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SYMPOSIUM REVIEW

The primate reticulospinal tract, hand function and functional recovery

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Abstract The primate reticulospinal tract is usually considered to control proximal and axial muscles, and to be involved mainly in gross movements such as locomotion, reaching and posture. This contrasts with the corticospinal tract, which is thought to be involved in fine control, particularly of independent finger movements. Recent data provide evidence that the reticulospinal tract can exert some influence over hand movements. Although clearly secondary to the corticospinal tract in healthy function, this could assume considerable importance after corticospinal lesion (such as following stroke), when reticulospinal systems could provide a substrate for some recovery of function. We need to understand more about the abilities of the reticular formation to process sensory input and guide motor output, so that rehabilitation strategies can be optimised to work with the innate capabilities of reticular motor control.

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Multiple descending pathways link the brain to the spinal cord, allowing transmission of commands for voluntary movement to spinal motoneurons, Sherrington's 'final common path' via which all motor acts must be relayed to the muscular apparatus. Without these central and peripheral pathways, even the most complex cortical processing is frustrated, as patients with capsular stroke, spinal cord injury and motoneuron disease are only too aware.

Concepts of the relative function of the different descending pathways owe much to the seminal work of Kuypers (1981). Using macaque monkeys, Lawrence & Kuypers (1968*a*) made bilateral surgical lesions of the corticospinal tract – the largest and most important of the motor pathways. Immediately after the lesion, animals showed a flaccid paralysis. In the succeeding days and weeks they recovered considerable motor function, such that they could climb and run around their cages nearly normally. By contrast to this well recovered gross locomotor function, their hand movements remained impaired. Whilst some ability to grasp returned, they never recovered the fine, independent finger movements which are the hallmark of primate manual dexterity.

To investigate further which structures permitted recovery of hand function in the absence of the corticospinal tract, Lawrence & Kuypers (1968*b*) subjected the recovered animals to further selective surgical lesions of the remaining motor pathways. Cutting the lateral brainstem pathways (comprising mainly the rubrospinal tract) led to a loss of grasping with the hand, which never recovered; gross locomotor movements were relatively unaffected. By

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contrast, cutting the medial brainstem descending systems (mainly reticulospinal and vestibulospinal) produced severe impairment of gross movements, but animals remained able to grasp food if it was placed close to the hand.

These results – published over 40 years ago – have set the scene for much subsequent work, and established a conceptual framework for the relative contributions of the major pathways. As regards control of the hand, they suggest a hierarchy of importance. Powerful cortico-motoneuronal (CM) connections – which are unique to the corticospinal tract of Old World primates – have a special role in the production of fine fractionation of small groups of muscles, leading to independent finger movements (Lemon, 1993; Schieber, 2004 cf. Schieber, 2011). Even in the absence of CM connections, the primate corticospinal tract can control fine grasp via strengthening connections to C3/C4 propriospinal interneurons (Sasaki *et al.* 2004). Second in importance comes the rubrospinal tract, which makes monosynaptic connections to motoneurons innervating distal muscles involved in finger movements (Mewes & Cheney, 1991). Last on the list – if it appears at all – is the reticulospinal tract.

Subsequent work on the reticulospinal tract in non-primates has focused on a role in locomotion (Drew *et al.* 1986; Matsuyama & Drew, 2000), in postural adjustments (Prentice & Drew, 2001; Schepens & Drew, 2004), and in reaching (Schepens & Drew, 2004, 2006), although it is clear that these actions are not solely the preserve of reticular systems, but involve the coordinated activity of corticospinal and reticulospinal outputs (Drew *et al.* 2004). In primates, neurons in the reticular formation also modulate their activity powerfully during reaching movements (Buford & Davidson, 2004). This modulation is tuned to a preferred reach direction, as commonly found for cells in the arm representation of primary motor cortex (Georgopoulos *et al.* 1986). Because current concepts emphasise the role of reticulospinal output in reaching and locomotor movements, studies which seek to map outputs from the primate reticular formation have usually ignored muscles acting on the digits (Davidson & Buford, 2004, 2006; Davidson *et al.* 2007).

