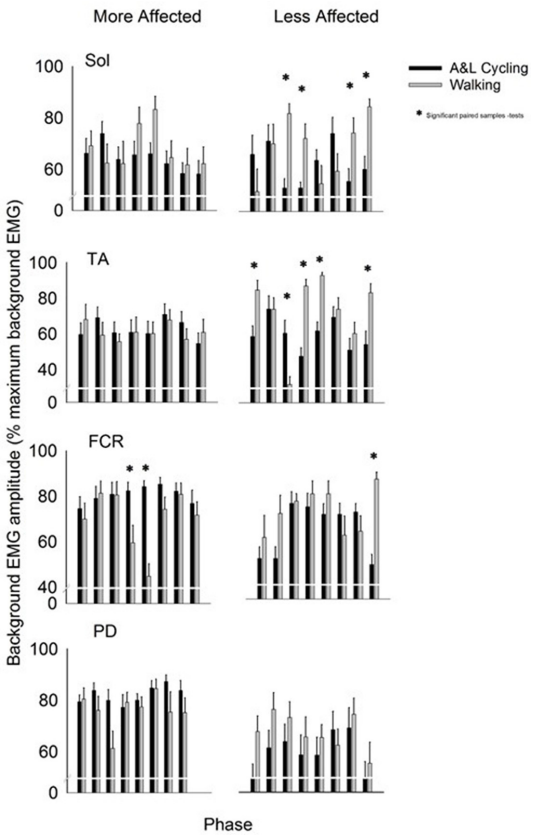

FIGURE 2 | Background EMG amplitudes for muscles of the more and less affected arm and leg averaged across all participants. Black bars are for A&L cycling and gray bars are for walking tasks. The EMG amplitudes are means (± s.e.m.) from all participants and are normalized to the peak control (i.e., background) EMG recorded in each task. Significant difference between tasks (*) were calculated with a paired samples *t*-test. Abbreviations are: Sol, soleus; TA, tibialis anterior; FCR, flexor carpi radialis; and PD, posterior deltoid.

In the arms, there were few differences in the pattern of background amplitude as differences in timing of the peaks {task-phase interaction for only the MA FCR [$F_{(7, 70)} = 4.036$, $p = 0.001$, $d = 0.977$]}. There was significant phase-dependent modulation for both tasks in the MA FCR and LA FCR seen as a significant main effect of phase [$F_{(7, 70)} = 3.507$, $p = 0.003$, $d = 0.954$ and $F_{(7, 70)} = 3.616$, $p = 0.002$, $d = 0.958$ respectively]. Statistically significant differences between tasks were found in the MA FCR [$F_{(1, 10)} = 13.941$, $p = 0.004$, $d = 0.919$], LA FCR [$F_{(1, 10)} = 6.909$, $p = 0.027$, $d = 0.649$], and MA PD [$F_{(1, 10)} = 7.382$, $p = 0.022$, $d = 0.688$] but only a few significant *post-hoc* differences were apparent between A&L cycling and walking for the MA FCR and LA FCR (see * in **Figure 2**). When the number

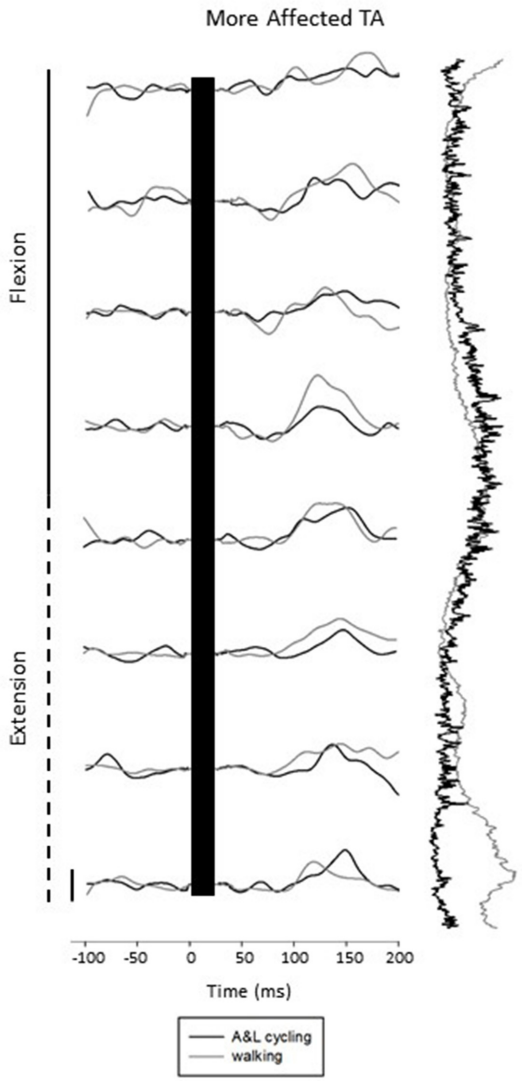

FIGURE 3 | Subtracted electromyographic (EMG) traces of the more affected tibialis anterior (TA) from a representative participant evoked by superficial radial and superficial peroneal nerve stimulation during A&L cycling and walking. The stimulus artifact has been removed from each trace and replaced by a black bar extending from time 0 out to ∼30 ms post stimulus. Background EMG during A&L cycling and walking is shown to the right of the trace plotted vertically. Calibration bar represents 10 μV.

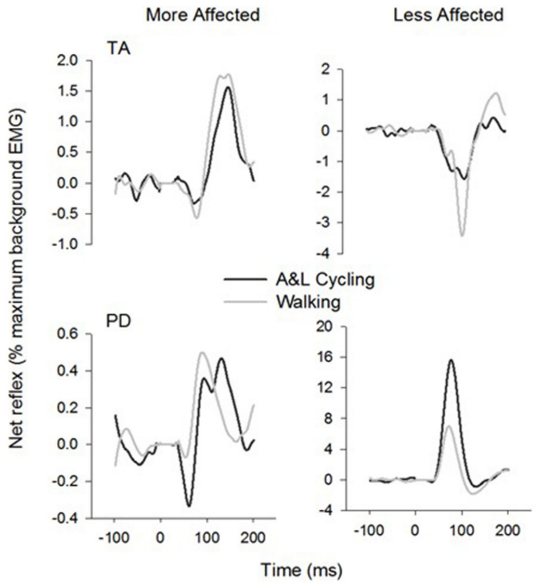

FIGURE 4 | Ensemble grand average subtracted reflex traces from all phases and all subjects of A&L cycling and walking. There is a similar pattern of cutaneous reflex modulation across tasks. Note that despite some changes in amplitudes, the general pattern is conserved.

of phases with significant differences is considered, as described for the arm muscles above, there were 3 differences out of 32 for SR+SP stimulation trials.

REFLEX MODULATION

Figure 3 shows subtracted EMG traces for A&L cycling (black line) and walking (gray line) for MA TA taken from one participant during SP+SR nerve stimulation. The figure displays subtracted EMG traces for each phase moving top to bottom from flexion to extension. To the right of the subtracted traces control EMG for A&L cycling (black line) and walking (gray line) is plotted vertically. Data in this figure visually illustrates similarities for cutaneous reflexes between A&L cycling and walking across 8 phases of movement.

