The medial reticular formation: a brainstem substrate for simple action selection?

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Abstract

The search for the neural substrate of vertebrate action selection has focused on structures in the fore- and mid- brain, particularly on the basal ganglia. Yet, the behavioural repertoire of decerebrate and neonatal animals suggests the existence of a relatively self-contained neural substrate for action selection in the brainstem. We propose that the medial reticular formation (mRF) is this substrate's main component, reviewing evidence that the mRF's inputs, outputs, and intrinsic organisation are consistent with the requirements of an action selection system. We argue that the internal architecture of the mRF is composed of interconnected neuron clusters; our quantitative model of this anatomy suggests the mRF's intrinsic circuitry constitutes a small-world network, and may have evolved to reduce axonal wiring. We use computational models to enumerate and illustrate potential configurations of action representation within the internal circuitry of the mRF. We show that each cluster's output could represent activation of an action component; thus, co-activation of a set of these clusters would lead to the co-ordinated behavioural response observed in the animal. New results are presented that provide evidence for an alternative scheme: inputs to the mRF are organised to contact clusters, but recruit a pattern of reticulo-spinal neurons from across clusters to generate an action. We propose that this reconciles the anatomical structure with behavioural data showing action sequencing is degraded, rather than individual actions lost, as the mRF is progressively lesioned. Finally, we consider the potential integration of the basal ganglia and mRF substrates for selection and suggest they may collectively form a layered/hierarchical control system.

1 Introduction

All animals must continuously sequence and co-ordinate behaviors appropriate to both their context and current internal state if they are to survive. It is natural to wonder what parts of the nervous system — the neural substrate — evolved to carry out this action selection process. For simpler animals, like the nematode worm *C. elegans* and the leech, a circumscribed behavioural repertoire is handled by specialist neurons that direct motor responses to specific stimuli (de Bono & Maricq, 2005; Kristan et al., 2005; Stephens et al., 2008) * The sensory apparatus and motor behaviours are largely a product of these animals' ecological niche, and hence so too is the neural network that handles the action selection process.

By contrast, vertebrates (particularly mammals) have a behavourial repertoire that is both extensible (by learning new action-outcome pairings) and flexible (by applying existing actions

*That is not to say their behaviours are reducible to simple sensory-motor reflexes. The locomotive behaviour of *C. elegans* after the detection of food depends on how well-fed they are (de Bono & Maricq, 2005): the internal milieu plays a role even with a brain of just 302 neurons. Even the idea of a stereotyped sensory-motor reflex in small-scale animals may be particularly misleading. They often display a stochastic motion response to repeated stimuli that stands in contrast to the highly repeatable movements of vertebrates.

to new contexts). The evolution of this broader scope for behaviour seems related to the evolution of a central nervous system, the coalescing of all neural circuits into a single "brain" and the appearance of many "inter-neurons" between the primary sensory and motor neurons. Complexity of behaviour alone does not and cannot prove complexity of the underlying generating circuity (Braitenberg, 1984), but flexibility and extensibility seem to require something interposed between sense and action.

The elaboration of the vertebrate nervous system has led to multiple, partially segregated neural systems that lie interposed between primary sensory and motor circuits. Each of the elaborated sensory, homeostatic, memory, planning, and emotion neural systems could in principle guide behaviour; yet each is essentially competing for access to a single final common motor pathway (Sperry, 1952) formed by the motor neurons of the spinal cord and cranial nerve nuclei. It has thus been proposed that the vertebrate brain has co-evolved (or co-opted) specialised and centralised neural systems for action selection (Prescott et al., 1999; Redgrave et al., 1999; Prescott, 2007), to handle both the competition between systems accessing the final motor pathway and the open-ended nature of a flexible, extensible behavioural repertoire.

The basal ganglia have been central to recent proposals for the neural substrate of the vertebrate action selection system (see, for example, Mink & Thach, 1993; Graybiel, 1995; Doya, 1999; Kropotov & Etlinger, 1999; Redgrave et al., 1999; Rubchinsky et al., 2003; Grillner et al., 2005, and chapters in this volume). This collection of nuclei in the fore- and mid-brain are intimately involved in motor control: damage to the basal ganglia causes a wide variety of disorders with motor symptoms, such as Parkinson's disease (Zigmond & Burke, 2002). Moreover, in keeping with the hypothesis of evolved specialised action selection structures, they have been identified in all mammal species, homologous structures exist in the other amniotes (birds and reptiles), and the basic circuitry is conserved over all jawed vertebrates (Reiner et al., 1998).

We have previously argued that, of all the structures of the vertebrate brain, the basal ganglia have the necessary inputs, outputs, and internal connectivity to function as the central switch of an action selection system (Redgrave et al., 1999; Prescott et al., 1999). Computational modeling of the intrinsic basal ganglia circuitry demonstrated that it is capable of resolving competition between action-representing signals such that the basal ganglia output expresses the selection of the most appropriate action(s) and suppresses the others (Gurney et al., 2001a,b; Humphries et al., 2006b). At the same time, we readily acknowledged that the basal ganglia do not form the complete vertebrate action selection system (Prescott et al., 1999; Redgrave et al., 1999; Prescott, 2007).

The basal ganglia cannot be directly involved in all forms of action selection. Decerebrate animals and altricial (helpless at birth) neonates do not have fully intact basal ganglia, but are capable of expressing spontaneous behaviors and co-ordinated and appropriate responses to stimuli. During decerebration the entire brain anterior to the superior colliculus is removed, leaving only the hindbrain intact (Figure 1a). Yet the chronic decerebrate rat can, for example, spontaneously locomote, orient correctly to sounds, groom, perform co-ordinated feeding actions, and discriminate food types (Woods, 1964; Lovick, 1972; Berntson & Micco, 1976; Berridge, 1989). Such animals clearly have some form of intact system for simple action selection that both enables them to respond to stimuli with appropriate actions (more complex than simple spinal-level reflexes), and enables them to sequence behaviors — as demonstrated by the orienting, grasping (with jaw), and chewing initiated by placing food within their whiskers.

Even in intact animals, basal ganglia outputs do not directly control all the hindbrain and midbrain circuits that underpin these behaviours. Instead, these circuits may be controlled by parallel systems for action selection in other contexts (Swanson, 2000; Zahm, 2006). In particular, Holstege has championed the idea of the "emotional motor system" that co-ordinates somatic and autonomic responses to valent stimuli, centred on the midbrain periacqueductal gray and the inputs it receives from the central amygdala and lateral hypothalamus (Holstege,

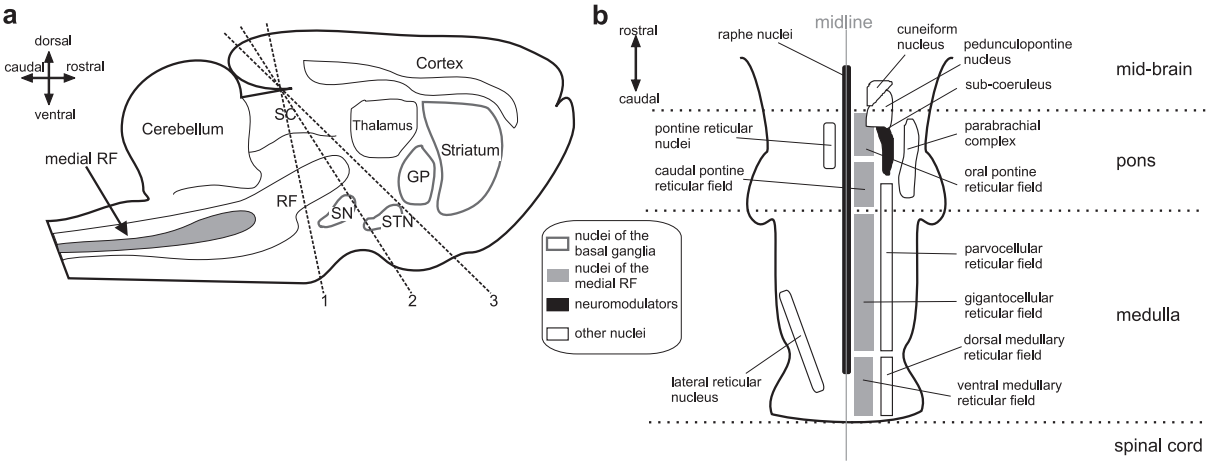

Figure 1: Anatomical locations of the putative action selection systems. (a) The relative locations of major nuclei and structures including the basal ganglia and the medial reticular formation (RF) shown on a cartoon sagittal section of rat brain. The dashed lines show the location of the three most-common decerebration lines — all the brain rostral to the line is removed, leaving hindbrain and spinal cord intact. GP: globus pallidus. SN: substantia nigra. STN: subthalamic nucleus. SC: superior colliculus. (b) Principal reticular formation fields, and associated nuclei in a schematic horizontal section from spinal cord to decerebration line 1 in (a). The raphe nuclei sit either side of the midline, and the other nuclei and fields are distributed symmetrically about the midline — the main fields and nuclei are illustrated to the right of the midline, those on the left are found beneath those on the right. The main components of the putative brainstem action selection system are in the medial RF. We retain names of major regions from Paxinos & Watson (1998) for consistency, but rename as "fields" rather than "nuclei" to reflect the lack of strong criteria for subdivisions (and extend the names to cover all cells in the medial RF at that anterior-posterior level).

1995). It seems then that a neural circuit must both handle the co-ordination of simpler behaviours, and may arbitrate between multiple parallel brain systems by lying interposed between them and the final common motor pathway (Zahm, 2006).

Is there then a brainstem substrate for action selection? Such a substrate should have the necessary properties of a system specialised for action selection. We believe these to be the following (Redgrave et al., 1999). First, the system requires inputs that provide information about an animal's internal state and external context. Second, the system requires a method for computing the urgency (or salience) of each available action from the provided information, in some "common currency" that allows comparison of their relative levels of support. Third, the system must have an internal configuration that allows for both the representation and the resolution of competition between actions. Fourth, the system must have outputs allowing the expression of the selected action. In addition, we may identify the substrate by the effect that manipulations of it have on the performance of actions.

Of the intact structures in the brainstem of both neonatal and decerebrate animals, we proposed that only the medial reticular formation (mRF) fulfills these criteria (Humphries et al., 2007), and is then the most likely substrate of a generalised simple action selection mechanism. This chapter fleshes out our argument that the mRF has the necessary properties of an action selection system. In particular we illustrate modelling of action selection in its numerous forms: conceptual models of brain function form the overarching theme; quantitative models of anatomy let us constrain the possible computations and representational forms supported by the neural system; quantitative models of dynamics let us explore the implications for action selection in the input-output relationships of the neural system.

Historically, we are not the first to note that the mRF may function as some form of selection device. Warren McCulloch and colleagues proposed the mRF was a "mode selector", which set the global behavioural state of an animal — such as escape, feeding, and so on. To demonstrate

the plausibility of their proposal, they created one of the first computational neuroscience models, and showed their interpretation of the mRF's structure could perform selection of signals (Kilmer et al., 1969). However, their emphasis was on the *ascending* projections of the RF, the connections to thalamus and cortex being responsible for setting the overall state of the animal. Our emphasis is on the dominant *descending* projections of the mRF, and the potential they have to directly control motor behaviour.