Despite this background, there are clear indications in previous literature that the reticulospinal tract may contribute to finger movements in some circumstances (Lemon, 2008). Lawrence & Kuypers (1968*b*) reported that animals with combined corticospinal and rubrospinal lesions completely lost the ability to grasp food, and that this never recovered. However, paradoxically, they could climb around their cages well, which involved gripping the cage bars well enough to support their whole body weight. The reticulospinal tract was the only major surviving descending pathway in these animals. Although Davidson & Buford (2006) did not investigate muscles acting on the fingers, they found many sites in the reticular formation where stimulation could elicit activity in muscles acting around the wrist, the most distal joint investigated. The acoustic startle reflex – which is most likely mediated via the reticulospinal tract – can produce activation in intrinsic hand muscles when it is abnormally facilitated in patients with hyperekplexia (Brown *et al.* 1991*c*). Finally, Ziemann *et al.* (1999) reported that transcranial magnetic stimulation over the primary motor cortex in human subjects could elicit responses in ipsilateral hand muscles. The characteristics of these responses suggested that they were mediated via a brainstem (probably reticulospinal) pathway, which was assumed to be activated in turn by corticoreticular projections (Keizer & Kuypers, 1989).

To clarify this issue further, we carried out experiments in anaesthetised macaque monkeys in which inputs to motoneurons from the corticospinal and medial brainstem pathways were directly compared by intracellular recording of synaptic potentials (Riddle *et al.* 2009; Fig. 1). We found both mono- and disynaptic excitatory postsynaptic potentials (EPSPs) in motoneurons following electrical stimulation of the medial longitudinal fasciculus (MLF, mainly reticulospinal pathways). Such inputs were seen, even in motoneurons identified antidromically as projecting to intrinsic hand muscles (e.g. Fig. 1*E–H*). This is the first direct evidence that the reticulospinal tract can facilitate muscles acting on the fingers. However, we should be clear that reticulospinal inputs occurred only around 30% as often, and had an amplitude only 20% as great, as those from the corticospinal tract (Fig. 1*I–L*).

Although inputs to motoneurons are obviously an important measure of the function of a descending pathway, the majority of the spinal terminals of both corticospinal and reticulospinal tracts are not found on motoneurons, but on segmental interneurons. These cells are almost always viewed as 'interposed interneurons', i.e. relay cells whose role is to form an oligosynaptic route for descending information to reach the motoneuron. Such a concept probably fails to do justice to the rich range of possibilities provided by the spinal circuitry. Stimulation of the primate reticulospinal tract does elicit some EPSPs in motoneurons at disynaptic latency, meaning that some of the interneuron recipients of reticulospinal terminals can provide a relatively 'straight through' pathway. However, stimulation of the corticospinal tract in an awake monkey produces no measurable disynaptic response (Olivier *et al.* 2001). When inhibition is antagonised by systemic administration of strychnine, disynaptic corticospinal EPSPs in the monkey can be unmasked, but the great majority of these arise from C3/4 propriospinal interneurons, not segmental pathways (Alstermark *et al.* 1999). Corticospinal terminals on segmental interneurons in primates clearly do not function merely as a disynaptic pathway to motoneurons.

Previous work suggested that the reticulospinal and corticospinal tracts contact interneurons placed medially and laterally within the intermediate zone, respectively (Kuypers *et al.* 1960), although there is considerable overlap in the spatial distribution of terminals. It is interesting to know the extent to which the two tracts provide convergent input to interneurons, or whether each contacts a 'private' pool of interneurons not accessible by the other pathway. To investigate this, we made extracellular recordings from intermediate zone interneurons in the cervical enlargement in awake behaving monkeys, and measured the responses following stimulation of reticulospinal and corticospinal tracts (Riddle & Baker, 2010; Fig. 2). Of the cells which gave any response, 48% received input from both tracts (Fig. 2*E*). This might be expected for circuits targeting more proximal muscles involved in locomotion, posture or reaching, given the previous work in cat suggesting shared cortical/reticular control for these functions (Drew *et al.* 2004). However, when analysis was restricted to cells which seemed involved in the control of the digits, similar proportions of convergence between the two descending tracts were seen (Fig. 2*F* and *G*).