General conservation in the pattern of reflexes between tasks can be seen in **Figure 4** where grand average reflex traces from SP+SR nerve stimulation during A&L cycling (black line) and walking (gray line) are plotted. Although some expected differences in amplitude were observed, general patterns of modulation (i.e., sign of response) are similar. Between tasks facilitation was seen bilaterally in the arms and seen in the MA leg while the in the LA leg suppression was observed.

Net reflexes evoked in the legs and arms following SP+SR nerve stimulation for all participants are plotted as bars in **Figure 5**. Values for A&L cycling (black bars) and walking (gray bars) are normalized and expressed as percentages of the peak background value for each phase for each participant. In the legs, there were no significant main effects of phase or task for any muscle and there were no interaction effects indicating that the pattern and amplitude of reflexes was similar between A&L cycling and walking. In the arms, there was a significant main effect of task in the MA PD and LA PD [$F_{(1,\ 10)} = 7.267$, $p = 0.022$, $d = 0.781$ and $F_{(1,\ 10)} = 17.780$, $p = 0.002$, $d = 0.966$]. While no significant differences in MA PD were detected by paired t-tests, there were significant differences for the LA PD between A&L cycling and walking across phases (see * in **Figure 5**).

Reflex amplitude is typically uncoupled from rhythmic background EMG amplitude in NI participants. To examine the extent to which reflex amplitudes were related to background EMG during A&L cycling and walking in stroke participants, we calculated Pearson's correlation coefficient. Across all eight muscles

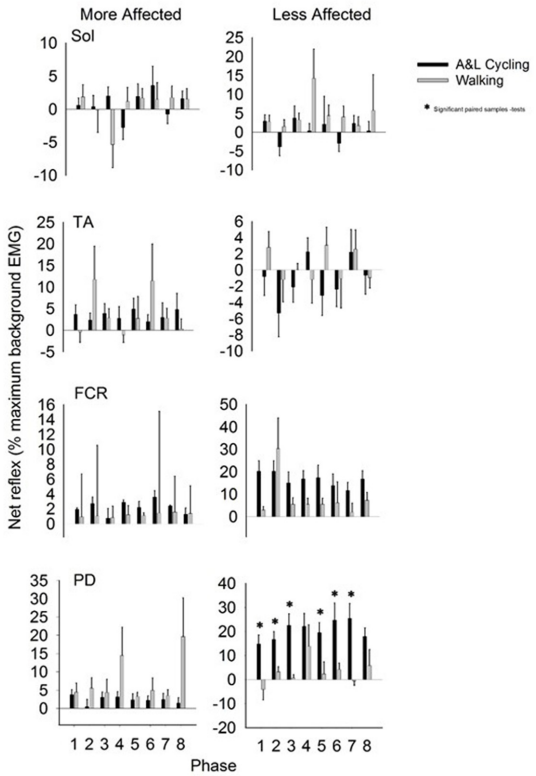

FIGURE 5 | Net cutaneous reflex from SP+SR stimulation for muscles of the more and less affected arm and leg averaged across all participants. Black bars are for A&L cycling and gray bars are for walking tasks. Net cutaneous reflexes are means (± s.e.m) from all participants and are normalized to the peak control (i.e., background) EMG recorded in each task. Significant difference between tasks (*) were calculated with a paired samples *t*-test. Abbreviations are: Sol, soleus; TA, tibialis anterior; FCR, flexor carpi radialis; and PD, posterior deltoid.

Table 1 | Correlation coefficients between the net reflex response and background EMG during A&L cycling and walking tasks.

Muscle	A&L cycling	Walking
MA SOL	0.052	0.053
LA SOL	0.251	0.035
MA TA	0.097	0.153
LA TA	0.254	0.103
MA FCR	0.047	0.120
LA FCR	0.269	0.097
MA PD	0.051	0.141
LA PD	0.133	0.071

The critical value for this 2-tailed comparison ($p < 0.05$) for 12 participants was 0.58. Abbreviations in text.

for each participant across all phases of A&L cycling and walking no significant correlations were found (see **Table 1**).

MATHEMATICAL PCA

The summary for the principal components analysis for combined SP+SR nerve stimulation in A&L cycling and walking is shown in **Figure 6**. The subplot on the left is for the variance accounted for (%VAF) from each principal component of background EMG amplitudes and the subplot on the right is for %VAF of cutaneous responses. Across both tasks, five common factors explained more than 86% of the variance for background EMG and 90% of the variance for the cutaneous response. There was a substantial difference between A&L cycling and walking in the magnitude of variance accounted for by the first principal component of background EMG and reflex modulation with 40–69% in cycling and only 22–29% in walking.

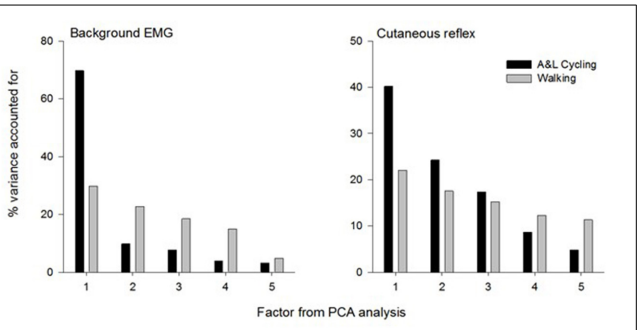

FIGURE 6 | Summary of principal component analysis for background EMG and cutaneous response in A&L cycling and walking. Bars represent the variance accounted for by each factor.

DISCUSSION

The purpose of this experiment was to evaluate the extent to which common neural regulation is conserved across locomotor tasks despite reduced supraspinal input after stroke. There were some but few significant differences between A&L cycling and walking for EMG amplitude modulation and net cutaneous reflex modulation (see Results) indicating that A&L cycling and walking have preserved modulation patterns after stroke. Some muscles displayed significant phase-dependent reflex modulation where no correlation to background EMG was present. Mathematical analysis revealed a dependence on five common factors explaining more than 86% of the variance for background EMG and 90% of the variance for the cutaneous reflex. These data suggest that after a stroke common neural patterning from conserved subcortical regulation in the arms and legs is conserved across locomotor tasks involving arm and leg movement. These results have translational implications for rehabilitation where A&L cycling could be usefully applied to recover walking function.

THE ROLE OF SUPRASPINAL INPUT

When comparing the results from this study of mathematical extraction of variance to results from a similar study by Zehr et al. (2007) in NI participants, some differences can be noted. Firstly, in this study, more principal components are required to explain less variance. Here, five components are required whereas only four principal components are required to explain 93% of the variance across tasks in a NI population (Zehr et al., 2007). We suggest the additional components could reflect the reduced extent of supraspinal regulation following stroke. Secondly, a larger division in the %VAF by the first principal component is

seen when comparing NI participants and stroke participants. When comparing between walking and A&L cycling in NI participants, the largest difference in %VAF for the first principal component is approximately 30% whereas for stroke participants the largest difference is approximately 45% (see **Figure 6**). Again, this indirect observation may be ascribed to reduced supraspinal input following a stroke rendering integrations between the arms and legs more complex without the fine-tuning provided by an intact supraspinal system.