2 Where and what is the mRF?

The reticular formation (RF), broadly defined, is the main central mass of neurons that extend from the border with spinal cord, running through the medulla and pons, and terminating in the mesencephalon, underneath the superior colliculus (optic tectum in non-mammalian vertebrates) — see Figure 1. Clearly specifying the constituents of the "reticular formation" is fraught with problems (Blessing, 1997). In the major reference work on the rat nervous system, Jones (1995) does not attempt a clean definition of the RF's extent or constituents. Rather, in common with other contemporary reviews (Holstege, 1995; Newman, 1995), Jones (1995) emphasises three major columns of cells on the long axis of the RF: a midline-hugging column of serotonergic cells, a large-celled medial column, and a smaller-celled lateral column (Figure 1b). The difficulties principally revolve around two problems: what constitutes a continuation of the lateral column, rather than a discretely-identifiable nucleus; and the sub-divisions of the medial column along all three axes of the brain.

Our interest here is with the medial column of larger neurons, and thus we may side-step the first problem to some extent. The second problem requires some resolution. The rat brain atlas of Paxinos & Watson (1998) labels sub-divisions of the medial column as "nuclei", and a rather large number of them. Jones (1995) softens this stance and calls them "fields" to reflect the lack of strong criteria for demarcating the cell groups. Blessing (1997) takes this further: using the "paragigantocellular" field an example, he argues that on no grounds – cytoarchitecture, neurochemistry, or projections – can each "field" or "nucleus" be clearly dissociated from the tissue surrounding it. Indeed, Blessing (1997) is strongly critical of the whole concept of a "reticular formation" and the loaded nature of that label: literally "net-like", it conjures an impression of impenetrability and a mass of cells that respond as one — an impression embraced by earlier authorities on the RF (Scheibel & Scheibel, 1967).

We have sympathy with Blessing's position, and are not keen to add to the proliferation of names; at the same time we agree with Jones that, if we are to distinguish any sub-divisions of the medial column, then the term "field" is better than "nucleus" to signify the continuity of the structures. We see no compelling reason to distinguish the multiple fields of the medial RF in the dorsal-ventral or medial-lateral axes. For our purposes the medial RF column is all the cells with bifurcating anterior-posterior axons that reach the spinal cord, and all the other cells interspersed among them. These run in parallel with the lateral RF column through the medulla and pons, up to the caudal/oral pons border. Along the anterior-posterior axis, there appears to be some minor distinctions within the medial column: the "giant cells" appear part-way through the medulla, there is a cell-body light gap at the medulla-pons transition, and large cells disappear in the oral pons (Newman, 1985; Jones, 1995). Whether this distinctions correspond to anything other than anatomical variation is not clear.

Our choice is though consistent with the RF of simpler vertebrates. In the lamprey, possibly the simplest extant vertebrate, four regions of the RF contain all spinally-projecting neurons, and these form a medial column arranged along the anterior-posterior axis (Dubuc et al., 2008). The lamprey is in many respects the epitome of our argument that the mRF forms a critical part of specialised action selection circuits. Like all vertebrates, the lamprey brain has the three primary divisions into hindbrain, midbrain, and forebrain, with homologues for many major regions of mammalian brains, including the basal ganglia. Yet, as the origin of around

90% of all axons reaching the spinal cord, the lamprey mRF is truly the final arbiter for access to the final common motor pathway.

3 Manipulations of mRF alter actions

An intact mRF is trivially necessary for action selection in the sense that lesions to specific parts of it cause coma and even death in humans (Parvizi & Damasio, 2003). Substantial cytoskeletal lesions have also been found in the mRF of Parkinson's disease patients (Braak et al., 2000). Thus, like the basal ganglia, damage to the mRF may make a significant contribution to the symptomatic motor deficits of this disease.

Early studies showed that stimulation of the RF resulted in motor responses (Magoun & Rhines, 1946). Electrical stimulation of specific mRF regions can elicit locomotion in both mammals and lamprey (Kinjo et al., 1990; Whelan, 1996; Deliagina et al., 2002). Neurons within other regions of the mammalian mRF are critical for the maintenance of posture (Mori, 1987), the control of feeding behaviours (Lund et al., 1998), and the generation of eye movements (Moschovakis et al., 1996). In a comprehensive review, Siegel (1979) found multiple competencies were attributed to the mRF because its neural activity correlated with a wide range of responses to stimuli and with naturally occurring behaviours. He concluded that the only way to reconcile these conflicting data was to assume that mRF neuron activity controlled the specific muscle groups required to perform the behavior or response being tested.

These studies are all consistent with Kuypers' classical concept of distinct lateral and medial descending motor control systems (Kuypers, 1964). Drawing together neuroanatomical and lesion studies, he proposed that the cortical-spinal and rubro-spinal tracts, terminating in the lateral spinal cord, were primarily responsible for skilled movements requiring the distal musculature, and that the reticulo-spinal tract, terminating in the medial spinal cord, was primarily responsible for gross movements requiring the proximal (or axial) musculature. Lesions of the medial system do not affect skilled movement, but do impair motor performance; conversely lesions of the lateral system (or decortication) partially impair skilled movement, but do not impair overall motor performance (Iwaniuk & Whishaw, 2000). The behavioural repertoire of the decerebrate animal and the lamprey are thus both consistent with them only having Kuypers' medial system intact.

4 Inputs to the mRF

A substrate for action selection should have access to all the information necessary to compute an appropriate subsequent action. Numerous studies have demonstrated mRF neurons responding to a wide variety of stimuli, and many respond to multiple sensory modalities (Siegel, 1979; Scheibel, 1984). Classically, the small neurons in the lateral brainstem — the parvicellular area — were thought to relay sensory input to the medial brainstem (Scheibel & Scheibel, 1967). However, neurons in the parvicellular area receive input from a limited range of sensory sources (Shammah-Lagnado et al., 1992), and many sensory systems provide primary or secondary afferents directly to the mRF.

The mRF receives input from each of the body's sensory, pain, vestibular (balance), visceral (organs), proprioceptive (muscle and joint), cardiovascular, and respiratory systems. Many of these have been demonstrated anatomically. Direct inputs have been traced from secondary nuclei in the whisker (Kleinfeld et al., 1999), auditory (Cant & Benson, 2003), and vestibular systems (Yates & Stocker, 1998). The proprioceptive information carried by the ascending dorsal column is directly relayed to the mRF via collaterals from the gracile and cuneate nuclei (Salibi et al., 1980). And the spino-reticular tract and collaterals from the spinothalamic tract, the primary routes for pain signals to the brain, are a major source of fibres reaching the mRF (Fields & Basbaum, 1978).

These anatomical inputs are consistent with the multi-modal responses recorded from mRF neurons. Individual neurons respond to somatic stimuli (Segundo et al., 1967), and many respond to the stimulation of multiple body locations (Bowsher, 1970; Schulz et al., 1983). A recent study of freely moving rats has shown that a single mRF cell can respond to visual, vestibular, olfactory, auditory, and tactile stimuli (Martin et al., 2007). Remarkably, some presentations evoked sustained activity for seconds after the stimulus was withdrawn.

Such extensive activity may be a direct motor command elicited by the stimulus. Single lamprey reticulo-spinal neurons have a sub-threshold response linearly related to the force of mechanical stimulation applied to the head, but supra-threshold stimulation evokes sustained spiking that lasts for several minutes (Prisco et al., 2000). Sustained spiking by a set of responsive reticulo-spinal cells initiates locomotion by driving the spinal cord central pattern generators (Dubuc et al., 2008). The somatic stimulation is directly relayed to the reticulo-spinal cells by the dorsal trigeminal nerve (Prisco et al., 2000), showing that mRF cells can translate saliency of sensory information directly into motor activity.

Internal state changes also activate mRF neurons. Experimental manipulations of the cardiovascular (blood pressure and cardiac rhythm) and respiratory (rhythm, lung inflation and deflation) systems all activated mRF neurons (Langhorst et al., 1983). Again, many of the recorded neurons showed responses to manipulations of both systems. Moreover, a combined study showed many mRF neurons respond to stimulation of multiple somatic regions and to manipulation of both cardiovascular and respiratory systems (Langhorst et al., 1996). Thus, it seems the mRF has access to all information made available by an animal's external and internal sensory and monitoring systems. Moreover, because these inputs converge on single neurons, they are in a position to extract correlated input, providing a basis for the computation of an action's salience.

5 Outputs of the mRF

A substrate for action selection should also be able to express the outcome of the selection competition. The majority of neurons in the mRF project extensively to all levels of the spinal cord and to the cranial nerves (Torvik & Brodal, 1957; Eccles et al., 1976; Jones, 1995). Axons of individual reticulo-spinal neurons can contact multiple spinal levels on both sides of the spinal cord (Peterson, 1979). Recent studies have shown the majority of reticulo-spinal neurons synapse on spinal inter-neurons (Matsuyama et al., 2004). The anatomy of the mRF's output is thus consistent with the ability to control the axial musculature (trunk, limbs, neck) and the face.

Reticulo-spinal neurons have direct control over the activity of central pattern generators (CPGs) located in the spinal cord (Matsuyama et al., 2004) and the brainstem (Lund et al., 1998). The control of lamprey locomotion and posture is particularly well established. CPGs located in each spinal segment burst fire on alternate sides to contract the muscle fibres on each side of the body, with each CPG bursting in an overlapping sequence along the spinal cord, causing the undulating wave of motion that propels the lamprey (Grillner et al., 1995). Swimming initiated by any stimulus is preceded by bilateral activity of reticulo-spinal cells, and total activity correlates with locomotion intensity (Deliagina et al., 2000). (Similarly, though the details remain poorly worked out, Noga et al. (2003) have provided evidence that mRF reticulo-spinal neurons directly drive the putative mammalian locomotion CPG). Asymmetry in the left-right mRF activity levels encodes turning towards the side with the greatest activity (Deliagina et al., 2000).

Changes in lamprey posture occur either on its long axis (tilt) or around the long axis (roll). Rolling to one side causes activity in a group of mRF cells on the opposite side that return the lamprey to dorsal side up, with the maximum number of active cells corresponding to the maximum displacement from vertical (90° of roll). Tilting is corrected by two bilateral groups

of mRF cells, one firing to correct for upward tilt, the other to correct downward tilt; both have maximum activity at maximum displacement from horizontal (Deliagina et al., 2002).

Individual lamprey reticulo-spinal cells, like their mammalian counterparts, project to different combinations of spinal neuron classes. This in turn correlates with the wide variety of spinal interneuron activity patterns elicited by stimulation of single reticulo-spinal cells (Dubuc et al., 2008). Yet each reticulo-spinal cell has the same effect on each spinal segment it projects too (Deliagina et al., 2002). Thus, there is evidence not only that individual mRF neurons contact structures able to directly express action, but also that their activity levels may encode the degree of behavioural activation, and that asymmetry in their activation encodes both movements and postural changes.

6 Internal circuitry of the mRF

The effects of manipulations of the mRF on behaviour and its external connectivity together make a compelling case for the involvement of the mRF in action selection. Demonstrating that it is able to represent and resolve action competitions is impeded by the lack of a clear picture of its internal anatomy. We describe here our recent work to solve this problem.

6.1 Known anatomy of the mRF

Classic Golgi staining work by the Schiebels (Scheibel & Scheibel, 1958, 1967) showed the existence of giant-bodied neurons with bifurcating axons and disc-like radial dendritic trees. They proposed that the giant neurons were arranged along the rostro-caudal axis like "a stack of poker-chips". Others have repeatedly described similar cells using a variety of staining techniques (see e.g. Valverde, 1961; Ramon-Moliner & Nauta, 1966; Bowsher & Westman, 1971; Newman, 1985). However, little work had been done to integrate more recent anatomical studies of the RF into a coherent picture of its internal structure. Therefore, we conducted an extensive literature review, leading us to propose the following structural organisation (Humphries et al., 2006a).