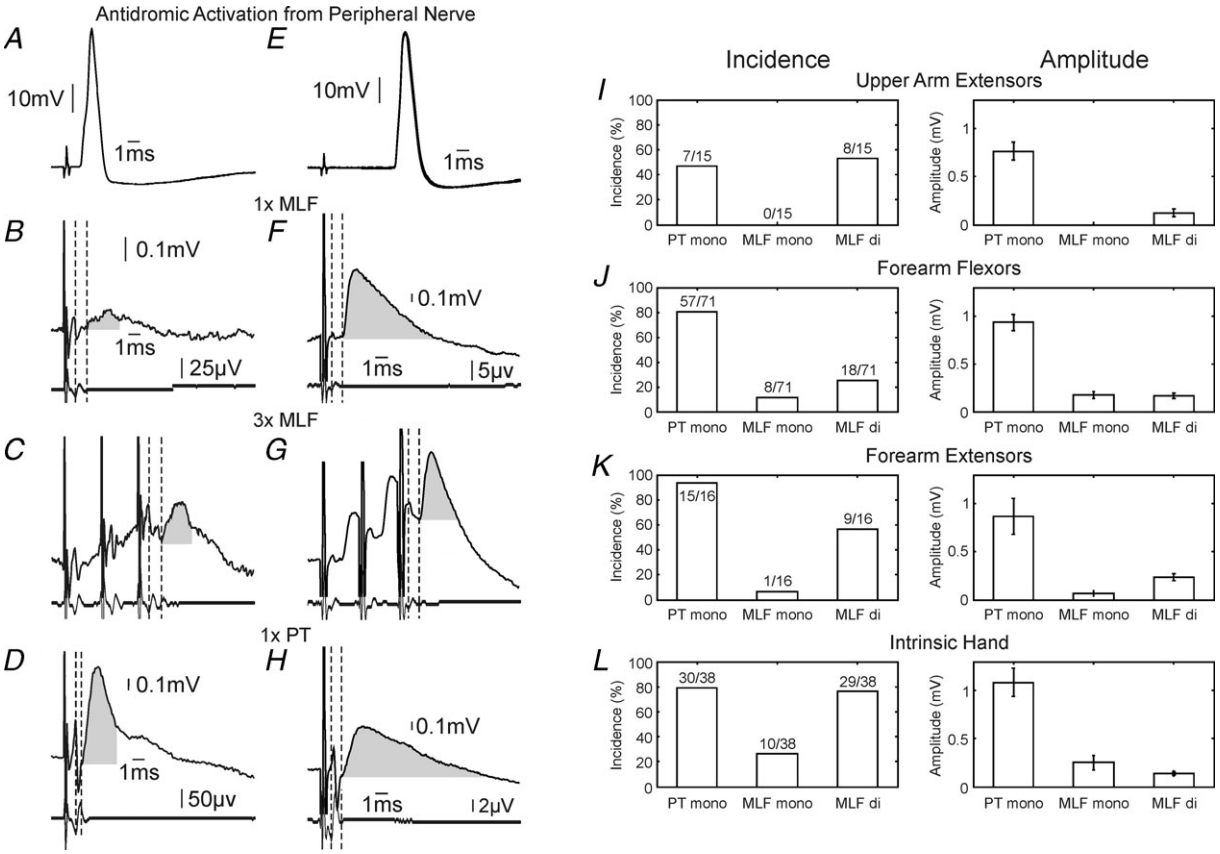

Figure 1. Primate cervical spinal motoneurons receive mono- and disynaptic reticulospinal input
A–D, example motoneuron projecting to forearm flexors that received disynaptic reticulospinal inputs. *A*, antidromic activation from median nerve above the elbow (overlain single sweeps); there was no activation from the median nerve at the wrist (not shown). *B* and *C*, disynaptic reticulospinal excitatory postsynaptic potentials (EPSPs) following a single 300 μA stimulus to the ipsilateral medial longitudinal fasciculus (MLF) (*B*), and a train of 3 stimuli (*C*). *D*, monosynaptic EPSP evoked in this cell following single 300 μA stimulus to the contralateral pyramidal tract (PT). Each panel shows averaged intracellular records (top) with simultaneously recorded epidural volleys below. Vertical dashed lines highlight the segmental latency of the response; EPSPs are shaded. Scale bars in *B* also apply to *A* and *C*. *E–G*, example monosynaptic EPSP evoked following reticulospinal activation in a spinal motoneuron projecting to thenar muscles. *E*, antidromic activation from median nerve at the wrist. *F* and *G*, monosynaptic EPSPs following single (*F*) and train of three (*G*) stimuli to MLF. *H*, monosynaptic EPSP after stimulation of contralateral PT. *I–L*, bar graphs of incidence (left) and mean amplitude (right) of monosynaptic EPSPs from the contralateral PT (PT mono), monosynaptic EPSPs evoked from the ipsilateral MLF (MLF mono) and disynaptic EPSPs from the ipsilateral MLF (MLF di). The numbers above each column in the incidence plots give the raw numbers of motoneurons. Error bars in amplitude plots are SEM. Amplitude of disynaptic EPSPs are measured from the response to the last of a train of 3 or 4 shocks. Each panel illustrates results from motoneurons innervating different categories of muscles. Reproduced from Riddle *et al.* (2009).