Within the framework of comparing muscle synergies in NI and to those present after stroke, alterations in the number of modules extracted is often observed. This is likely attributable to altered spinal cord excitability interacting with changes in descending motor regulation. Impaired upper limb function is associated with decreased number of reflex synergies (Trumbower et al., 2010, 2013) and reductions in voluntary synergy structures during isometric tasks (Roh et al., 2011), when compared to NI participants. During walking, changes in the modular organization of muscle synergies is also demonstrated post-stroke where there is a reduction in the number of synergies extracted (Clark et al., 2010) and modified recruitment organization (Gizzi et al., 2011). Our results are similar in that the components extracted are changed compared to NI participants, however, here we report instead an increase in the number of principal components. Diminished cortical modulation consequent to a stroke lesion could cause deficits in muscle synergy coordination leading to the observed functional impairments in locomotion following a stroke. These may be characterized during locomotion as an increased number of principal components, each accounting for a lower %VAF than is found in the intact nervous system.

Conservation in nervous system control across task has been previously ascribed to the action of locomotor central pattern generators (CPG) modulating transmission in cutaneous pathways by premotoneual gating. However, differences between NI and stroke participants could arise from reduced supraspinal regulation of alphamotoneuronal and interneuronal activity caused by the stroke lesion (Dobkin, 2004, 2005). Descending supraspinal input can regulate reflex output through either modulation of excitability in the interneuron reflex pathways or through the internal networks that are part of the CPG itself (Zehr, 2005; McCrea and Rybak, 2008). Alterations in descending supraspinal regulation of interneuronal reflex pathways during rhythmic activity explains differences in neural conservation of locomotor tasks between stroke and NI participants. Some conservation of these mechanisms is still observed, thus implicating the spinal cord and subcortical areas in neural regulation across locomotor tasks.

Comparisons between the more and less affected limbs in stroke participants, can reveal the effects of reduced supraspinal input on reflex modulation. Responses in the tibialis anterior at approximately 80 ms were small or absent during walking in stroke participants, in those with hereditary spastic paraparesis and in those with a spinal cord injury (Jones and Yang, 1994; Zehr et al., 1998a; Duysens et al., 2004). Specifically, an absence of end-swing suppression in the TA (normally observed in NI participants) was noted however end-stance facilitations remained. This suggests that suppressions may be under the control of the cortex while facilitations are under the control of spinal CPGs (Duysens et al., 2004). In the data presented here (see **Figure 4**), this fits nicely as in the MA TA (influenced by the lesioned cortex but still under the control of spinal CPGs) mainly facilitations are present and in the LA TA mainly suppressions are present. Therefore an intact cortex and corticospinal tract are required for full expression of the full range of reflex modulation during locomotion.

EVIDENCE FOR CONSERVED "COMMON CORE"

Common control across rhythmic movement tasks could be the result of a common core of subcortical elements expressing neural activity to produce the basic pattern of arm and leg movement (Zehr et al., 1997, 2007; Zehr, 2005). That is, a central mechanism is likely responsible for regulating various types of rhythmic movement in a similar oscillatory fashion. Measurements of muscle activity across various rhythmic tasks have shown a consistent frequency relationship between arm and leg movements for walking, cycling, creeping and swimming which could be indicative of spinal interconnections between the upper and lower spinal CPGs that are engaged in the locomotor function (Wannier et al., 2001). Indeed, propriospinal linkages between the fore and hindlimbs have been identified in the cat (Lloyd, 1942; Gernandt and Megirian, 1961; Miller et al., 1973) and data on interlimb responses obtained in persons with cervical spinal cord injury (Calancie, 1991; Calancie et al., 1996) suggests that quadrupedal links between forelimb and hindlimb coordination are conserved in humans (Dietz et al., 2001; Wannier et al., 2001; Zehr et al., 2009).

The main results of this experiment demonstrate the persistence and modulation of reflexes during A&L cycling and walking after stroke despite the interruption of some descending regulation of interneuronal excitability arising from the supraspinal lesion. The overall similarities in modulation patterns for background EMG and cutaneous reflexes provide insight into the status of neural control circuits in the damaged nervous system (Zehr and Duysens, 2004). A contribution from subcortical and presumed spinal locomotor pattern generating networks is implicit in the observations here where networks for arm and leg coordination could reside in subcortical areas as damage to the brain following stroke does not seem to significantly affect common neural regulation (Zehr et al., 2004).These results add to existing evidence that portions of the neural circuitry regulating rhythmic arm and leg movements remain accessible and intact after stroke (Zehr and Duysens, 2004; Ferris et al., 2006; Zehr and Loadman, 2012; Zehr et al., 2012).

TRANSLATIONAL APPLICATIONS

The neural similarities between A&L cycling and walking observed here have translational implications for rehabilitation where A&L cycling could be usefully applied to recover walking function. This can be achieved by activation of a set of similar residual neural pathways to strengthen interlimb neuronal coupling to improve walking performance after stroke (Zehr, 2005; Ferris et al., 2006; Balter and Zehr, 2007; Zehr et al., 2007, 2009, 2012; Klimstra et al., 2009; Zehr and Loadman, 2012). In addition, A&L cycling is similar to walking in terms of muscle

activity and joint ranges of motion (Zehr, 2005; Balter and Zehr, 2007).

Our experimental methods do not allow us to effectively delineate the specific locus of the observed reflex (intra- vs. interlimb) given we are using simultaneous stimulation of both the hand and foot (see Figure 5 in Nakajima et al., 2013). However, the presence of cutaneous reflexes seen here confirms that neuronal pathways linking the arms and the legs remain partially conserved in stroke providing a substrate for training induced plasticity to improve function. Combined arm and leg stimulation can be used as an index for arm and leg coupling where stimulation likely converges in reflex pathways from cutaneous inputs for the hand and foot to produce the responses observed (Nakajima et al., 2013). Cutaneous inputs and associated modulation of reflex amplitudes could serve as probes to monitor ensuing neuroplastic adaptations in interlimb pathways resulting from targeted rehabilitation (Wolpaw, 2010; Zehr and Loadman, 2012). In addition, the use of principal component analysis could provide a useful means of evaluating rehabilitation effects where reductions in the number of principal components and variance explained by each component could suggest improved control.

CONCLUSION

In general, background locomotor EMG was similar between A&L cycling and walking where similar phase dependent modulation patterns were observed. Modulation of cutaneous reflexes from hand and foot stimulation suggest a conserved "common core" of subcortical regulation of locomotion despite altered descending supraspinal input from the stroke lesion. These results have translational implications for rehabilitation where A&L cycling could be usefully applied to improve walking function.

AUTHOR CONTRIBUTIONS

Taryn Klarner, Trevor S. Barss, Pamela Loadman, Yao Sun, Chelsea Kaupp, and E. Paul Zehr contributed to the experimental design. Taryn Klarner, Trevor S. Barss, Yao Sun, and Chelsea Kaupp conducted the experiments. Taryn Klarner, Trevor S. Barss, Yao Sun, and Chelsea Kaupp participated in analysis of the data. Taryn Klarner and E. Paul Zehr wrote the paper but all authors commented on and approved the final draft of the MS.