We identified two main neuron classes. The *projection* neurons extend a bifurcating axon, predominantly sending the major branch caudally to the spinal cord and the minor branch rostrally toward the midbrain (the giant neuron of the Scheibels' Golgi studies belongs to this class). They make excitatory contacts on their targets, mostly via collaterals regularly branching from the main axon. Typically medium-to-giant in size, projection neurons have a characteristic radial dendritic field extending in the coronal (vertical, medio-lateral) plane but limited in the rostro-caudal axis. The dendrites thus seem positioned to sample from the multiple fibre tracts traversing the RF along the rostro-caudal axis, carrying the axons of many spinal, cortical, and sensory systems. Figure 2a shows the spatial relationships between these tracts, and the projection neurons' dendritic fields and axon trajectories. The *inter-neurons* project their axon almost entirely within the RF, predominantly along the medio-lateral axis, and make inhibitory contacts with their targets. There is good functional evidence for localised intra-mRF inhibition (Holmes et al., 1994; Iwakiri et al., 1995).

We proposed that mRF neurons are arranged into a series of stacked *clusters* (Figure 2b), each comprising a mix of projection and inter-neurons, and each delimited by the initial collateral from the projection neurons' axons — which occurs roughly 100μm from the initial bifurcation. In other words, a cluster's rostral and caudal borders are defined by the first collateral in those directions from the projection neurons' axons. Thus, the inter-neurons project only within the cluster, and the projection neurons only contact neurons outside the cluster. This cluster structure is replicated on both sides of the midline (on both sides of the raphe nuclei in Figure 1b).

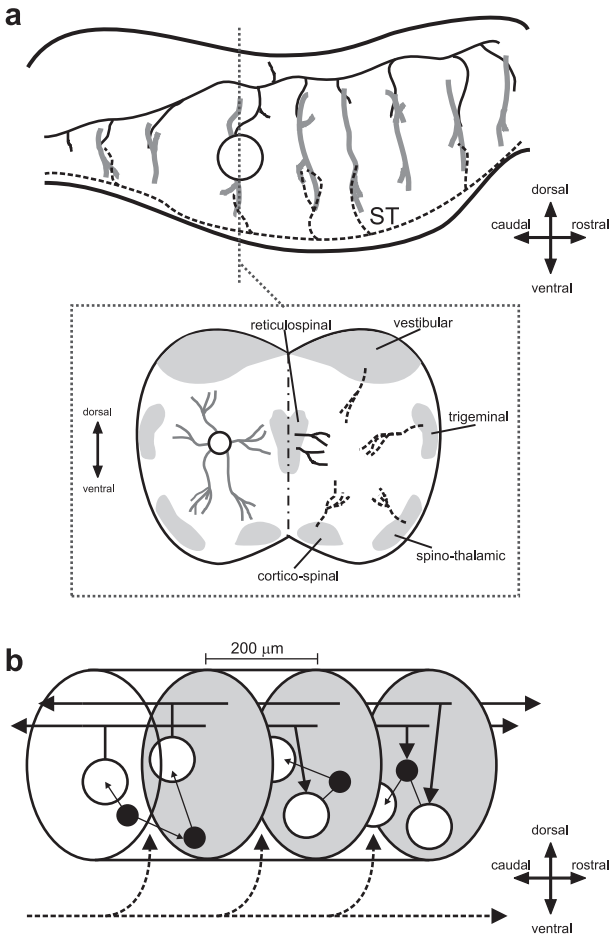

Figure 2: Anatomical organisation of the vertebrate medial reticular formation (mRF). (a) Organisation of the fibre tracts and orientations of the projection cells. The cartoon sagittal section of the brainstem shows the dendritic trees (thick grey lines) of the projection neurons (one neuron body shown, open circle) extending throughout the mRF along the dorso-ventral axis but extending little along the rostro-caudal axis. These dendritic trees contact axon collaterals of both passing fibre systems (black dashed line) and far-reaching axons of the projection neurons (the axon of the depicted neuron body is shown by the black solid line); the example fibre system is the spinothalamic tract (ST). A cartoon coronal section through the brainstem illustrates the radial dendritic tree of the projection neurons in this plane, with dendrite branches oriented towards axon collaterals emanating from the passing fibre tracts (grey regions). (b) The proposed mRF organisation: it comprises stacked clusters (3 shown) containing medium-to-large projection neurons (open circles) and small-to-medium inter-neurons (filled circles); cluster limits (grey ovals) are defined by the initial collaterals from the projection neuron axons. The projection neurons' radial dendritic fields allow sampling of ascending and descending input from both other clusters (solid black lines) and passing fibre systems (dashed black line). The inter-neurons project within their parent cluster.

6.2 An anatomical model of the mRF

In Humphries et al. (2006a) we specified a *stochastic* model that generated a network with the proposed cluster organisation. Six parameters completely describe the network's structure. Two parameters determine the size of the network: each of the N_c clusters has n neurons (the total number of neurons is thus $T = N_c \times n$). One parameter determines the class of neuron: a certain proportion ρ of neurons in each cluster are deemed to be the projection neurons, the remainder are inter-neurons.

The other three parameters describe the connectivity and thus define the links between the neurons. The probability of each projection neuron contacting a given cluster is $P(c)$. This models the probability of the projection neuron's axon extending a collateral into that cluster. If a collateral is extended, then $P(p)$ is the probability of the projection neuron forming a connection with any given neuron in that cluster. Finally, $P(l)$ denotes the probability of an inter-neuron forming a connection with any other given neuron in its own cluster. We also proposed an alternative generating model for the cluster structure, based on the stochastic model, in which the neurons were wired together by a procedure analogous to the neural development process (Humphries et al., 2006a); we refer to them collectively as the anatomical model.

6.3 Structural properties of the mRF

Quantifying anatomy in this way generates useful, and often surprising, insights of its own accord, as well as providing a sound basis for exploring dynamics of the neural system. First, just by specifying a set of parameters sufficient to describe its structure we can identify missing data. Estimates for the number of clusters N_c, number of neurons per cluster n, the proportion of projection neurons ρ, and the probability of contacting a cluster $P(c)$ could be determined from available anatomical data (Humphries et al., 2006a). The synaptic connection parameters $P(p)$ and $P(l)$, on the other hand, do not have supporting values in the literature, and thus these were free parameters of the mRF anatomical model.

Studying the model across the parameters' ranges then informs us of the range of topologically distinct classes that the anatomy could fall in to. And having identified the possible classes, we can examine why the anatomy may have evolved to this state. We found that, to the extent it captures the mRF's organisation (and for all realistic values of the parameters given above), the anatomical model predicts the mRF is likely to be a *small-world*, but not *scale-free*, network at the individual neuron level (Humphries et al., 2006a). A small-world network has two defining properties: its nodes are more clustered — more locally inter-connected — than would be expected if the same number of total links were made at random; its nodes are also linked by shorter paths than would be expected if the same number of total links were made uniformly. Small-worlds have been found in many real-world networks, including connections between airports, electricity grids, and food webs, suggesting that some general organisational principle is at work (see Albert & Barabasi, 2002, for review).

Why then is the mRF a small-world network? What functional advantages does it bestow? The structural properties of a small-world network imply certain dynamic properties — of rapid cross-network synchronisation, consistent stabilisation, and persistent activity — that may all be critical to the representation and resolution of competition between actions (briefly reviewed in Humphries et al., 2006a). However, the presence of a small-world may also imply structural constraints. For example, Mathias & Gopal (2001) demonstrated that, in a one-dimensional ring of nodes, small-world networks were formed when attempting to the find the optimal trade-off between total wire length and shortest path length.

Could the cluster structure have thus evolved to optimise neural connectivity? Other neural structures appear to have optimised component placement to minimise total wiring length (Cherniak, 1994). This may be a priority of neural design, as it reduces energy usage during creation and maintenance of axons, and signal propagation along them (Laughlin & Sejnowski,

2003). We therefore asked if the cluster structure could reduce total axonal wire-length, testing the two hypotheses illustrated in Figure 3. First, the cluster structure could reduce the wiring connecting together neurons fixed in particular positions: that is, the neuron placement is critical, for example due to the position of input fibres, and the wiring is arbitrary to some extent. Second, the cluster structure could reduce the length of wiring required to achieve a particular network configuration: that is, the internal wiring is critical and the neuron position is arbitrary to some extent. The second hypothesis is akin to the problem of component placement optimisation (Cherniak, 1994).

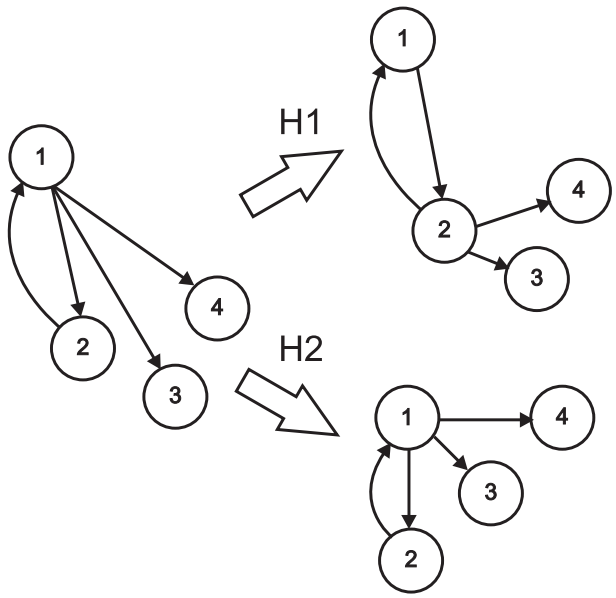

Figure 3: Two hypotheses of wiring efficiency. The total wiring length of a network (left) can be reduced in two ways. Hypothesis 1 (H1): if the node placement is crucial — due, say, to the position of the inputs to the network — then the wiring length may be minimised (for the same number of links) by moving the links while ensuring each node remains connected. Hypothesis 2 (H2): if the network configuration is crucial, then the wiring length may be minimised by moving the nodes while maintaining the links.

A set of cluster model networks were generated by varying the synaptic connection probabilities over their plausible ranges. Each neuron was assigned a three-dimensional position within the estimated volume of its anatomical cluster. The total axonal wire length was then computed by calculating the Euclidean distance between each pair of connected neurons and summing over all pairs. For each generated cluster model network, two random networks were created to test each of the two hypotheses: first, a *randomly-wired* network, to test if total wire length for the clustered neurons was less than for the randomly-wired neurons; second, a *randomly-positioned* network (ignoring cluster boundaries), to test if total wire length for the clustered neurons was less than for randomly-positioned neurons.

We found that total wire length for the cluster structure was greater than that of the corresponding randomly-wired network, but less than that of the corresponding randomly-positioned network, for every generated cluster model network (Humphries et al., 2007). Therefore, we concluded that the cluster structure of the mRF does not specifically reduce axonal wire length for a given neuron placement (first hypothesis), but wiring length is comparatively reduced for a given wiring configuration (second hypothesis), and thus may explain why the cluster structure has evolved.

7 Action representation in the mRF

Having examined both the structure of the mRF and possible reasons for the structure's existence, we turn now to the question of how that structure supports the representation and resolution of competition between actions. We begin by reviewing existing ideas on the functional organisation of the mRF.