One interpretation of these findings could be that the corticospinal and reticulospinal tracts are parallel pathways, with conceptually equivalent functions. As far as the hand is concerned, is the only difference the strength of input each provides to distally projecting motoneurons? The available evidence is that this is unlikely, and that important qualitative differences exist in how each tract functions in voluntary movement.

Fractionation

The first clear difference concerns the extent of divergence of single descending axons. Corticospinal axons do not only contact motoneurons innervating a single muscle. Rather, they diverge to a small number of motoneuron pools, co-facilitating multiple muscles (Buys *et al.* 1986). This is believed to allow the cortex ready access to functionally related groups of synergists (Schieber, 2001). By flexibly combining these synergistic groups, independent control of the digits can be achieved, although this has some major limitations (van Duinen & Gandevia, 2011). By contrast, reticulospinal axons branch extensively within the spinal cord, contacting many motoneuron pools. The same fibre may even make contacts in both cervical and lumbar enlargements (Peterson *et al.* 1975; Matsuyama *et al.* 1997; Matsuyama *et al.* 1999). Whilst the muscle groups coactivated are also likely to form functionally meaningful sets of synergists, the extent of the divergence will preclude fine fractionated control of the hand via reticulospinal pathways.

Flexor/extensor bias

Spike triggered averaging studies have allowed detailed quantitative assessment of which muscle groups are activated by single axons. The results show that corticospinal axons facilitate both contralateral extensor and flexor muscles, although connections are slightly stronger for extensors (Cheney *et al.* 1991). By contrast – at least for muscles acting at the wrist, elbow and shoulder –

