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The decision to move: response times, neuronal circuits and sensory memory in a simple vertebrate.

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Short title: **Decision to move**

5000 words including abstract, text, legends and refs ~ 7-8 pages of 11pt Arial;
now ~5294

Abstract (209 words)
All animals use sensory systems to monitor events around them and have to decide whether to move in response to external events. Response times are long and variable compared to reflexes, or fast escape movements. The complexity of adult vertebrate brains makes it difficult to trace the neuronal circuits underlying simple decisions to move. To simplify the problem, we study the nervous system and responses of hatchling frog tadpoles which swim when their skin is stimulated. Studying the neuron-by-neuron pathway from sensory neurons to the hindbrain neurons where the decision to swim is made has revealed two simple pathways where excitation sums to threshold in identified hindbrain neurons to initiate swimming. One is direct and leads to short, and reliable delays like an escape response. The other includes a population of sensory processing neurons which introduce noise and delay into responses. These neurons provide a brief, sensory memory of the stimulus, so when the tadpole responds, it can integrate stimuli occurring within a second or so of each other. We relate these findings to other studies on simple decisions and conclude that sensory memory makes a fundamental contribution to simple decision making and is present in the brainstem of a simple vertebrate at a surprisingly early stage in development.

1. Introduction

In 100 m sprint races, men take 120 to 165 ms to start moving [1]. Such response times have fascinated experimental psychologists since Helmholtz (1850) described methods to measure them [2]. Coordinated movements, like eye movements towards a new target, start after variable delays of 50 to 200 ms [3]. Why are these responses slow and variable when reflex movements and the rapid escape responses of animals like squid, crayfish and fish, have short and constant response times (RTs; < 20ms) [4-7].

Studies of response times have focussed on eye movements of people and other mammals, especially monkeys and the complex neuronal circuits in the prefrontal motor cerebral cortex which control them [8-10]. In the simplest experiments, subjects gaze at a light spot and are required to shift their gaze to another light spot when it comes on. Recordings of neuronal activity in mammals have shown that sensory information travels from the eyes to the cerebral cortex where it influences the ongoing firing of neurons. If the light only flashes briefly, then a "sensory memory" of the stimulus is needed and this too has been studied primarily in cerebral cortex. This memory only lasts for a second or so, and the usual proposal is that it is based on mutual re-excitation within small populations of neurons [11-13]. During the lead-up to the decision to move the eyes, recordings in primate and rat pre-frontal cortex have shown that the stimulus results in a slow and noisy build-up of firing frequency. In some neurons, peak firing rates correlate with the decision to move [8-10].

Many theories underlying decisions to move the eyes propose that an excitatory "decision signal" builds noisily to a threshold in cortical neurons and, when this is reached, the movement occurs [3, 14-16]. Variability in response times results from noise in the decision. However, the complexity of the cortex means that in no case can the neuron-by-neuron circuits and synaptic properties underlying a particular decision be defined. It is also unclear what the advantages are of slowing down decisions to move. Is it to give time for other stimuli and central states to be taken into account before a response is made?

Analysis of simpler neuronal circuits should help to understand the details of how neurons connected by synapses control the initiation of coordinated motor responses to a sensory stimulus. It is disappointing that the only cases where the neuron-by-neuron pathway from a sensory stimulus to a response have been traced are those for the rapid escape movements controlled by giant neurons in crayfish [6, 17] and in fish [18]. This is a consequence of the ease of study of giant neurons and the difficulties imposed by the small size of most neurons.

2. Why use tadpoles to study the initiation of movements?

Larval fish and amphibians provide useful models for the study of the foundations of vertebrate nervous organisation and function [19, 20]. We have investigated the neurons, and networks that allow hatchling *Xenopus laevis* tadpoles (Fig. 1a) to behave and survive [21-23]. This has led to some surprising new conclusions about the organisation of sensory systems, sensory memory and the neurons where the decisions to move are made [24-26].