7.1 Functional organisation of mRF

Many researchers have seen no functional organisation in the mRF. Early studies report stimulation of the RF resulting in either postural inhibition via descending projections to the spinal cord (Magoun & Rhines, 1946), or desynchronisation of the cortical EEG via ascending projections (Moruzzi & Magoun, 1949). This latter result famously gave rise to the concept of the ascending reticular activating system [†]. These results, along with the wide array of overlapping sensory inputs to the mRF that lack a demonstrable organisation (Segundo et al., 1967), led some researchers to assert that mRF output was only a function of general sensory arousal (Scheibel & Scheibel, 1967; Hobson & Scheibel, 1980).

Though still widely discussed, the division of the RF into just two systems (ascending, facilitatory and descending, inhibitory) was refuted soon after by Sprague & Chambers (1954). By applying micro-stimulation at or near threshold to mRF neurons of awake animals, they were able to elicit a multitude of single and multiple limb movements. They saw little of the reported postural inhibition. More recent micro-stimulation studies of the mRF in the medulla have demonstrated both multiple movement and multiple muscle responses following the injection of short trains of low-amplitude current pulses (Drew & Rossignol, 1990). (The same micro-stimulation applied to the lateral medullary RF did not consistently result in movement, further evidence that the mRF is the substrate of action selection in the brainstem). Neurons of the mRF thus have functionally specialised rather than general outputs.

How then might the mRF neurons be functionally organised? They are not topographically organised to match patterns of sensory input. No topographical projections to the mRF have ever been convincingly demonstrated, despite numerous attempts to find them (Segundo et al., 1967; Bowsher, 1970; Eccles et al., 1976). Groves et al. (1973) reported that tactile stimuli were encoded in rough somatotopic form in the RF, but the methods used could not distinguish between recording from neuron bodies and from passing fibres, and their recording sites covered the whole coronal extent of the brainstem (Angel, 1977). On the output side, Peterson (1979) proposed a crude anterior-posterior topography of the reticulo-spinal projections, based on the combinations of elicited responses in motorneurons related to the neck, back, forelimb, and hindlimb. However, other studies of this system found no anatomical topography of the spinal projections (Torvik & Brodal, 1957; Eccles et al., 1976), and neurons responding during movement of those body parts seem randomly inter-mingled (Siegel & Tomaszewski, 1983).

Beyond the work just detailed, there is little direct evidence on the functional organisation of the mRF. Rather, we can infer some potential forms of organisation from combining electrophysiology and anatomical data. We have thus explored the potential methods of representing and resolving action selection through simulation of new computational models. Given the paucity of guiding data, we cannot reach any firm conclusions here. Nonetheless, constructing and simulating computational models allows us to enumerate and illustrate the potential forms of action selection supported by the mRF.

[†]As noted by Blessing (1997), this concept has been particularly difficult to remove from the EEG literature and neurobehavioural textbooks, despite its vagueness. The location and strength of stimulation applied by (Moruzzi & Magoun, 1949) would have activated a large range of disparate structures and fibres of passage, thus in no sense is there some identifiable "activating system" located in the upper RF.

7.2 Action selection at the cluster level

We could hypothesise that clusters in the mRF are functionally as well as anatomically distinct and are, therefore, the representational unit in the brainstem action selection system (Humphries et al., 2007). Then the regions of cranial nerve nuclei and the spinal cord targeted by a cluster's projection neurons express the action selected by the mRF system. A variety of evidence supports this hypothesis.

Sensory input to the mRF may be arranged on a cluster-basis. Neighbouring mRF neurons have overlapping somatic sensory fields, but distal pairs do not (Schulz et al., 1983), and individual mRF neurons respond to multiple modalities (Martin et al., 2007). Neighboring pairs of mRF neurons have correlated activity in both the awake (Siegel et al., 1981) and anaesthetised (Schulz et al., 1985) animal. In both studies, all neuron pairs separated by more than 200 μm showed no correlations. Many projection neurons have correlated activity with multiple movements, and the activity of near-neighbour projection neurons often does not correlate with the same movement or set of movements (Siegel & Tomaszewski, 1983). There is thus evidence for neighbouring neurons having common activity patterns, and that those shared patterns are on the scale of single anatomical clusters. The correlated activity between near-neighbour projection neurons in waking animals (Siegel et al., 1981) would lead to the simultaneous recruitment of multiple muscle groups and movement types. We therefore proposed that sufficient activation of a cluster's projection neurons would lead to a co-ordinated behavioral response (Humphries et al., 2007).

There is evidence for intra-mRF localisation of actions and competition between them. Stimulation of a medial pons region inhibits locomotion elicited from medial medulla (Iwakiri et al., 1995). GABA antagonists injected into this medulla mRF region initiate locomotion (Kinjo et al., 1990), suggesting a local inhibitory circuit is involved. Separate groups of mRF cells seem to control motorneurons projecting to the trunk and hindlimb muscles (Szokol et al., 2008). We thus used simulations of a population-level model to explore possible action representations and competition resolution, assuming that the cluster itself was the key representational element.

7.2.1 Single-action configuration

The output of each cluster could represent a complete action. The maximum number of representable actions is thus just N_c, and grows by 1 with each additional cluster. Action selection in such a circuit requires a winner-takes-all (WTA) competition, to reduce the set of potential actions to just the most appropriate one. To form a WTA-like circuit in a fully connected cluster structure (Figure 4b) the projection neuron population of each cluster must receive greater input (i.e. inhibition) from its corresponding inter-neuron population than from the combined input of its inter-cluster connections; otherwise the net effect of any sensory input to the network would be excitatory (in a symmetrical network).

One option for implementing such a WTA-like network is that the inhibitory *intra*-cluster connection from the cluster's inter-neuron population to its projection neuron population is very strong compared to any excitatory *inter*-cluster projections. Thus input from other clusters to both the inter-neuron and projection neuron populations will result in a net inhibitory effect on the projection neuron population. Indeed, synapse counts from projection neuron dendritic trees suggest this may be the case. Roughly 45% of the synapses on a projection neuron are GABAergic (Jones et al., 1991) — and thus inhibitory — and inter-neurons are the primary (perhaps only) source of GABAergic input (Holmes et al., 1994). Yet the proportion of inter-neurons to projection neurons is much smaller than this value. Thus, an inter-neuron input to a projection neuron would have a disproportionately larger effect than a projection neuron input, as it forms more synapses.

Simulation of a population-level model with such an architecture shows that the cluster

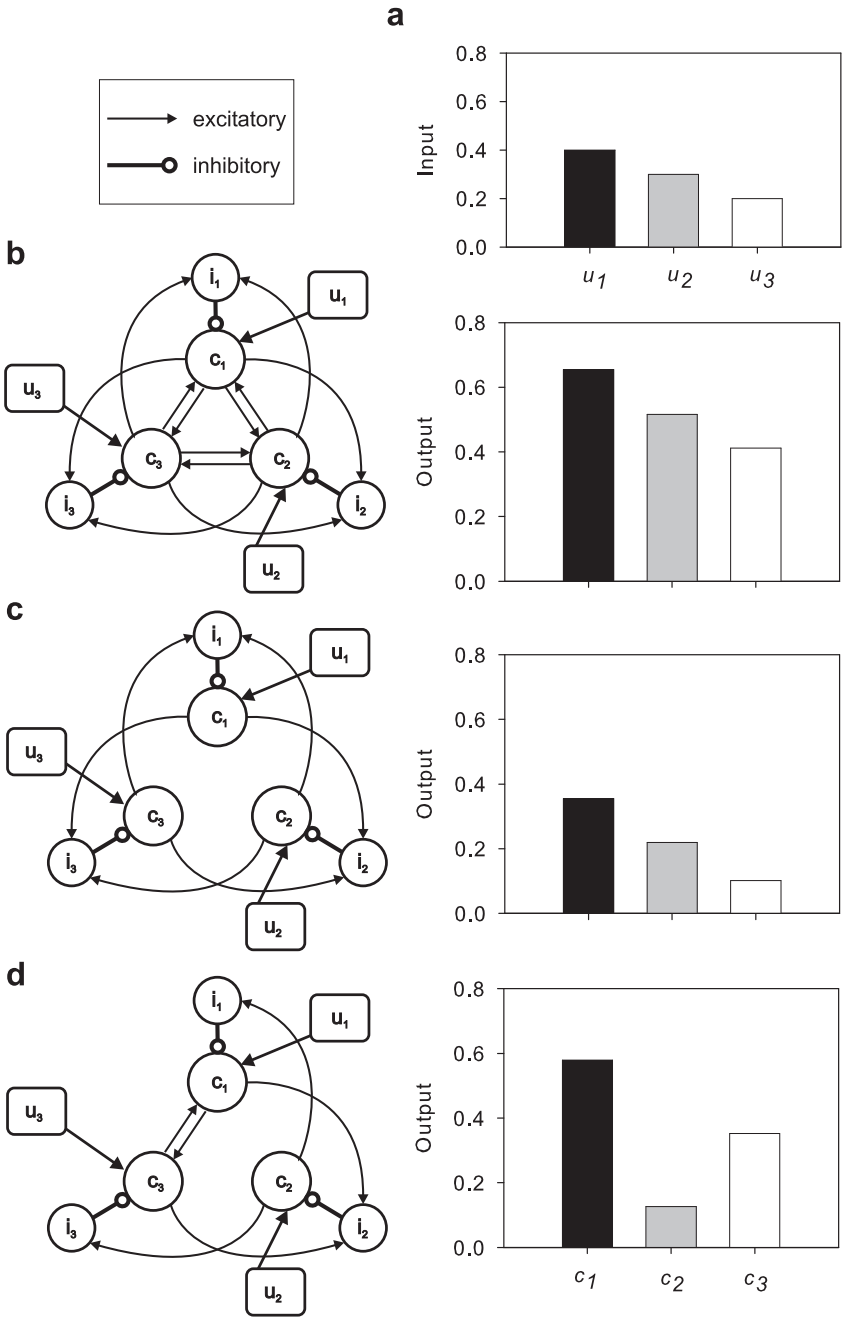

Figure 4: Potential configurations of the mRF cluster architecture as an action selection mechanism. (These illustrate connection schemes, not relative physical location.) Each configuration was instantiated as a population-level model and given the input values in (a). Cluster-specific total afferent input (u_n) targets only the cluster's projection neuron population (c_n), whose outputs drive some form of coherent behavioral response to that particular combination of input from sensory, pain, respiratory etc systems. A cluster's inter-neuron population (i_n) contacts only the projection neuron population. (b) Each cluster's projection neuron population represents a single action. Competition between actions is putatively resolved by a winner-takes-all (WTA) type circuit, formed by stronger relative weighting of the inhibitory within-cluster inter-neuron connections (open circles) than of the excitatory projection neurons connections to other clusters (arrows). However, the simulation outputs show that such a single-action configuration does not act as a winner-takes-all (WTA) circuit, but as an amplified relay of the inputs. (c) With all inter-cluster excitatory connections to projection neurons removed, a traditional WTA circuit seems to be created; yet the simulation outputs show that this does not form a WTA circuit either. Moreover, it does not account for the existence of the long-range axons. (d) Each cluster's projection neuron population represents a sub-action. Specific wiring configurations may create a circuit in which the sensory activation of a single cluster recruits other clusters representing compatible (or essential) sub-actions, via the inter-cluster connections between projection neurons. The combination of sub-actions then creates the coherent behavioral response observed in the animal. In simulation, the sub-action configuration results in appropriate selection for the given inputs: activation of cluster 1 (c_1) results in concurrent recruitment of cluster 3, and inhibition of cluster 2.

structure can implement soft selection — that is, simultaneous selection of more than one action. Some thresholding of output would be required to implement hard selection — a true WTA competition— a threshold possibly set by the amount of cluster output required to sufficiently activate target neurons in the cranial nerve nuclei and spinal cord. However, the outputs for this simulation are, roughly, just the ratio of the corresponding inputs, which reduces the mRF architecture to a simple relay system.