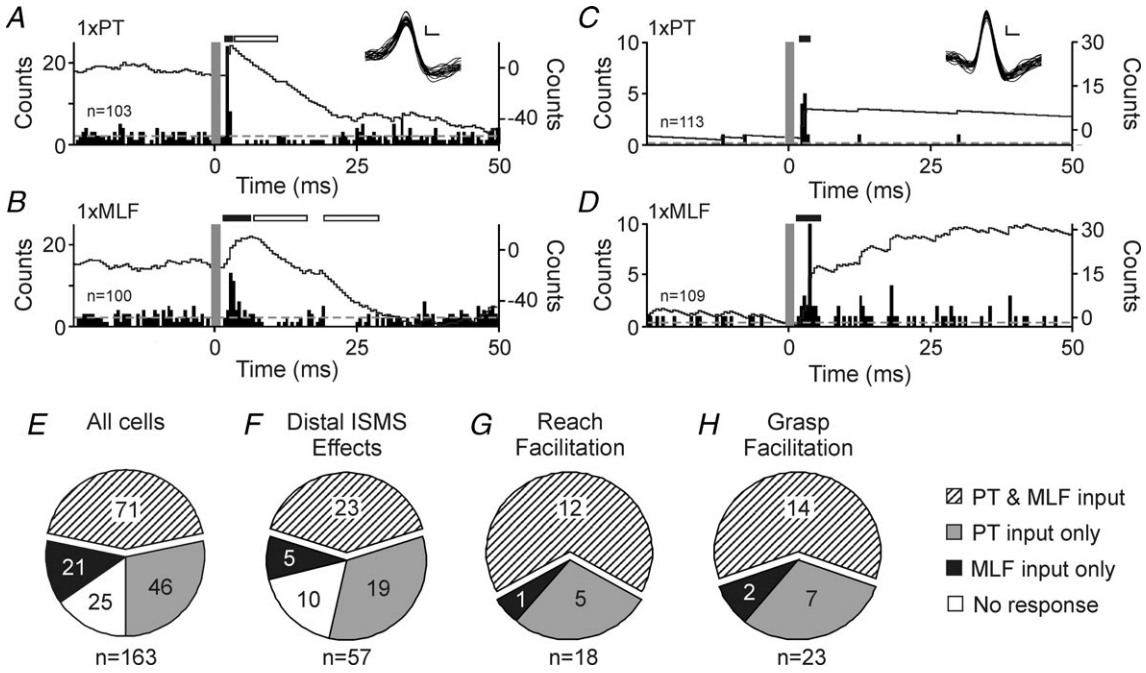

Figure 2. Primate cervical spinal interneurons receive convergent excitatory corticospinal and brainstem input
A and *B*, single cell example of convergent facilitation. Each panel shows peri-stimulus time histogram (PSTH, left-hand ordinate) with overlain cumulative sum (CUSUM, right-hand ordinate). Stimulus delivery at time zero. Dashed grey line represents mean pre-stimulus baseline activity. PSTH bin width 0.5 ms. Stimulus artifact dead times are replaced by dark grey bars and corresponding regions of the CUSUM are blanked. Significant ($P < 0.01$, *Z* test) changes from baseline are highlighted with filled (facilitation) or open (suppression) bars above the PSTH. Overlain spike waveforms shown in inset, scale bars 1 ms, 2 μV. Responses to: *A*, single 300 μA PT stimulus; *B*, single 300 μA stimulus to medial longitudinal fasciculus (MLF). *C* and *D*, similar responses in a different cell, also recorded in the intermediate zone of the cervical enlargement. *E*, pie chart showing the proportion of cells recorded in two monkeys which received convergent input, or input from only one pathway. *F*, similar display, but constructed only for cells recorded at spinal sites where intraspinal microstimulation (ISMS) yielded low threshold twitches of the digits or wrist. *G*, constructed only for cells which showed a facilitation of discharge during voluntary reaching movements. *H*, constructed only for cells with facilitated discharge during voluntary grasping movements. Reproduced from Riddle & Baker (2010).

the reticulospinal tract tends to facilitate flexors and suppress extensors ipsilaterally, and facilitate extensors and suppress flexors contralaterally (Davidson & Buford, 2006; Davidson *et al.* 2007). However, it is not clear whether reciprocal flexor/extensor activation by the reticulospinal tract also holds true for muscles acting on the digits. In the work of Riddle *et al.* (2009), connections to forearm flexors and extensors did not show obvious consistent differences in incidence or amplitude (see Fig. 1*J* and *K*) – although the relatively small numbers of motoneurons recorded, and the inability to separate out wrist *versus* finger muscles in that study means that this issue remains an important unknown in reticulospinal organisation.

Laterality

The reticulospinal tract is a bilaterally organised system: a single axon may innervate both sides of the cord (Jankowska *et al.* 2003; Schepens & Drew, 2006; Davidson *et al.* 2007), and stimulation within the reticular formation evokes bilateral activity (Davidson & Buford, 2006; Davidson *et al.* 2007). Again, it is worth noting that this key principle of reticulospinal organisation has been elucidated in more proximal muscles, and nothing is known of the bilateral organisation of projections to muscles acting on the digits. By contrast, the corticospinal tract is more lateralised, with around 85% of fibres which originate in one hemisphere decussating at the medulla and descending contralaterally (Kuypers, 1981; Rosenzweig *et al.* 2009). Corticospinal axons show substantial crossing of the midline at segmental level. This means that fibres from the ipsilateral tract can cross to influence the contralateral cord, but also that axons from the contralateral tract cross to make connections within the ipsilateral hemicord (Rosenzweig *et al.* 2009). Against this anatomical background, it might be expected that extensive ipsilateral corticospinal outputs influencing motoneurons would be apparent. However, in cat (Edgley *et al.* 2004; Jankowska *et al.* 2005) the majority of ipsilateral effects produced by corticospinal tract stimulation appear to pass via the reticulospinal tract, activated by corticoreticular collaterals of the corticospinal neurons – a similar conclusion to that reached for the pathway mediating ipsilateral motor evoked potentials in humans (Ziemann *et al.* 1999). In monkey, we have recently shown using multiple complementary methods that the ipsilateral corticospinal output to the upper limb appears negligible (Soteropoulos *et al.* 2011; Fig. 3).