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NeuroControl of movement: system identification approach for clinical benefit

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Progress in diagnosis and treatment of movement disorders after neurological diseases like stroke, cerebral palsy (CP), dystonia and at old age requires understanding of the altered capacity to adequately respond to physical obstacles in the environment. With posture and movement disorders, the control of muscles is hampered, resulting in aberrant force generation and improper impedance regulation. Understanding of this improper regulation not only requires the understanding of the role of the neural controller, but also attention for: (1) the interaction between the neural controller and the "plant", comprising the biomechanical properties of the musculaskeletal system including the viscoelastic properties of the contractile (muscle) and non-contractile (connective) tissues: neuromechanics; and (2) the closed loop nature of neural controller and biomechanical system in which cause and effect interact and are hence difficult to separate. Properties of the neural controller and the biomechanical system need to be addressed synchronously by the combination of haptic robotics, (closed loop) system identification (SI), and neuro-mechanical modeling. In this paper, we argue that assessment of neuromechanics in response to well defined environmental conditions and tasks may provide for key parameters to understand posture and movement disorders in neurological diseases and for biomarkers to increase accuracy of prediction models for functional outcome and effects of intervention.

Keywords: afferent feedback modulation, neuromechanics, system identification, ageing, stroke, movement disorders

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Introduction

Posture and movement disorders in neurological diseases like stroke and in ageing are of increasing clinical concern; due to both an increasing incidence and prevalence as a result of aging of the society as well as increasing awareness of socioeconomic impact, i.e., disability and as a result, loss of autonomy. Disability can be translated to the inability to adequately cope with daily environmental challenges.

Our body segments interact with fixed and moving obstacles and objects in the environment. This involves exchange of mass, energy, linear or angular momentum in order to produce adequate posture and movement patterns. For example when reaching and grasping objects, the right amount of muscle force is required to properly control the joint impedance.

During walking, the mechanical interaction between the leg segments and other body parts requires continuous control. To reduce the impact of posture and movement disorders in neurological diseases it is crucial to investigate how the "altered" system adapts to varying tasks and environmental conditions. Both the neural system (controller) and the muscles ("motor") are end-effectors at the level of the joint. System adaptability may subsequently be translated to the modulatory capacity of the neuromuscular system. Understanding of the modulatory capacity of the neuromuscular system in terms of mechanics, i.e., neuromechanics will ultimately allow for relating specific system states to the global level of function. Of key importance is the notion that components determining the neuromechanics continuously interact within a closed loop. For example, the proprioceptive muscle spindle and Golgi tendon organs sense muscle states, information is processed and subsequently fed back to the muscle (basic control loop, **Figure 1**).

In this paper we argue that modulatory capacity of the neuromechanical system can best be assessed when properties of the neural and biomechanical system are addressed synchronously. This paper illustrates the role for neuromechanics in understanding and eventually addressing movement disorders in a variety of diseases and clinical states. System identification (SI) is the required technique to address the closed-loop interaction between neural controller and biomechanical, i.e., musculoskeletal system. Neuromechanical parameters in response to environmental challenges may provide: (1) for key parameters to understand posture and movement disorders in neurological diseases; (2) may be used as biomarkers to increase accuracy of prediction models for functional outcome and; (3) evaluate the effects of intervention.

The Clinical Problem

Movement Disorders in Neurological Diseases

Loss of mobility after upper motor neuron diseases like stroke is still conceptually being related to the phenomenon of spasticity, i.e., muscle hypertonia with velocity dependent resistance of joint to passive stretching (Lance, 1980). However, spasticity or signs of exaggerated reflex activity are typically assessed under passive conditions. Hence it may not be surprizing that the relation between degree of spasticity at the level of joints and global functional level is not straightforward (Ada et al., 1998). It has become evident that upper motor neuron diseases like stroke and cerebral palsy (CP) also result in secondary biomechanical changes of muscles, tendons and connective tissue (Vattanasilp et al., 2000; Hof, 2001; Lieber et al., 2004; Gracies, 2005a,b; Dietz and Sinkjaer, 2007; Mirbagheri et al., 2009; Smith et al., 2011). Moreover, it is increasingly well agreed that mobility disorders are the result of a complex interplay between primary neural factors and secondary biomechanical changes which is environment- and task dependent (van der Krogt et al., 2012) and may change over time, e.g., during the recovery phase after stroke (van der Krogt et al., 2015) and/or due to chronological ageing (Groenewegen et al., 2012).

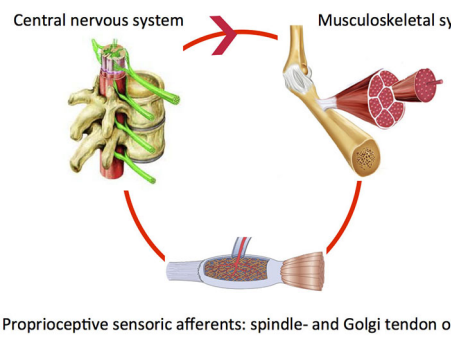

FIGURE 1 | Closed loop of sensing, processing and appropriate action: peripheral (spinia) reflexes.

Proper planning of interventions to improve mobility requires understanding of aforementioned interplay at any given moment in time. This requires identification of neuromechanical factors that contribute to improper limb impedance, i.e., resistance to external manipulation under various environmental and task dependent conditions (Krutky et al., 2010; van der Krogt et al., 2012). Observed structural changes, i.e., shortening and stiffening of muscles with loss of sarcomeres, stiffening of muscles through fibrosis and changing tendon properties may be concomitant detrimental outcome secondary to impaired neural control or may compensate for the primary detrimental effects of impaired neural control. On which component should interventions be aimed and at what stage? What is the limiting factor during functional tasks? Increased stiffness around limbs in upper motor neuron disease is commonly treated by either attempts to lower reflex activity or stretching of viscoelastic tissue by e.g., botulinum toxin, splinting, casting or surgery, depending on the assumed main contributor to the observed limb dynamics. Targeted intervention requires identification of neural and non-neural, biomechanical components, which cannot be separated by task (instruction) alone, i.e., as under both passive vs. active conditions neural and non-neural contributors play a role, although their relative contributions may differ. Also, appearance of neural and non-neural contributors both depend on manipulations of acceleration, speed and position.

Evidence is emerging that in stroke patients, rehabilitation induces compensatory strategies, instead of addressing primary neurological repair, i.e., restitution (Kwakkel et al., 1999, 2006; de Haart et al., 2004; Geurts et al., 2005; Buurke et al., 2008; van Kordelaar et al., 2013). Stroke patients unable to fully extend shoulder and elbow because of a flexion synergy, appeared to solve a reaching task problem by leaning forward i.e., exhibiting compensating trunk movements. Similarly, from the absence of changes in timing of muscle activity patterns, it was concluded that functional gait improvement in stroke patients might be more related to compensatory strategies than restitution of muscle coordination patterns in the affected leg (Buurke et al., 2008). Asymmetry in weight bearing in stroke patients decreased during rehabilitation after stroke but increased again under demanding circumstances (de Haart et al., 2004). Thus, observed improvement in a patient's capacity to deal with environmental challenges is most likely due the compensatory part. Moreover,

interventions to improve functionality in patients after stroke with robotic therapy (Klamroth-Marganska et al., 2014) or early- applied constraint induced movement therapy (Kwakkel et al., Accepted) do not seem to address true neurological repair (Kwakkel and Meskers, 2014). Next to lack of fundamental understanding of functional recovery, i.e., adaptability to environmental challenges, assessment tools are lacking to properly identify restitution from compensation with high resolution. Neuromechanics may fill the void.