Removing the excitatory inter-cluster connections to the projection neurons leaves only the inter-cluster projections to inter-neurons and thus would seem more able to implement a WTA circuit (Figure 4c). However, simulation of this altered model shows it does not implement a WTA circuit either: the output of the clusters are little different from their input values. The presence or absence of the long-range connections appears to have little impact on the mRF's ability to act as a selection mechanism if each cluster is assumed to represent a single action.

7.2.2 Sub-action configuration

The existence of abundant long-range connections between projection neurons is not in doubt, and thus should be accounted for in a functional model of the mRF. It is possible that in the mRF some cluster-to-cluster projections preferentially target the inter-neuron populations, while others preferentially target the projection neuron populations. The output of a single cluster may then simultaneously inhibit some clusters and excite others. Excitation of a target cluster could correspond to recruitment of a compatible, perhaps essential, component of an action. Conversely, inhibition of a target cluster could correspond to the prevention of an incompatible, perhaps dangerous, component of an action. The output of each cluster thus activates a *sub-action*, a component part of a coherent behavior. This has a representational advantage over a single-action representation: the upper limit of potential unique sub-action combinations is $2^{N_c} - 1$, and grows by 2^{N_c-1} with each additional cluster.

An example of a sub-action configuration in the same three cluster model is shown in Figure 4d. In simulation, the outputs of both clusters 1 and 3 exceed the value of their inputs, and both have considerably greater output than cluster 2 (which has a much reduced output compared to its input). Thus, in this configuration, the output pattern is consistent with sub-actions 1 and 3 being activated, and sub-action 2 being suppressed.

Even in this simple example we can see that, while reduced, activity in the "losing" cluster(s) will rarely disappear completely. How then does this residual activity not affect the command encoded by the most active clusters? There is evidence that spinal cord circuits further clean-up the descending command signals, resulting in clean motor responses. Models have shown that the lamprey spinal locomotion CPG could band-pass filter its inputs from the mRF: the CPG oscillations — and hence swimming — are turned on within a range of mRF activity, but are off if the input is too low or too high (Jung et al., 1996). Conversely, the spinal circuit can amplify small differences in the descending commands: the asymmetry in the bilateral mRF activity encoding turning is a small percentage of the total activity, but the spinal circuits turn this into muscle contraction on only one side of the body (Deliagina et al., 2002). If all potential sub-action combinations could be similarly cleaned up by the spinal cord circuit(s), then only the ordering and total activity of the outputs is important.

Having demonstrated that the sub-action configuration works in principle, we did a preliminary assessment of its robustness over a range of inputs. The configuration depicted in Figure 4d supports just two actions, given that selection is based on the ordering of the output values: one action is clusters 1 and 3 both more active than cluster 2; the other action is cluster 2 more active than the others. We found that sub-action selection is robust over a wide range of inputs, with the majority of input combinations to the three clusters resulting in correct selection of either clusters 1 and 3 together, or cluster 2 alone (Humphries et al., 2007). The incorrect selections occurred for input combinations that were either all roughly equal, or when input to cluster 2 was roughly equal with either cluster 1 or 3 (and the other was low). Thus,

this simple model of a configuration of the mRF's anatomy lacks a mechanism for resolving selection competitions between closely-matched inputs.

7.3 Distributed action representation in the mRF

The proposed mapping of clusters to actions (or sub-actions) is not the only possibility: the anatomical organisation does not necessarily map directly onto a functional organisation. An alternative is suggested by a re-interpretation of the model of Kilmer et al. (1969). What if the actions are represented by the parallel long axons of the projection neurons, rather than the clustered neuron bodies? That is, a few projection neurons from each (or many) of the clusters contribute their axons to a group which represents a single action (or sub-action). The activity transmitted by that axon group to the spinal cord thus recruits the appropriate musculature for the action.

Remarkably, the general structure of the Kilmer et al. (1969) model is still consistent with the known organisation of the projection neurons in the mRF. We thus tested this model in embodied form (the original authors' long-held wish) as a controller for a robot in a survival task, to evaluate the possibility of it forming an action selection mechanism (Humphries et al., 2005). We found the model as originally proposed could not sustain action selection, but, by evolving the model with a genetic algorithm, certain configurations could be found that did. Thus, the mRF may also be able to support action selection based on parallel representation of those actions. (However, inevitably, given its age, several aspects of the model were incorrect or implausible, or omitted features known from more modern studies of the mRF; this was in part the impetus for our work reviewed here).

Some evidence for this scheme has been found in studies of grooming behaviour under progressive decerebration (Berridge, 1989). The brainstem alone is sufficient to generate and sequence all elements of a stereotypical chain of grooming actions. Decerebration cuts placed progressively lower in the brainstem did not delete whole elements of that syntax, as might be predicted by the sub-action hypothesis. Rather, as more of the brainstem was lost, the sequencing of the whole chain became degraded, pointing to a widely distributed representation across the whole network.

7.4 Reconciling cluster-based and distributed action selection

A distributed representation of actions faces particular problems with generalisation and separation: similar patterns of sensory input should recall similar activity patterns (a loud noise to left should recruit motor commands for left-orienting irrespective of the exact amplitude) and different patterns of sensory input should recall substantially different activity patterns (corresponding to different motor commands).

We show this using a full dynamic version of the anatomical model, in which each neuron, rather than each population as above, is instantiated as a rate-coding unit (model details are given in the Appendix). Figure 5a shows that distributed input to the mRF does indeed struggle to generalise similar inputs and separate dissimilar inputs, if we read-out neuron output across all the projection neurons. If instead we read-out total activity at the cluster level rather than at the projection neuron level (Figure 5b) then we see no correlation between input and output similarity. Restricting inputs to a per-cluster basis, we find total cluster output has strong correlation between input and output similarity (Figure 5c) — this, being equivalent to the population-level models explored above, shows that the cluster-level action representation schemes can successfully generalise and separate their input space. More interesting is that, for the same input, the projection neuron output from across the whole mRF shows equally strong correlation between input and output similarity (Figure 5d). The model thus suggests a reconciliation of the evidence for cluster-based and distributed representations: anatomically, the clusters are organised to receive common sensory inputs that then recall distributed action

representations, and the synchrony of within-cluster cells in the mRF is caused by common sensory input.

Both of our conclusions here — cluster-based inputs increase similarity encoding, projection neuron read-out as good as cluster-based read-out — may not strike the reader as particularly surprising. Switching to a lower-dimensional input space, and driving many neurons with the same input, may inevitably improve the correlation between input and output similarity. But that misses two key insights: first, that input-output similarity is a problem at all; second, that only by studying the anatomical and dynamic models did we find a basis for reducing the input space. Future work will elaborate and further probe this reconciling hypothesis. For example, representational capacity is unknown, and depends on the threshold between "similar" and "dissimilar", potentially set by circuits in spinal cord.

8 Integration of the action selection systems

The mRF cluster model's inability to resolve competitions between (roughly) equally salient actions suggests the tantalising possibility that more complex action selection systems evolved partly to cope with ambiguous situations — complex systems which could, of course, encompass the basal ganglia. We sketch here how the proposed basal ganglia and mRF action selection mechanisms may interact.

There are three candidate control architectures that could encapsulate the combined action selection system, illustrated in Figure 6. First, a strict hierarchy of control, in which decisions made at higher levels limit those of lower levels. This is often taken to imply that lower levels encode more elementary actions than higher levels. The modelling work reported above supports this, and it is consistent with the decomposition of the control of grooming in rats: an intact basal ganglia is necessary to correctly sequence the components of the grooming routine (Berridge & Whishaw, 1992), but each component is encoded entirely within the brainstem (Berridge, 1989). The basal ganglia's primary route to the brainstem is via the pedunculopontine nucleus (PPN), which itself projects heavily into the mRF (Jones, 1990; Delwaide et al., 2000). Some functional and anatomical data, therefore, support a hierarchical architecture in which the basal ganglia dictates control of the mRF output (Figure 6a).

The second alternative is a layered architecture, such as Brooks' subsumption architecture (Brooks, 1991). Increasingly complex computations are supported by higher layers of this architecture and, while all layers compute in parallel, higher layers can veto the output of lower layers. There is considerable evidence that the sensorimotor mappings within the vertebrate brain are organised in this fashion (Prescott et al., 1999). Do basal ganglia and mRF circuits thus run in parallel, with basal ganglia output able to veto mRF if necessary? (Figure 6b). The motor effects of Parkinson's disease (Zigmond & Burke, 2002), in which the basal ganglia are jammed in "off" mode, suggests it is continually vetoing lower layers. In addition, the paradoxical results of Parkinson's disease interventions point to the existence of parallel systems. Following drug treatment with L-DOPA, parkinsonian patients regain voluntary movement but continue to have problems controlling their axial musculature (Lakke, 1985), which is under the direct control of the mRF. Moreover, surgical interventions often destroy sections of the basal ganglia: the patients' recovery of voluntary movement after surgery (Marsden & Obeso, 1994) thus suggests destruction of the basal ganglia releases other action selection systems to work. Anatomically, this design has potential: the basal ganglia and mRF do receive separate inputs, and the basal ganglia can bypass the mRF and access the spinal cord via the PPN. However, this basal ganglia-PPN-spinal circuit may be limited to postural control only (Takakusaki et al., 2004).

The third alternative is a combined hierarchical/layered system, given the data reviewed above that support each of those elements. In addition, a combined system incorporates some form of heterarchy in the control decomposition, in that lower levels can influence higher levels.