Contraction strength

Evidence from PET scanning suggests that activity in the primary motor cortex increases rapidly as force increases, but that the rate of rise tails off as high forces are reached (Dettmers *et al.* 1996). In a task involving production of only weak forces, the discharge of single corticomotoneuronal cells correlates strongly with digit force (Maier *et al.* 1993). The size of the correlation coefficient (average of 32 Hz N^{-1} for positively correlated, and 21 Hz N^{-1} for negatively correlated cells), coupled with a typical maximum sustained firing of these cells of $<$200 Hz (Cheney & Fetz, 1980; Lemon *et al.* 1986; Maier *et al.* 1993) implies that only weak forces can be encoded by the corticospinal outflow.

The reticulospinal system is also involved in coding movements with weak to moderate levels of force (Buford & Davidson, 2004); however, it seems that it may become relatively more important for strong contractions. Ipsilateral motor evoked potentials, which are likely to be mediated via the reticulospinal tract (Ziemann *et al.* 1999), are easier to evoke against a high background contraction (Alagona *et al.* 2001). Interestingly, when normal subjects attempt to make a unimanual contraction, there is some involuntary 'mirroring' of contraction on the contralateral side (Armatas *et al.* 1994; Mayston *et al.* 1999; Sehm *et al.* 2010), which is especially apparent at high forces (Zijdewind & Kernell, 2001). Several studies have investigated possible cortical mechanisms behind mirroring (Zijdewind *et al.* 2006; Sehm *et al.* 2010). However, one contributor could also be greater use of reticulospinal output at higher force levels, with a consequent loss in the ability to direct activity selectively to one side.

Role in recovery after corticospinal lesion

Lawrence & Kuypers (1968*b*) emphasised the importance of the rubrospinal tract in mediating the recovery of hand function in monkey, and indeed rubrospinal output has been demonstrated to strengthen after unilateral corticospinal lesion (Belhaj-saif & Cheney, 2000). However, the available evidence suggests that the rubrospinal tract is almost absent in humans (Nathan & Smith, 1955), making a major contribution from that source in man unlikely. In patients who have suffered corticospinal lesion (e.g. stroke survivors), this leaves the reticulospinal tract as the most likely candidate descending pathway for functional recovery of hand movements. Since the reticulospinal tract does activate hand muscles in healthy individuals (albeit weakly), functional recovery would require only the strengthening of this pre-existing output, and not the growth of an entirely new category of connections not previously present. Our own preliminary data show that reticulospinal outputs do indeed strengthen after recovery from corticospinal lesion (Zaaimi *et al.* 2009).

An important feature of functional recovery is that it is incomplete, and often appears constrained to produce impoverished movements compared to normal dexterous human hand use. Much of what we know about the differences between corticospinal and reticulospinal

outputs (as outlined above) is consistent with the residual deficits experienced by stroke survivors. Recovered hand movements are poorly fractionated (Lang & Schieber, 2003, 2004; Raghavan *et al.* 2006), and often voluntary activation of one muscle is accompanied by unwanted activity in other muscles (Bourbonnais *et al.* 1989; Dewald *et al.* 1995). There is an imbalance in activation of flexors and extensors: whereas flexors may be excessively active, leading to spasm and ultimately to spasticity, the extensors are frequently weak (Kamper *et al.* 2003). Extensor weakness may have the greatest impact on hand function, and its recovery is the best predictor of restored hand function (Fritz *et al.* 2005). Mirror movements are more common and extensive in stroke survivors than healthy adults (Nelles *et al.* 1998). For a review of some of the changes in motor cortical circuits after stroke see Ward (2011).

Motor processing within the reticular formation

This review has so far focused on the reticulospinal tract, and seen this as one component of the descending systems linking the cerebral cortex to spinal output. There is a danger that such a view sees the computations