Mobility/Balance Impairments and Falls in the Elderly

Multiple integrated systems are involved in balance, which all are prone to age related deterioration (Sturnieks et al., 2008; Engelhart et al., 2014; Pasma et al., 2014a), i.e., proprioception, vision and vestibular function. Age related impairments of the motor system are mainly characterized by sarcopenia, i.e., loss of muscle mass: an important clinical problem in elderly (Rolland et al., 2008; Bijlsma et al., 2013). Sarcopenia implies a reduction in parallel sarcomeres affecting muscle strength. However, ageing is also related to loss of sarcomeres in series (Narici et al., 2003), increased tendon compliance (Narici et al., 2008), architectural changes, i.e., a decrease in fiber pennation angle (Narici et al., 2003), and selective atrophy of muscle IIa fibers (Brown and Hasser, 1996). Force-length and force- velocity relations may become sub-optimal (Narici et al., 2008; Raj et al., 2010). Muscle power is generally more affected than muscle force, which in turn is more affected than muscle mass (Macaluso and De Vito, 2004). Changes in fiber type composition and architecture may be responsible next to the changes in neural factors, a reduction in motor unit number and thereby change in recruitment (Evans, 1997) and changes in the neuromuscular junction (Rudolf et al., 2014). A tight interaction between sarcopenia and changes of the neural controller has been suggested (Kwan, 2013). Cognitive capacity is also suggested to play a role in balance (Maki and McIlroy, 2007). Low cognitive status, i.e., defined with respect to normal cognition based on cut-off values of the Mini-Mental State Examination, Montreal Cognitive Assessment and Visual Association Test, was found to be associated with a lower ability to maintain balance in elderly outpatients (Stijntjes et al., 2014). Longitudinally, impairment in cognition was suggested to precede loss of muscle strength in the oldest old (Taekema et al., 2012). Primary deficits may be compensated for by secondary adaptive strategies, e.g., co-contraction to increase stability (Milner, 2002; Benjuya et al., 2004). Unreliable sensory input may be actively down weighted in favor of reliable information in a redundant system: a process called sensory reweighting (Peterka, 2002; Pasma et al., 2012; Assländer and Peterka, 2014). In elderly, motor function has been found to be associated with an increased cognitive demand (Ranking et al., 2000); however this compensation may be detrimental in case of double tasking (Schaefer and Schumacher, 2011) or cognitive decline (Stijntjes et al., 2014).

Quantification of interrelations of the age-related factors and identifying adaptive strategies is essential for understanding and designing proper intervention in case of mobility/balance impairments and falls: which system to address by training, stimulation or pharmacological intervention; sensory, sensorimotor integration (coordination); cognition (double tasking) or the motor part (strength and power training). Neuromechanical analysis is a promising method to observe these interrelated properties.

The Nervous System: Afferent Feedback Modulation and Supraspinal Control

Human afferent feedback loops can be discerned into a spinal and a supraspinal loop (**Figure 2**). Key questions are: (1) what is the nature of altered properties of (supraspinal) control and in what way do they relate to the observed movement disorders? and (2) What are underlying neurophysiological processes and where are they located?

Properties of the neural controller were studied extensively by experiments evoking reflex responses by electrical stimulation (Lourenço et al., 2006) or mechanical perturbation (Lee and Tatton, 1982; Lewis et al., 2005; Pruszynski et al., 2011) exhibiting short and long latency reflex responses. The fact that the long latency reflex appears to be depressed by the known group II afferent blocker Tizanidine (Grey et al., 2001; Maupas et al., 2004; Meskers et al., 2010) is regarded supporting evidence for the at least partial mediation of the long latency reflex by group II afferents and the involvement of group II pathways in upper and lower limb spasticity. A number of underlying pathophysiological processes have been described, i.e., persistent inward currents, diminished post-activation depression and loss of presynaptic inhibition that induces hyper excitability of motor neurons and afferents, probably as a compensation for reduced functional neural and muscular activation in neural disorders (D'Amico et al., 2014). The concept of hyperreflexia translates to the clinical picture of enhanced reaction to tendon taps and velocity dependent resistance to manipulation, corresponding to the Lance definition of spasticity (Lance, 1980).

However, Burne et al. (2005) stated that spasticity is due to enhanced baseline activity and therefore only observed under passive conditions. This implies that under active conditions, it is not hyperreflexia that is the problem, but modulation of afferent feedback as *a condition sine qua non* for proper motor function.

What is the substrate of this modulation and how does it work out in a functional way? Experiments identified the long latency reflex as the primary carrier of modulatory action (Pruszynski and Scott, 2012) as it was found to be dependent on instruction (Rothwell et al., 1980; Krutky et al., 2010), pharmacological agents like Tizanidine (Meskers et al., 2010), Transcranial Magnetic Stimulation (TMS; van Doornik et al., 2004; Pruszynski et al., 2011; Perenboom et al., 2015), task (Hallett et al., 1981) and scaled to task related urgency (Crevecoeur et al., 2013). According to optimal control theory, reflexes are adapted continuously and instantaneously based on manipulation of sensory information during voluntary movement (Pruszynski and Scott, 2012). Evidence for cortical involvement in the long latency reflex period is ample; whether modulation is located spinally of cortically is yet unknown (**Figure 2**, Perenboom et al., 2015).

The Plant: Muscle and Passive Viscoelastic Structures

The musculoskeletal system in which muscle force is distributed can be regarded as the plant, the mechanical filter through which the neural controller comes to expression: high frequency modulations may be filtered by muscle activation and co-contraction when addressing effects of force production, e.g., in the hand or on the ground. Both position dependent elastic (spring) and velocity dependent viscous (damper) forces act on the masses of the limbs and environment. These forces are determined by non-contractile connective tissue and contractile muscle tissue, both in series and parallel to each other and dependent on state of activation (e.g., de Vlugt et al., 2010). The elastic properties of the connective tissue may be described by a logarithmic function; the elastic-like behavior of the muscle fibers behave according to the force-length characteristic originating from the sliding contractile filaments (Huxley and Simmons, 1971; Thelen, 2003). The velocity dependent properties are dominated by the specific force-velocity characteristic of the contractile tissue (Hill, 1938). However, for fast length changes these characteristics are not sufficient in describing muscle mechanics due to the phenomenon known as short range stiffness resulting in high stiffness over a short length range beyond which the muscle abruptly transits into a more viscous-like Behavior (Rack and Westbury, 1974; Campbell and Lakie, 1998; Cui et al., 2008; Van Eesbeek et al., 2010).

Control and Plant Interaction

Control and plant interaction provide for different strategies for modulation of impedance, i.e., mechanical viscoelasticity from connective tissues, and/or mechanical viscoelasticity from continuous neural activation), and/or reflexive activations and/or co-contraction (Milner, 2002). Co-contraction provides instantaneous resistance, just as the connective tissues but is costly in terms of metabolic energy. Connective tissue in parallel to the muscle lacks control freedom, only substantially contributes in extreme joint angles. The serial tendon may store and release energy to amplify muscle power. Afferent feedback is energy efficient, but comes with a time delay that may threat postural stability. These strategic control possibilities require concerted action of supraspinal reflex control (with a time delay) and adjustment of internal models; the latter serves to improve movement properties (speed, precision, energy) from the use of *a priori* knowledge of the neuromechanical system (Wagner and Smith, 2008; Crevecoeur and Scott, 2014).