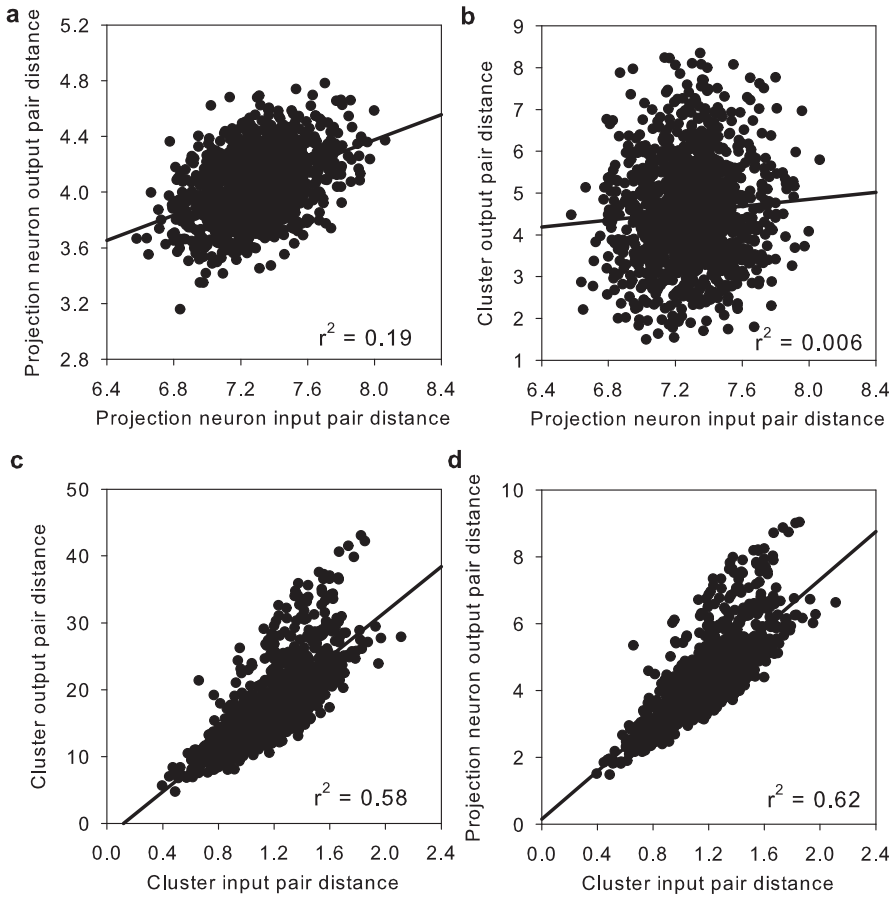

Figure 5: The cluster model of the mRF can encode similarity of its cluster inputs only. A full mRF anatomical model was built with 8 clusters and 40 projection neurons per cluster, and instantiated as a dynamic model using rate-coding neurons (see Appendix). We tested the model with randomly generated input vectors, each element taking a value in the interval $[0, 1]$. We provided vectors of input to each projection neuron (panels a,b) or to each cluster (panels c,d) — in this case, all projection neurons in the same cluster received the same input; 50 input patterns were tested for each. At equilibrium, we read out the vector of projection neuron output (panels a,d) or total cluster output (panels b,c). We computed the Euclidean distance between each pair of input vectors and between the corresponding pair of output vectors: the closer the pair, the more similar the vectors. For each input-output combination, this gave $(50 \times 49)/2 = 1225$ unique pairs of input-output similarity, plotted in each panel. A perfect correlation across all pairs would show that relative input similarity was encoded perfectly by relative output similarity. We found that distributing input across all projection neurons resulted in weak correlation between input and output similarity for both (a) projection neuron and (b) total cluster output. Distributed input is thus unable to reliably generalise by recalling either similar cluster or projection neuron output. (c) Cluster input and output show a strong positive correlation of similarity: similar input vectors gave rise to similar output vectors, dissimilar input vectors gave rise to dissimilar output vectors. (d) Similarly, cluster input and projection neuron output show a strong positive correlation of similarity.

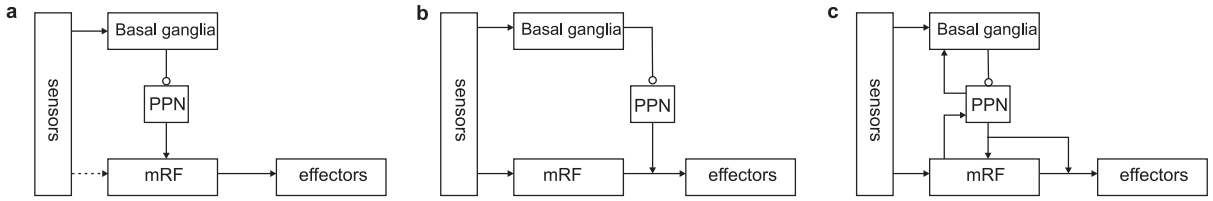

Figure 6: Alternative schemes for integrating the action selection substrates. (a) An hierarchical architecture: lower levels represent increasingly simple actions, selected by the higher layers. This is consistent with the output of the basal ganglia reaching the mRF via the pedunculopontine nucleus (PPN), and with the results of our modelling work. (b) A layered architecture: the mRF and basal ganglia form separate layers in a control system dealing with increasingly complex stimuli, the higher layers being able to veto the output of the lower layers. This design is consistent with the separate sensory input to the basal ganglia and mRF, and with the basal ganglia's access to the spinal cord via the PPN. (c) A combined architecture: the competences of each layer contribute to the whole system. This is consistent with the evidence for feedback pathways within the neural systems, particularly between the PPN and the basal ganglia. Arrows: excitatory pathways; open circles: inhibitory pathways.

Anatomically, the PPN projects extensively into the basal ganglia (Inglis & Winn, 1995), and the mRF may project to PPN (Jones, 1995) — see Figure 6c. There is little research on what these ascending projections may be encoding, though the known properties of the PPN and mRF suggest, respectively, attentional arousal and motor feedback.

9 Further questions about the mRF

The current work is intended to move us closer to an understanding of the neural substrate of action selection in the vertebrate brain. Naturally it has opened up many questions, for which we can only hazard answers. Particularly difficult to understand is how the mRF is successfully wired up to turn patterns of sensory input into appropriate motor output. Questions about wiring have three distinct contributions from evolution, development, and plasticity. How did the mRF evolve through the vertebrate lineage? Does the lamprey embody the original locomotion-dominant solution, suitable for water, later adapted for land-based vertebrates and the greater elaboration of cortex? We know, for example, that mammalian mRF projection neurons receive input from the cortico-spinal pathway (Scheibel, 1984), not present in lamprey, and hence there is not a clean separation between the medial and lateral musculature controlling systems (Iwaniuk & Whishaw, 2000).

How does the mRF input and output reach the right targets during development? At birth, rat mRF already contains all the neurons present in adult. Over the first two post-natal weeks the principal change is a massive growth then reduction in the number of dendritic spines (Hammer et al., 1981), suggesting a rapid phase of axonal wiring then massive pruning. We have already shown that a stochastic over-growth-then-pruning model can generate the proposed adult cluster structure (Humphries et al., 2006a), but this presupposed the presence of cues for axonal growth in the appropriate axes (anterior-posterior for projection neurons; medial-lateral for interneurons), and only addresses the internal structure, not the input-output wiring. A key example of correct wiring is the inputs to ventrolateral medulla, where many projection neurons controlling cardiac and respiratory system muscles are located (Blessing, 1997). Many, but not all, projection neurons from elsewhere in the mRF give off collaterals to this region, presumably to recruit cardio-respiratory changes in synchrony with changes in motor activity; aberrant wiring here would render an animal largely unable to function. Are mRF synapses plastic over the animal's lifetime, beyond initial development? It is often implicitly assumed that all excitatory synapses in the central nervous system are plastic. Plasticity has been indirectly (Breedlove et al., 1979) and directly (Alford et al., 1995) observed at synapses from afferent inputs to projection neurons. Yet when we consider inputs to the ventrolateral medulla, we

again must pause to consider that any such changes would have a direct effect on basic survival.

We looked at the difficulties of successfully wiring up both input-output and internal connectivity by attempting to evolve 'brainstem-only' sub-action guided robots on a simple survival task, in which the robot had to gather food in one location and consume it in another (Humphries & Prescott, 2006). Each robot was controlled by a 6-cluster population-level model, representing 6 sub-actions (4 movement, 2 consumptive), with 8 sensory inputs (4 external, 4 internal). A genetic algorithm attempted to maximise the mean energy of the robot through successful co-ordination of all sub-actions in appropriate contexts, by evolving the wiring within the mRF model and between the sensory inputs and each cluster. We found that reliable wiring could not be evolved, despite trying many different search variants. The few successful evolved models were not robust, relying on a very high rate of energy return from consumed food, and their emergent behaviour was highly stereotyped. Hence this work nicely demonstrated the sheer complexity of the wiring task faced in the real mRF.

Beyond wiring, we have not touched here on the many potential roles for neuromodulators in the mRF. Receptors have been found for serotonin (Stevens et al., 1992; Fay & Kubin, 2000), noradrenaline (Stevens et al., 1994), and acetylcholine (Stevens et al., 1993). Principal sources are of these are, respectively, the brainstem raphe nuclei, subcoeruleus (Jones, 1995), and PPN and adjacent cholinergic cell bands (Jones et al., 1991) — though local cholinergic cells within mRF are also numerous (Jones, 1990; Holmes et al., 1994). Given the wide variety of roles ascribed to neuromodulators in the brain (Krichmar, 2008), any speculation here would be purely idle: serotonin, for example, is particularly strongly implicated in regulating activity of CPGs for whisking Hattox et al. (2003) and locomotion (Jordan et al., 2008); acetylcholine plays a role in initiating locomotion from mRF of medulla (Kinjo et al., 1990). What we do know is that neuromodulation in the mRF comes from both local and top-down sources.

Recent advances suggest we may soon get key information to address both these general questions and the specific hypotheses we have raised. Combined behavioural and neural recording in semi-intact preparations of suitable model species provides unparalleled data on functional organisation. Semi-intact lamprey work has featured heavily in our discussions here; ongoing work on the afferent control of locomotion from mesencephalic and higher structures promises to shed light on the integration of action selection systems (Dubuc et al., 2008). Mesce et al. (2008) have produced compelling evidence that dedicated leech interneurons control components of whole behaviours, and each receive multi-modal sensory input; they drew attention to the strong analogy between this arrangement and the idea of "sub-action" co-ordinating clusters we proposed (Humphries et al., 2007). Wiring of the mRF too is under new scrutiny. Recent work has established genetic markers for specific proteins that identify sub-populations of reticulo-spinal cells for characterisation of their inputs, outputs, and electrophysiology (Bretzner & Brownstone, 2008). Further, there are now mouse lines expressing selective neurotoxins for mRF cells (Kamal Sharma, personal communication), promising future studies relating specific cell loss to effects on behaviour. With this new data, and given the comparatively small numbers of neurons involved, we can test hypotheses of mRF wiring in full-scale models in the near future.

10 Final remarks

The reticular formation is a strange beast: where some see an undifferentiated neuron mass, responsive only to global sensory input, others see a conglomeration of functionally-specific units. Both views contain an element of truth. The dense ascending input and intra-RF connectivity point to a system capable only of responding to stimulation with increased activation. Yet, stimulation of individual neurons within it elicits discrete, repeatable movements. We hope that by proposing the mRF as an action selection system we may unify these disparate views: the dense web of inputs provide the ability to extract correlated sensory information, the internal

connectivity provides the substrate for the co-ordination of behavioural components, and the individual neurons drive the appropriate motor systems.

Our proposals partially rest on the structure of the mRF: if the cluster structure is an accurate depiction of the mRF's internal anatomy, then a likely method of representing and resolving action competitions is that the activity of a cluster's projection neuron population encodes the relative selection of an action component. This sub-action configuration has the advantage of both providing a functional role for the collaterals of the long-range axons, and increasing the representational capacity of the system. It is possible that both clustered and parallel action representations co-exist: competing complex behaviours may be represented by parallel axon activity that recruits the necessary sub-actions for each behaviour by activating the appropriate clusters. Combining these representational schemes with the potential control decomposition across the basal ganglia and mRF makes for a fascinating, if daunting, proposition. At the very least, we hope our work inspires a re-evaluation of the mRF's functional significance.

Acknowledgements
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A Basic form of the computational models

All computational models used leaky rate-coding units: the population-level models (section 7.2) to represent the average firing rate of that population; the full model (section 7.4) to represent the firing rate of a single neuron. The change in activity a is given by

$$\tau \dot{a} = -a + I, \tag{1}$$

where I is the summed, weighted, total of all unit outputs that reach this unit, and τ the time-constant. Output y of the unit is rectified to the interval $y \in [0, 1]$.

A single instantiation of a 3 cluster anatomical model was used to derive the connection parameters of the population-level computational model. Each 100 neuron cluster had 80 projection neurons and 20 inter-neurons. The weights between neural populations were scalars proportional to the total number of connections between them. Details and the specific connection matrices used are given in (Humphries et al., 2007).