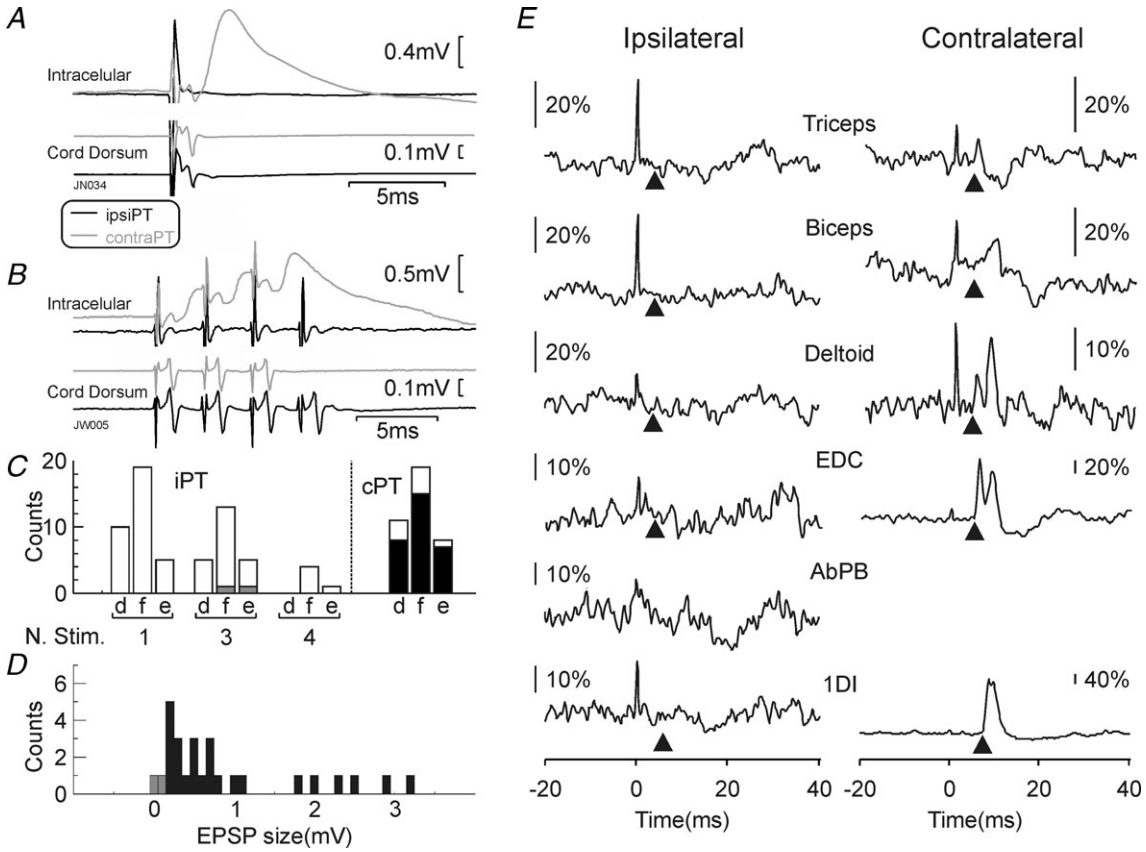

Figure 3. Lack of effects on primate forearm muscles following stimulation of the ipsilateral pyramidal tract (PT)
A, example averaged intracellular recordings from a forearm flexor motoneuron in which an EPSP is evoked by a single stimulus to contralateral PT (300 μA, $n = 36$, black trace) but not to ipsilateral PT (300 μA, $n = 37$, grey trace). *B*, averaged intracellular recordings from a different forearm flexor motoneuron showing EPSPs evoked by multiple stimuli to contralateral PT (3 stimuli, $n = 30$) but not to ipsilateral PT (4 stimuli, $n = 55$). In *A* and *B* intracellular recordings are shown above cord dorsum records. *C*, bar graph showing the types of motoneurons tested with each stimulus (d: intrinsic hand muscles; f: forearm flexors; e: forearm extensors), and maximum number of stimuli used. Bars to the right of the dotted line correspond to contralateral PT (single stimulus). Grey bars indicate oligosynaptic responses, black bars monosynaptic responses, white bars no responses. *D*, distribution of postsynaptic response amplitudes from PT stimulation; black corresponds to contralateral PT effects, grey bars to the two ipsilateral PT effects seen. *E*, averages of rectified EMG from muscles ipsilateral or contralateral to the stimulating electrode, following stimulation of the PT at 500 μA. At this intensity, there was no spread to the contralateral pyramid. Arrows mark onset latency of responses in contralateral muscles, and have been duplicated at the same latency on ipsilateral traces for reference. Abbreviations: 1DI, first dorsal interosseous; AbPB, abductor pollicis brevis; EDC, extensor digitorum communis. Scale bars give amplitude of rectified EMG as a percentage of the pre-stimulus baseline level. Reproduced from Soteropoulos *et al.* (2011).

associated with movement as the exclusive preserve of the motor areas of the cortex, with subcortical regions acting merely as 'relays'. Contrary to this, we already know that substantial processing capability resides within the spinal cord. Spinal circuits can generate rhythmic activity associated with locomotion (Guertin, 2009), and cancel unwanted oscillations which would lead to tremor (Williams & Baker, 2009; Williams *et al.* 2010). Spinal interneurons show preparatory changes in activity during an instructed delay period (Fetz *et al.* 2002).