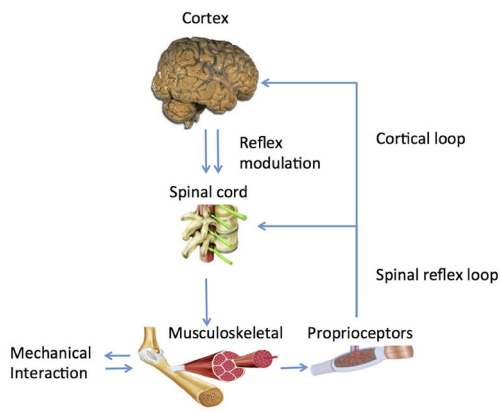

FIGURE 2 | Main human control loops consisting of a peripheral, spinal loop and a central, cortical loop. Reflex modulation takes its effect in the peripheral loop while it is mediated by suprapspinal centers and peripheral afferent signals.

Although it becomes evident that upper motor neuron diseases related movement disorders are the result of a complex, environment- and task dependent interplay (Mirbagheri et al., 2004; van der Krogt et al., 2012) between primary neural and secondary biomechanical changes of muscles, tendons and connective tissue (Vattanasilp et al., 2000; Hof, 2001; Fridén and Lieber, 2003; Lieber et al., 2004; Gracies, 2005a,b; Dietz and Sinkjaer, 2007; Mirbagheri et al., 2009; Smith et al., 2011), clinical studies on the precise interaction, i.e., both temporal (dynamic stability analysis) and spatial (nonlinear dynamics), between controller and plant are scarce.

Kamper et al., 2001 addressed the potentiating effect of the mechanical part i.e., stiffening of intrafusal muscle on the controller. Increased size of motor units may stress the controller by violation of the Henneman's size principle replacing a proportional with a strenuous "bang-bang" type of control (Hermes and LaSalle, 1969). From a control engineering point of view, decreased thresholds (Hidler and Rymer, 1999) or increased reflex gains result in mechanical instability of the controlled plant. A clear example of such an instability or oscillation is the phenomenon of clonus, a stereotypic, sustained, fast, repetitive and self-generated movement of mostly distal joints of patients with upper motor neuron diseases which is elicited by short force or torque perturbations by physicians or environment (e.g., floor contact). A simulation study showed that increased tissue viscoelasticity acting as an amplifier for increased reflex gain, by means of simulated changes in threshold and gain of the spinal motor unit pool is conditional for clonus (**Figure 3**, de Vlugt et al., 2012).

System Identification and Parameter Estimation (SIPE) Techniques

Tight coupling between afferent sensory information, neural controller, efferent commands and motor properties makes it difficult quantify individual contributors by routine clinical examination (Lorentzen et al., 2010). Improper forces evoked by the neural system are either feedback related, i.e., movement velocity sensitive, feed-forward related i.e., improper voluntary control or by increased baseline muscle activity. Non-neural contributors are altered viscous (damper) and elastic (stiffness, spring) properties of contractile muscle and non-contractile tissue. Tissue properties may be modulated by neural activity. Neural activity is modulated by task instruction. Neural and non-neural components cannot be separated by task (instruction) alone, i.e., as under both passive vs. active conditions neural and non-neural contributors play a role, although their relative

contributions will differ. Also, expression of neural and non-neural contributors is depending on limb manipulations in terms of acceleration, speed and position.

Therefore, if the expression of the full interacting neuromuscular system is addressed, a SI approach is required. SI is the formal description of dynamical systems behavior derived from input-output relations (**Figure 4**, Kearney and Hunter, 1990; Kearney et al., 1997). Essential in (closed loop) SI is the application of precise and well-known external perturbations, applied by robot manipulators (**Figure 5**, Peterka, 2002; van der Helm et al., 2002; van der Kooij and van der Helm, 2005; Schouten et al., 2006; Palazzolo et al., 2007; Volpe et al., 2009; Balasubramanian et al., 2012). Black box identification approaches relate input perturbations to output signals, i.e., force, torque, position, angle, EMG to estimate integral system behavior. A *closed loop* system approach is a special form of SI that is required to prevent erroneous conclusions in case of cause and effect interrelations (van der Kooij et al., 2005; Westwick and Perreault, 2011; Campfens et al., 2013). This will be the case during functional tasks when the human controller is within the assessed loop and/or when the applied perturbations are part of the task. System responses may be directly, e.g., tissue properties and by constant neural activation or with a certain time delay i.e., reflexes. The differences between the response and the disturbance in means of amplitude (gain) and time delay can be displayed by a Frequency Response Function (FRF), which consists of two parts, a gain and a phase curve (**Figure 6**, e.g., Engelhart et al., 2014). For instance, during balance maintenance, a gain factor between a platform perturbation and resulting muscle activity, ankle torque or body sway is a valid way to express the overall performance of the balance control system. This gain factor is a measure of the resilience of the system (Engelhart et al., 2014). The phase curve discriminates between mass, spring damper characteristics of the system and identifies delayed neural controller related reflexive responses. Neuromechanical modeling can subsequently be fitted to FRF's in a least squares sense to translate input-output behavior into physiologically meaningful parameters (van der Helm et al., 2002; de Vlugt et al., 2003; Schouten et al., 2008). Gray box approaches with pre-assumptions regarding underlying neurophysiology assist in further identification of individual components. Manipulation of the frequency content of the perturbation signal (van der Helm et al., 2002), virtual damping environment (de Vlugt et al., 2002; Meskers et al., 2009) or application of negative and positive force fields (Engelhart et al., Accepted) may specifically provoke or supress reflex activity. By manipulation of sensory channels the process of relative down- and unweighting of sensory information can be assessed (Pasma et al., 2012, 2014a,b) Assländer and Peterka, 2014; Multiple perturbations and multiple-input multiple-output (MIMO) System Identification and Parameter Estimation (SIPE; e.g., Perreault et al., 1999; Engelhart et al., 2014) are required to

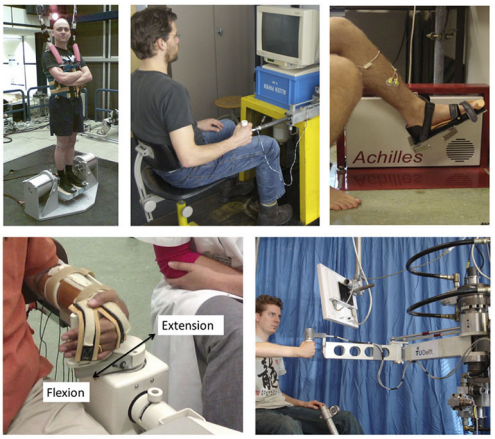

FIGURE 5 | Examples of robot manipulators used to apply position/angular or force/torque perturbations for SI purposes during stance (one Degree-of Freedom, DoF; rotational ankle perturbator; left upper corner), the ankle joint (one DoF rotational, upper right), the wrist joint (one DoF rotational, lower left) and the upper extremity (one DoF linear perturbator; upper middle and a two DoF; lower right corner).