A single instantiation of an 8 cluster model was used for the full dynamic model. Each cluster had 50 neurons, with 80% projection neurons. The connection probabilities were set as $P(p) = 0.1$, $P(c) = 0.25$ (the "spatially-uniform" model from Humphries et al. (2006a)), and $P(l) = 0.25$. All excitatory connections had a weight of 0.1; all inhibitory connections had a weight of -0.924. This ensured that the total magnitude of inhibitory and excitatory weights was equal for the network. Unit time constant was set to $\tau = 2$ms (Yen & Chan, 1993). The differential equations were solved using exponential Euler and a time-step of 0.1 ms. The simulations were run until either equilibrium was reached or 1000 time-steps elapsed. Equilibrium was defined as the total change in a over all units on consecutive time-steps being less than 10^{-6}. Every simulation reported here reached equilibrium before the time-step limit.

References

Albert, R., & Barabasi, A.-L. (2002). Statistical mechanics of complex networks. *Rev. Mod. Phys.*, *74*, 47–97.

Alford, S., Zompa, I., & Dubuc, R. (1995). Long-term potentiation of glutamatergic pathways in the lamprey brainstem. *J Neurosci*, *15*, 7528–7538.

Angel, A. (1977). Processing of sensory information. *Prog. Neurobiol.*, *9*, 1–122.

Berntson, G. G., & Micco, D. J. (1976). Organization of brainstem behavioral systems. *Brain Res. Bull.*, *1*, 471–483.

Berridge, K. C. (1989). Progressive degradation of serial grooming chains by descending decerebration. *Behav. Brain Res.*, *33*, 241–253.

Berridge, K. C., & Whishaw, I. Q. (1992). Cortex, striatum and cerebellum: control of serial order in a grooming sequence. *Exp. Brain Res.*, *90*, 275–290.

Blessing, W. W. (1997). *The Lower Brainstem and Bodily Homeostasis*. New York: Oxford University Press.

Bowsher, D. (1970). Place and modality analysis in caudal reticular formation. *J. Physiol.*, *209*, 473–486.

Bowsher, D., & Westman, J. (1971). Ultrastructural characteristics of the caudal and rostral brain stem reticular formation. *Brain Res*, *28*, 443–457.

Braak, H., Rub, U., Sandmann-Keil, D., Gai, W. P., de Vos, R. A., Jansen Steur, E. N., Arai, K., & Braak, E. (2000). Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. *Acta Neuropathol. (Berl.)*, *99*, 489–495.

Braitenberg, V. (1984). *Vehicles: Experiments in Synthetic Psychology*. Cambridge, MA: MIT Press.

Breedlove, S. M., McGinty, D. J., & Siegel, J. M. (1979). Operant conditioning of pontine gigantocellular units. *Brain Res Bull*, *4*, 663–667.

Bretzner, F., & Brownstone, R. M. (2008). Characterization of genetically identified reticulospinal pathways. In *2008 Neuroscience Meeting Planner*, (p. Program No. 576.3). Washington, DC: Society for Neuroscience.

Brooks, R. A. (1991). New approaches to robotics. *Science*, *253*, 1227–1232.

Cant, N. B., & Benson, C. G. (2003). Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. *Brain Res. Bull.*, *60*, 457–474.

Cherniak, C. (1994). Component placement optimization in the brain. *J. Neurosci.*, *14*, 2418–2427.

de Bono, M., & Maricq, A. V. (2005). Neuronal substrates of complex behaviors in C. elegans. *Annu Rev Neurosci*, *28*, 451–501.

Deliagina, T. G., Zelenin, P. V., Fagerstedt, P., Grillner, S., & Orlovsky, G. N. (2000). Activity of reticulospinal neurons during locomotion in the freely behaving lamprey. *J Neurophysiol*, *83*, 853–863.

Deliagina, T. G., Zelenin, P. V., & Orlovsky, G. N. (2002). Encoding and decoding of reticulospinal commands. *Brain Res Rev*, *40*, 166–177.

Delwaide, P. J., Pepin, J. L., De Pasqua, V., & de Noordhout, A. M. (2000). Projections from basal ganglia to tegmentum: a subcortical route for explaining the pathophysiology of parkinson's disease signs? *J. Neurol.*, *247 Suppl 2*, 75–81.

Doya, K. (1999). What are the computations of the cerebellum, the basal ganglia and the cerebral cortex? *Neural Netw.*, *12*, 961–974.

Drew, T., & Rossignol, S. (1990). Functional organization within the medullary reticular formation of intact unanesthetized cat. I. Movements evoked by microstimulation. *J. Neurophysiol.*, *64*, 767–781.

Dubuc, R., Brocard, F., Antri, M., Fnelon, K., Garipy, J.-F., Smetana, R., Mnard, A., Ray, D. L., Prisco, G. V. D., Pearlstein, E., Sirota, M. G., Derjean, D., St-Pierre, M., Zielinski, B., Auclair, F., & Veilleux, D. (2008). Initiation of locomotion in lampreys. *Brain Res Rev*, *57*, 172–182.

Eccles, J. C., Nicoll, R. A., Rantucci, T., Taborikova, H., & Willey, T. J. (1976). Topographic studies on medial reticular nucleus. *J. Neurophysiol.*, *39*, 109–118.

Fay, R., & Kubin, L. (2000). Pontomedullary distribution of 5-HT2A receptor-like protein in the rat. *J Comp Neurol*, *418*, 323–45.

Fields, H. L., & Basbaum, A. I. (1978). Brainstem control of spinal pain-transmission neurons. *Annu. Rev. Physiol.*, *40*, 217–248.

Graybiel, A. M. (1995). Building action repertoires: memory and learning functions of the basal ganglia. *Curr. Opin. Neurobiol.*, *5*, 733–741.

Grillner, S., Deliagina, T., Ekeberg, O., el Manira, A., Hill, R. H., Lansner, A., Orlovsky, G. N., & Wallen, P. (1995). Neural networks that co-ordinate locomotion and body orientation in lamprey. *Trends Neurosci*, *18*, 270–279.

Grillner, S., Hellgren, J., Menard, A., Saitoh, K., & Wikstrom, M. A. (2005). Mechanisms for selection of basic motor programs - roles for the striatum and pallidum. *Trends Neurosci*, *28*, 364–370.

Groves, P. M., Miller, S. W., Parker, M. V., & Rebec, G. V. (1973). Organization by sensory modality in the reticular formation of the rat. *Brain Res*, *54*, 207–224.

Gurney, K., Prescott, T. J., & Redgrave, P. (2001a). A computational model of action selection in the basal ganglia I: A new functional anatomy. *Biol. Cybern.*, *85*, 401–410.

Gurney, K., Prescott, T. J., & Redgrave, P. (2001b). A computational model of action selection in the basal ganglia II: Analysis and simulation of behaviour. *Biol. Cybern.*, *85*, 411–423.

Hammer, R. P. J., Lindsay, R. D., & Scheibel, A. B. (1981). Development of the brain stem reticular core: an assessment of dendritic state and configuration in the perinatal rat. *Dev Brain Res*, *1*, 179–190.

Hattox, A., Li, Y., & Keller, A. (2003). Serotonin regulates rhythmic whisking. *Neuron*, *39*, 343–352.

Hobson, J. A., & Scheibel, A. B. (1980). The brainstem core: Sensorimotor integration and behavioral state control. *Neurosci. Res. Program Bull.*, *18*, 1–173.

Holmes, C. J., Mainville, L. S., & Jones, B. E. (1994). Distribution of cholinergic, GABAergic and serotonergic neurons in the medial medullary reticular formation and their projections studied by cytotoxic lesions in the cat. *Neuroscience*, *62*, 1155–78.

Holstege, G. (1995). The basic, somatic, and emotional components of the motor system in mammals. In G. Paxinos (Ed.) *The Rat Nervous System, Second Edition*, (pp. 137–154). New York: Academic Press.

Humphries, M. D., Gurney, K., & Prescott, T. J. (2005). Is there an integrative center in the vertebrate brainstem? a robotic evaluation of a model of the reticular formation viewed as an action selection device. *Adapt. Behav.*, *13*, 97–113.

Humphries, M. D., Gurney, K., & Prescott, T. J. (2006a). The brainstem reticular formation is a small-world, not scale-free, network. *Proc. Roy. Soc. B.*, *273*, 503–511.

Humphries, M. D., Gurney, K., & Prescott, T. J. (2007). Is there a brainstem substrate for action selection? *Phil Trans R Soc B*, *362*, 1627–1639.

Humphries, M. D., & Prescott, T. J. (2006). Distributed action selection by a brainstem neural substrate: an embodied evaluation. In S. Nolfi, G. Baldassarre, R. Calabretta, J. Hallam, D. Marocco, O. Miglino, J.-A. Meyer, & D. Parisi (Eds.) *From animals to animats 9: Proceedings of the Ninth International Conference on Simulation of Adaptive Behaviour*, vol. LNAI. Volume 4095., (pp. 199–210). Berlin, Germany: Springer Verlag.

Humphries, M. D., Stewart, R. D., & Gurney, K. N. (2006b). A physiologically plausible model of action selection and oscillatory activity in the basal ganglia. *J Neurosci*, *26*, 12921–12942.

Inglis, W. L., & Winn, P. (1995). The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. *Prog. Neurobiol.*, *47*, 1–29.

Iwakiri, H., Oka, T., Takakusaki, K., & Mori, S. (1995). Stimulus effects of the medial pontine reticular formation and the mesencephalic locomotor region upon medullary reticulospinal neurons in acute decerebrate cats. *Neurosci. Res.*, *23*, 47–53.

Iwaniuk, A. N., & Whishaw, I. Q. (2000). On the origin of skilled forelimb movements. *Trends Neurosci.*, *23*, 372–376.

Jones, B. E. (1990). Immunohistochemical study of choline acetyltransferase-immunoreactive processes and cells innervating the pontomedullary reticular formation in the rat. *J Comp Neurol*, *295*, 485–514.

Jones, B. E. (1995). Reticular formation: Cytoarchitecture, transmitters, and projections. In G. Paxinos (Ed.) *The Rat Nervous System, 2nd Edition*, (pp. 155–171). New York: Academic Press.

Jones, B. E., Holmes, C. J., Rodriguez-Veiga, E., & Mainville, L. (1991). GABA-synthesizing neurons in the medulla: their relationship to serotonin-containing and spinally projecting neurons in the rat. *J. Comp. Neurol.*, *313*, 349–367.

Jordan, L. M., Liu, J., Hedlund, P. B., Akay, T., & Pearson, K. G. (2008). Descending command systems for the initiation of locomotion in mammals. *Brain Res Rev*, *57*, 183–191.

Jung, R., Kiemel, T., & Cohen, A. H. (1996). Dynamic behavior of a neural network model of locomotor control in the lamprey. *J Neurophysiol*, *75*, 1074–1086.

Kilmer, W. L., McCulloch, W. S., & Blum, J. (1969). A model of the vertebrate central command system. *Int. J. Man Mach. Stud.*, *1*, 279–309.

Kinjo, N., Atsuta, Y., Webber, M., Kyle, R., Skinner, R. D., & Garcia-Rill, E. (1990). Medioventral medulla-induced locomotion. *Brain Res. Bull.*, *24*, 509–516.

Kleinfeld, D., Berg, R. W., & O'Connor, S. M. (1999). Anatomical loops and their electrical dynamics in relation to whisking by rat. *Somatosens. Mot. Res.*, *16*, 69–88.

Krichmar, J. L. (2008). The neuromodulatory system: A framework for survival and adaptive behavior in a challenging world. *Adaptive Behavior*, *16*, 385–399.