Similarly, it is likely that significant processing capability resides within the reticular formation. Reticular nuclei receive sensory input from the periphery (Leiras *et al.* 2010), the vestibular system (Peterson & Abzug, 1975; Troiani *et al.* 1976), neck proprioceptors (Pompeiano *et al.* 1984; Srivastava *et al.* 1984), and audition (Lingenhohl & Friauf, 1992). This ideally places the reticular formation to modify and shape motor commands to suit the sensory background against which they occur. One known example where this occurs is the acoustic startle reflex, which is likely to involve reticulospinal circuits (Brown *et al.* 1991*b*) and can modify its outputs according to the posture at the time of the auditory input (Brown *et al.* 1991*a*).

In addition to sensorimotor integration, the reticular formation also seems to play a role in preparation for a voluntary movement. Reticular neurons show tuned delay period activity (Buford & Davidson, 2004). Human voluntary reaction times can be shortened by around 70 ms if the response cue is replaced by a loud sound, thought to engage reticular circuits mediating the acoustic startle reflex (Valls-Sole *et al.* 1995). This 'StartReact' paradigm suggests that reticular circuits can store the details of a motor programme, which can be rapidly released by a suitable reticular input (Valls-Sole *et al.* 1999).

Such observations are of particular importance when we consider the impact of reticulospinal pathways on recovery after lesion. Stroke does not produce a pure corticospinal lesion: both cortical and subcortical strokes are likely also to damage corticoreticular connections (some of which are collaterals of corticospinal fibres; Keizer & Kuypers, 1989; Kably & Drew, 1998). If we view the reticular formation as a passive relay station, then loss of corticoreticular input will prevent the reticulospinal system from making any useful contribution to recovery. However, if we credit the reticular formation with an autonomous ability for the sensory guidance of movement, a useful contribution to functional movements could be made even in the face of substantial loss of cortical control. The truth probably lies somewhere in between these two extreme viewpoints; knowing the details of just how much reticular autonomy is possible is important to understand the limitations to recovery.

Understanding processing in the cerebral cortex has been greatly facilitated by the ordered arrangement of the neural elements. Early delineation of cortical laminae paved the way for concepts of a cortical 'microcircuit' (Douglas & Martin, 1991), and application of electrophysiological, morphological and molecular methods for neural phenotyping has allowed the identification of a plethora of neuronal types (Markram *et al.* 2004; Toledo-Rodriguez & Markram, 2007) . Likewise, segregation of cortical areas by cytoarchitectonic criteria (Brodmann, 1909) paved the way for an understanding of areal specialisation and somatotopic organisation. This spatial organisation of function allows meaningful conclusions to be drawn from brain imaging studies, which must average spatially over voxels at the millimetre scale. By contrast, the motor reticular formation poses considerable challenges. There is no discernable laminar organisation, and there has been little characterisation of the local circuits. Segregation of the different reticular nuclei is made on gross features such as cell size and density, and often boundaries are indistinct (Sakai *et al.* 2009). Penetration into the reticular formation with a microelectrode reveals a confusing lack of orderly somatotopy (Davidson & Buford, 2006). We thus seem a long way from being able to propose a canonical reticular microcircuit.

One useful approach to understanding the capabilities of cortical circuits has been to investigate the generation of oscillatory activity. Measurement of detailed cellular and synaptic properties *in vitro* has allowed the construction of computational models, capable of reproducing the observed network dynamics. Many different circuit topologies are now understood to be capable of rhythmogenesis (Whittington *et al.* 2011). Importantly, oscillations in sensorimotor cortex can also be observed in awake behaving animals (Witham & Baker, 2007), providing a link to functionally relevant circuit behaviour. Nothing comparable can be attempted on the basis of current knowledge of the reticular formation. However, there are some clues in the literature that oscillations may also form part of the repertoire of reticular circuits, as acoustic startle responses appear to initiate a burst of ∼14 Hz oscillations (Grosse & Brown, 2003). Understanding reticular oscillations may therefore start to give an insight into the computational operations of which these circuits are capable. This could allow principled therapy for patients recovering from lesions, which would work with the capabilities of this important motor structure.

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