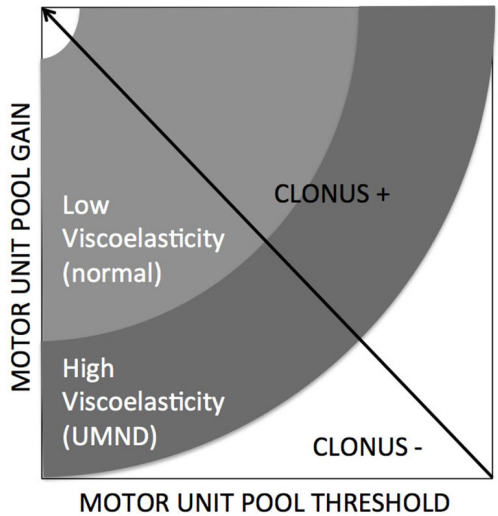

FIGURE 3 | Clonus is emerging when specific conditions are met, being combinations of neural factors (gain and threshold) and altered/increased tissue viscoelasticity (de Vlugt et al., 2012).

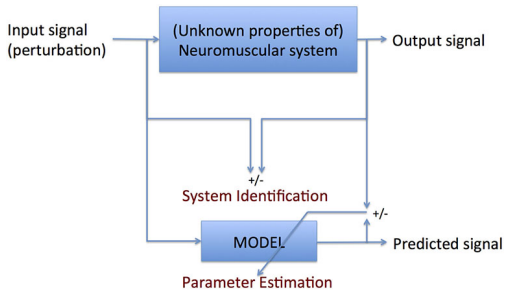

FIGURE 4 | Principle of system identification (SI): formal description of the comparison between input and output signal parameter estimation (PE): translation of the formal description into meaningful parameters. SI requires no *a priori* knowledge of the system to be identified; PE does.

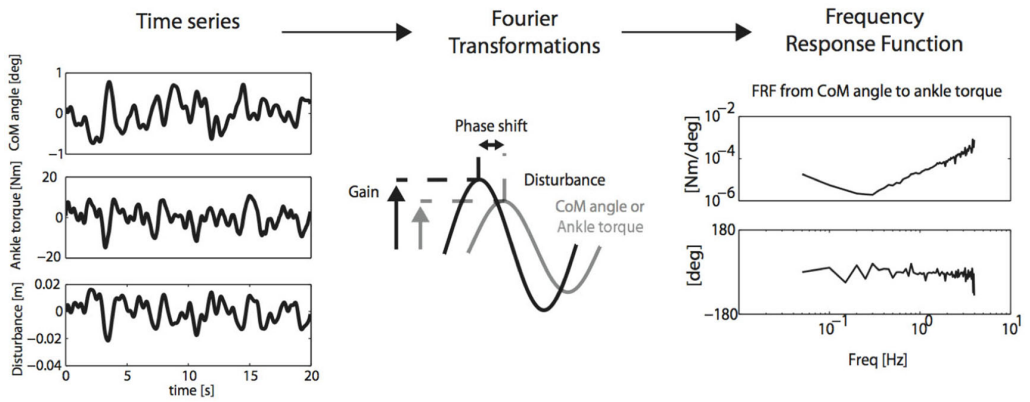

FIGURE 6 | SI and PE (SIPE): perturbation signals are related to CoM cangle and corrective ankle torque by Fourier transformation and calculation of the Frequency Response Function (FRF) of the neuro-muscular controller, describing gain and phase of aforementioned relations. FRF's may subsequently be translated into physiologically meaningful parameters by neuromuscular modeling (Engelhart et al., 2014).

identify the contributions of individual limbs in a multi-link system and to assess different segmental control.

A particular problem of biological systems in general and neuromuscular system in particular is its non-linear (Kearney and Hunter, 1988; Palazzolo et al., 2007; Klomp et al., 2013) and time variant behavior. A clear example of non-linearity is the ability of humans to adapt to the environment and task demands. A solution is to linearize the system by reducing the work-space over which system properties are addressed (Mirbagheri et al., 2001; van der Helm et al., 2002; Schouten et al., 2008), i.e., very small changes in joint angle and muscle activation. The downside of this approach is that it is very hard to relate system behavior to functional tasks. Another example of non-linearity is related to the neurophysiology of the underlying structures, e.g., the unidirectional sensitivity of the muscle spindle. The neuromuscular system appears to be very sensitive to violation of linear assumptions (Klomp et al., 2014). Thus, non-linear models are required. These were successfully applied in open loop conditions (Van Eesbeek et al., 2010; de Vlugt et al., 2012; de Gooijer-van de Groep et al., 2013). Time variant behavior of stiffness and reflexes (Ludvig et al., 2011; van Eesbeek et al., 2013; Lee and Hogan, 2014) can be assessed using a cascade of linear models with time-varying parameters, so called linear parameter varying (LPV) identification (Verhaegen and Verdult, 2007).

Clinical Application of SIPE

There are potentially three clinically relevant applications of SIPE: (1) understanding of pathophysiological mechanisms that determine the relation between initial neural damage and its functional consequences; (2) assessment to select proper therapy; and (3) biomarkers for prediction of (functional) outcome and early predictors of therapy success. During active task conditions, evidence was found for impaired reflex modulation in the upper limb in stroke patients (Meskers et al., 2009, **Figures 7B**). This in is concordance with earlier findings using neurophysiological techniques (Mazzaro et al., 2007; Trumbower et al., 2013) and SI under passive conditions (Mirbagheri et al., 2001). In one particular experiment, patients were asked to maximally resist random force perturbations applied to the handle of a one degree-of-freedom (DOF) haptic wrist perturbator (Schouten et al., 2006). Subjects were visually informed on the position of the handle for motivation purposes. Linear SI and neuromuscular modeling fitting the perturbation signal to the resulting angular wrist rotations were used to identify main characteristics of the reflex loop, i.e., velocity dependent reflex gain, time delay and intrinsic stiffness and viscosity. In this study the stiffness component was a combination of tissue properties modulated by non-velocity dependent neural activation. Stroke patients therefore showed lower stiffness compared to healthy controls as a reflection of the paresis, e.g., the decreased capacity for active torque production (**Figure 7A**, Kamper et al., 2006). Phase margins were calculated as a measure of the mechanical (in) stability of the addressed control loop, i.e., the tendency to oscillate, estimated by calculating the phase shift (phase margin) needed to reach instability of the total system of manipulator and subject. Increased stability of the reflex loop in stroke patients was found (**Figure 7C**). This adds to the evidence that functional improvements after stroke are primarily the result of compensation strategies with the unaffected limb (de Haart et al., 2004; Buurke et al., 2008; van Kordelaar et al., 2012, 2013). Also, evidence was found that elderly reduce postural responses to perturbations less compared to young subjects in case of increasing external force fields (Engelhart et al., Accepted).