Kristan, W. B., Calabrese, R. L., & Friesen, W. O. (2005). Neuronal control of leech behavior. *Prog Neurobiol*, *76*, 279–327.

Kropotov, J. D., & Etlinger, S. C. (1999). Selection of actions in the basal ganglia thalamocortical circuits: review and model. *Int. J. Psychophysiol.*, *31*, 197–217.

Kuypers, H. G. (1964). The descending pathways to the spinal cord, their anatomy and function. *Prog. Brain Res.*, *11*, 178–202.

Lakke, J. P. (1985). Axial apraxia in Parkinson's disease. *J. Neurol. Sci.*, *69*, 37–46.

Langhorst, P., Schulz, B., Schulz, G., & Lambertz, M. (1983). Reticular formation of the lower brainstem. A common system for cardiorespiratory and somatomotor functions: discharge patterns of neighboring neurons influenced by cardiovascular and respiratory afferents. *J. Auton. Nerv. Syst.*, *9*, 411–432.

Langhorst, P., Schulz, B. G., Seller, H., & Koepchen, H. P. (1996). Convergence of visceral and somatic afferents on single neurones in the reticular formation of the lower brain stem in dogs. *J. Auton. Nerv. Syst.*, *57*, 149–157.

Laughlin, S. B., & Sejnowski, T. J. (2003). Communication in neuronal networks. *Science*, *301*, 1870–1874.

Lovick, T. A. (1972). The behavioural repertoire of precollicular decerebrate rats. *J. Physiol.*, *226*, 4P–6P.

Lund, J. P., Kolta, A., Westberg, K. G., & Scott, G. (1998). Brainstem mechanisms underlying feeding behaviors. *Curr. Opin. Neurobiol.*, *8*, 718–724.

Magoun, H. W., & Rhines, R. (1946). An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.*, *9*, 165–171.

Marsden, C. D., & Obeso, J. A. (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain.*, *117*, 877–897.

Martin, E. M., Pavlides, C., & Pfaff, D. W. (2007). Neurons in the medullary reticular formation with multimodal sensory response capacities. In *2007 Neuroscience Meeting Planner*, (p. Program No. 403.11). San Diego, CA: Society for Neuroscience.

Mathias, N., & Gopal, V. (2001). Small worlds: How and why. *Phys. Rev. E*, *63*, 021117.

Matsuyama, K., Mori, F., Nakajima, K., Drew, T., Aoki, M., & Mori, S. (2004). Locomotor role of the corticoreticular-reticulospinal-spinal interneuronal system. *Prog. Brain Res.*, *143*, 239–249.

Mesce, K., Esch, T., & Kristan, W. (2008). Cellular substrates of action selection: a cluster of higher-order descending neurons shapes body posture and locomotion. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*, *194*, 469–481.

Mink, J. W., & Thach, W. T. (1993). Basal ganglia intrinsic circuits and their role in behavior. *Curr. Opin. Neurobiol.*, *3*, 950–957.

Mori, S. (1987). Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. *Prog. Neurobiol.*, *28*, 161–195.

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroenceph. clin. Neurophysiol.*, (pp. 455–473).

Moschovakis, A. K., Scudder, C. A., & Highstein, S. M. (1996). The microscopic anatomy and physiology of the mammalian saccadic system. *Prog. Neurobiol.*, *50*, 133–254.

Newman, D. B. (1985). Distinguishing rat brainstem reticulospinal nuclei by their neuronal morphology. I. Medullary nuclei. *Journal fur Hirnforschung*, *26*, 187–226.

Newman, D. B. (1995). Anatomy and neurotransmitters of brainstem motor systems. *Advances in Neurology*, *67*, 219–243.

Noga, B. R., Kriellaars, D. J., Brownstone, R. M., & Jordan, L. M. (2003). Mechanism for activation of locomotor centers in the spinal cord by stimulation of the mesencephalic locomotor region. *J. Neurophysiol.*, *90*, 1464–1478.

Parvizi, J., & Damasio, A. R. (2003). Neuroanatomical correlates of brainstem coma. *Brain*, *126*, 1524–1536.

Paxinos, G., & Watson, C. (1998). *The Rat Brain In Stereotaxic Coordinates, 4th Edition*. San Diego, CA: Academic Press.

Peterson, B. W. (1979). Reticulospinal projections to spinal motor nuclei. *Annu. Rev. Physiol.*, *41*, 127–140.

Prescott, T. J. (2007). Forced moves or good tricks in design space? landmarks in the evolution of neural mechanisms for action selection. *Adapt Behav*, *15*, 9–31.

Prescott, T. J., Redgrave, P., & Gurney, K. (1999). Layered control architectures in robots and vertebrates. *Adapt. Behav.*, *7*, 99–127.

Prisco, G. V. D., Pearlstein, E., Ray, D. L., Robitaille, R., & Dubuc, R. (2000). A cellular mechanism for the transformation of a sensory input into a motor command. *J Neurosci*, *20*, 8169–8176.

Ramon-Moliner, E., & Nauta, W. J. (1966). The isodendritic core of the brain stem. *J Comp Neurol*, *126*, 311–335.

Redgrave, P., Prescott, T. J., & Gurney, K. (1999). The basal ganglia: A vertebrate solution to the selection problem? *Neuroscience*, *89*, 1009–1023.

Reiner, A., Medina, L., & Veenman, C. L. (1998). Structural and functional evolution of the basal ganglia in vertebrates. *Brain Res. Rev.*, *28*, 235–285.

Rubchinsky, L. L., Kopell, N., & Sigvardt, K. A. (2003). Modeling facilitation and inhibition of competing motor programs in basal ganglia subthalamic nucleus-pallidal circuits. *Proc. Natl. Acad. Sci. USA*, *100*, 14427–14432.

Salibi, N. A., Saade, N. E., Banna, N. R., & Jabbur, S. J. (1980). Dorsal column input into the reticular formation. *Nature*, *288*, 481–483.

Scheibel, A. B. (1984). The brainstem reticular core and sensory function. In J. M. Brookhart, & V. B. Mountcastle (Eds.) *Handbook of Physiology. Section 1: The Nervous System*, (pp. 213–256). Bethesda, Maryland: American Physiological Society.

Scheibel, M. E., & Scheibel, A. B. (1958). Structural substrates for integrative patterns in the brain stem reticular core. In H. H. e. a. Jasper (Ed.) *Reticular Formation of the Brain*. Boston: Little and Brown.

Scheibel, M. E., & Scheibel, A. B. (1967). Anatomical basis of attention mechanisms in vertebrate brains. In G. C. Quarton, T. Melnechuk, & F. O. Schmitt (Eds.) *The Neurosciences, A Study Program*, (pp. 577–602). New York: The Rockefeller University Press.

Schulz, B., Lambertz, M., Schulz, G., & Langhorst, P. (1983). Reticular formation of the lower brainstem. A common system for cardiorespiratory and somatomotor functions: discharge patterns of neighboring neurons influenced by somatosensory afferents. *J. Auton. Nerv. Syst.*, *9*, 433–449.

Schulz, G., Lambertz, M., Schulz, B., Langhorst, P., & Krienke, B. (1985). Reticular formation of the lower brainstem. A common system for cardio-respiratory and somatomotor functions. Cross-correlation analysis of discharge patterns of neighbouring neurones. *J. Auton. Nerv. Syst.*, *12*, 35–62.

Segundo, J. P., Takenaka, T., & Encabo, H. (1967). Somatic sensory properties of bulbar reticular neurons. *J. Neurophysiol.*, *30*, 1221–1238.

Shammah-Lagnado, S. J., Costa, M. S., & Ricardo, J. A. (1992). Afferent connections of the parvocellular reticular formation: a horseradish peroxidase study in the rat. *Neuroscience*, *50*, 403–425.

Siegel, J. M. (1979). Behavioral functions of the reticular formation. *Brain Res. Rev.*, *1*, 69–105.

Siegel, J. M., Nienhuis, R., Wheeler, R. L., McGinty, D. J., & Harper, R. M. (1981). Discharge pattern of reticular-formation unit pairs in waking and REM-sleep. *Exp. Neurol.*, *74*, 875–891.

Siegel, J. M., & Tomaszewski, K. S. (1983). Behavioral organization of reticular formation: studies in the unrestrained cat. I. Cells related to axial, limb, eye, and other movements. *J. Neurophysiol.*, *50*, 696–716.

Sperry, R. W. (1952). Neurology and the mind-brain problem. *American Scientist*, *40*, 291–312.

Sprague, J. M., & Chambers, W. W. (1954). Control of posture by reticular formation and cerebellum in the intract, anesthetized and unanesthetized, decerebrated cat. *Am. J. Physiol.*, *176*, 52–64.

Stephens, G. J., Johnson-Kerner, B., Bialek, W., & Ryu, W. S. (2008). Dimensionality and dynamics in the behavior of C. elegans. *PLoS Comput Biol*, *4*, e1000028.

Stevens, D. R., Birnstiel, S., Gerber, U., McCarley, R. W., & Greene, R. W. (1993). Nicotinic depolarizations of rat medial pontine reticular formation neurons studied in vitro. *Neuroscience*, *57*, 419–424.

Stevens, D. R., McCarley, R. W., & Greene, R. W. (1992). Serotonin1 and serotonin2 receptors hyperpolarize and depolarize separate populations of medial pontine reticular formation neurons in vitro. *Neuroscience*, *47*, 545–53.

Stevens, D. R., McCarley, R. W., & Greene, R. W. (1994). The mechanism of noradrenergic alpha 1 excitatory modulation of pontine reticular formation neurons. *J Neurosci*, *14*, 6481–6487.

Swanson, L. W. (2000). Cerebral hemisphere regulation of motivated behavior. *Brain Res*, *886*, 113–164.

Szokol, K., Glover, J. C., & Perreault, M.-C. (2008). Differential origin of reticulospinal drive to motoneurons innervating trunk and hindlimb muscles in the mouse revealed by optical recording. *J Physiol*, *586*, 5259–5276.

Takakusaki, K., Saitoh, K., Harada, H., & Kashiwayanagi, M. (2004). Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neurosci. Res.*, *50*, 137–151.

Torvik, A., & Brodal, A. (1957). The origin of reticulospinal fibers in the cat; an experimental study. *Anat. Rec.*, *128*, 113–137.

Valverde, F. (1961). Reticular formation of the pons and medulla oblongata: A golgi study. *J Comp Neurol*, *116*, 71–99.

Whelan, P. J. (1996). Control of locomotion in the decerebrate cat. *Prog. Neurobiol.*, *49*, 481–515.

Woods, J. W. (1964). Behavior of chronic decerebrate rats. *J. Neurophysiol.*, *27*, 635–644.

Yates, B. J., & Stocker, S. D. (1998). Integration of somatic and visceral inputs by the brainstem: functional considerations. *Exp. Brain Res.*, *119*, 269–275.

Yen, J. C., & Chan, S. H. (1993). Passive biophysical membrane properties of nucleus reticularis gigantocellularis neurons in brain slices from the rat. *Neurosci. Lett.*, *159*, 5–8.

Zahm, D. S. (2006). The evolving theory of basal forebrain functional-anatomical 'macrosystems'. *Neurosci Biobehav Rev*, *30*, 148–172.

Zigmond, M. J., & Burke, R. E. (2002). Pathophysiology of Parkinson's disease. In K. L. Davis, D. Charney, J. T. Coyle, & C. Nemeroff (Eds.) *Neuropsychopharmacology: The Fifth Generation of Progress*, (pp. 1781–1793). Philadelphia: Lippincott Williams & Wilkins.