Separation of the contributing factors to joint stiffness, i.e., intrinsic stiffness and reflex stiffness is important when choosing the right strategy to reduce increased joint stiffness in stroke (Mirbagheri et al., 2001; de Vlugt et al., 2010) and CP (de Gooijer-van de Groep et al., 2013; Sloot et al., 2015). Measurements in CP and controls showed on average a 5.7 times larger (p = 0.002) reflex torque and a 2.1 times larger tissue stiffness (p = 0.018) compared to controls (de Gooijer-van de Groep et al., 2013). There was a trend of increased reflex and baseline activity in the clinically high

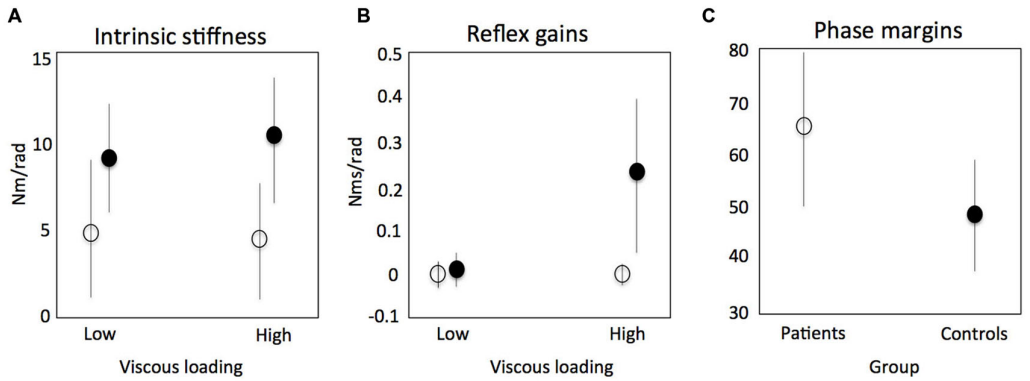

FIGURE 7 | Results of a study using system identification to identify intrinsic stiffness and reflex gains around the wrist in stroke patients. Continuous random torque perturbations had to be resisted maximally. Intrinsic stiffness (elasticity) for controls (black circle) and patients (open circle) respectively **(A)**; reflex gains (kv) as a function of increasing viscous load **(B)**; phase margins as a measure of the mechanical (in) stability of the addressed control loop, i.e., the tendency to oscillate, estimated by calculating the phase shift (phase margin) needed to reach instability of the total system of manipulator and subject **(C)**. Meskers et al. (2009).

graded spastic group and decreased reflex and background activity after spasticity treatment with botulinum toxin (Sloot et al., 2015). In stroke patients, triceps surae tissue stiffness was increased about three times and on average a five times increase in reflex torque was found. Differences in "type" of spasticity, i.e., ratio between tissue stiffness and reflex torque, between CP and stroke, may add to the understanding of this phenomenon; high variability in patients which scales with clinical phenotype may be the basis for a better selection of patients for treatment: the patients with relatively high reflex torque with reflex blocking agents and the patients with a relatively high tissue stiffness with casting, splinting and orthopedic surgery.

A recent study in healthy elderly, elderly with cataract, polyneuropathy and balance disorders using bilateral angular perturbations of a leg support surface showed specific responses of body sway and ankle torque (Pasma et al., 2014b). These responses allowed for calculation of sensory weighting i.e., the relative down- or up regulation of information of one sensory channel over the other. It appeared that proprioceptive information is weighted more with age, cataract and with impaired balance. In patients with polyneuropathy and with impaired balance proprioceptive information reweighting increased with the amplitude of disturbances. These results show the opportunity to detect the underlying cause of impaired balance in elderly using SI techniques and to apply target interventions to improve standing balance.

Neuromechanical parameters around the wrist respectively the elbow were shown to be predictors of functional outcome of arm-hand function after stroke as assessed by the Action Research Arm Test (ARAT; van der Krogt et al., 2015) and Fugl Meyer Assessment (FMA; Mirbagheri et al., 2012). These are the first steps to fully work down joint and limb function in its basic neuromechanical parameters, preferably under both passive and active conditions. Application of SIPE and addressing neuromechancial parameters longitudinally after events like stroke may substantially add to precision diagnostics, which will allow for application of the right therapy at the right time. Proper knowledge of the dynamics of neuromechanical properties in relation to functional outcome may facilitate assessment of the effects of novel, high tech and costly new treatment paradigms like robot training that currently do seem not to surpass that of conventional training (Kwakkel and Meskers, 2014). Identification of primary neurological repair vs. compensation is crucial. In stroke patients, the contribution of the paretic leg to resist external perturbations was found to be significantly smaller than the contribution of the paretic leg to weight bearing (van Asseldonk et al., 2006). These approaches may yield biomarkers to optimise therapy, which may require combinations of assessment- and training robots (Balasubramanian et al., 2012). Assessment during functional, active tasks is required when aiming for functional improvement. This requires closed loop approaches or SI using perturbations, which do not interfere with the task (Burdet et al., 2000). Non-linear and time variant SI is required as linear approaches are easily violated (Klomp et al., 2014). Combining peripheral perturbations with neurophysiological measurements like Electro Encephalography (EEG) yields properties of the sensor-controller-motor loop in more detail. Assessing cortical responses to fast muscle stretches yields stretch Evoked Potentials (strEP) that may serve as a measure of cortical sensorimotor activation in response to proprioceptive input (Campfens et al., 2015a). Afferent sensory pathway information transfer and processing can be assessed by calculation of the coherence between cortical activity and a peripheral position perturbation (position-cortical coherence, PCC; Campfens et al., 2015b). Aforementioned measures are disturbed in stroke patients and may be used to detect integrity of afferent and efferent pathways separately and propagation of signals over the cortex (Campfens et al., 2015a,b). High density EEG may further reveal cortical involvement and its

location in motor tasks (Yao and Dewald, 2005a; Yao et al., 2005b).

Besides the short-term interactions within instantaneous movement control, the long-term interaction between the controller and the plant is still underexposed. The interaction between the quality of the contractile tissues and cognition in aging, the impact of acute neural deprivation after stroke on contractile tissue properties and the unbalanced growth of skeletal and contractile tissues in CP may result in long term interrelated changes that are currently described but of which the mechanisms are yet not understood. This requires long term follow-up of patients with upper motor neuron disease and the process of ageing.

Future Work

Assessment and understanding of proper modulation of joint impedance to the task at hand as cornerstone of improving level of activity in patients sets the future direction. Questions to be addressed, comprise: (1) What are underlying pathophysiological mechanisms of impaired modulation and can these be worked down into the basic neural and mechanical components; (2) Does identification and quantification of these components translate into specific targets for intervention to improve function in patients with neurological diseases? and (3) Can these components serve as high-resolution biomarkers for prediction of (functional) outcome and early predictors of therapy success? In order to meet clinical demands, supraspinal motor control needs to be addressed in conjunction with sensor and motor characteristics taking environment and task into account. Only in this way we are able to understand the complex system interactions of primary deficits and compensations that underlie motor disorders in central neurological diseases. Neuromechanics play a key role. SI is a preferred tool for assessment. We are entering an exciting field of research, which may prove a key to fundamentally understand mobility disorders. The clinical urgency is clear, both qualitatively and quantitatively.

Conclusion

There is an urgent clinical need for assessment, identification and targeted intervention for disability inducing posture and movement disorders in neurological disease and ageing. What we fundamentally have to address is the underlying inappropriate interaction with the physical environment with inadequate neuromuscular force and impedance control of the patient. This requires assessment of both the neural controller component and the mechanical, "motor" component and most importantly their interaction. Promising tools are (closed loop) SI techniques to address neuromechanics in response to well defined environmental tasks and conditions. Clinical application is yet scarce, yet demanded.

Author Contributions

CGMM wrote a draft of the manuscript and performed the subsequent and final edit. JHDG, EDV and ACS wrote parts of the manuscript and commented on versions of the manuscript.

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