As in adult animals, tadpole response times for swimming following skin stimulation are long and variable. If touched on one side of the trunk with a fine hair, tadpoles flex unpredictably to left or right and then swim off [27]. The response times to swimming following a brief current pulse (Fig. 1b) were long and variable (median 102 ms, Inter Quartile Range 81-136 ms; Fig. 1c; [26]).

Tadpoles also have to decide which side will flex first. We have studied this by immobilising tadpoles so that recordings can be made from motor nerves as well as from individual neurons in the spinal cord and brain. When a near threshold current pulse is given to the skin on one side of the head, the first motor nerve burst has a ~0.5 probability of being on the stimulated or unstimulated sides (Fig. 1d; [25]). Reaction

times are shorter than behavioural responses but are still long and variable (stimulated side starts: median 25 ms, range 15 – 87, unstimulated side starts: median 35 ms, range 20 – 71) compared to reflexes (<10 ms; [28]). When the trunk skin is stimulated, the median delay to the first motor nerve firing on the unstimulated side was 40 ms (IQR 33–61; [26]).

In this review, we discuss where the delays and their variabilities arise in the tadpole's decision to swim. To set the scene we give an overview of the organisation of the tadpole touch sensory to motor response pathway and its organisation into five levels (3). Then the evidence on the neuron-by-neuron function of the touch sensory pathway is reviewed (4). The way this sensory pathway activates a brain decision mechanism for movement is then considered (5) and a neuronal network model of sensory memory is presented (6). The evidence on tadpole motor response pathways is then drawn together and compared to other movement decision systems (7) before a final conclusion (8).

Figure 1

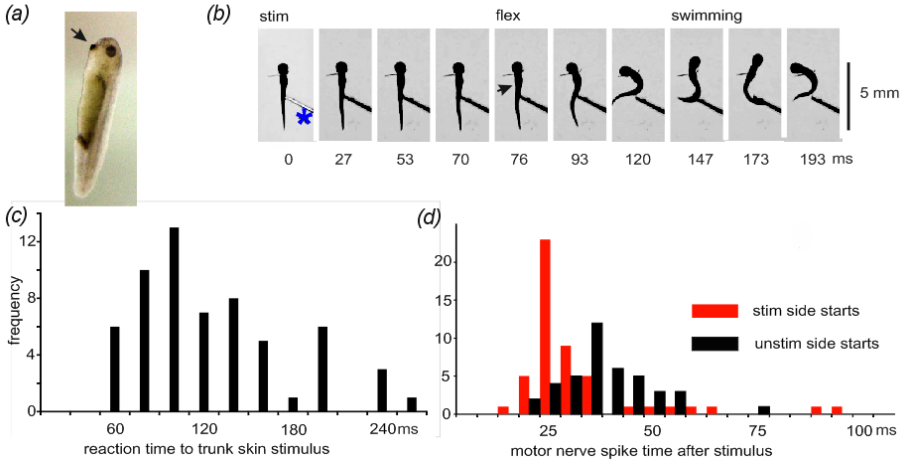

Figure 1 Tadpole responses to a brief skin stimulus. ***(a)*** A hatchling *Xenopus* tadpole, 5 mm long, hangs at rest from mucus secreted by its cement gland (arrow). ***(b)*** Video frames show a tadpole (dorsal view) flexing to left (arrowhead), then swimming following a current pulse to the right trunk (*). ***(c)*** Response times to the first flexion of swimming. ***(d)*** Delays to the first motor nerve activity of fictive swimming following a head skin stimulus in immobilised tadpoles.

3. Overview of the tadpole skin sensory swimming initiation pathway.

To find out about the different types of neuron, their anatomy, activity, and synaptic connections, we have used dye filled electrodes to record from pairs of neurons in the brain and spinal cord of immobilised tadpoles. This has allowed us to build a broad picture of how the neuronal networks they form are organised [21, 22]. The tadpole skin touch to motor pathway has five functional stages (Fig. 2; cf [29].

(1) Touch sensory neurons for the head skin lie in the trigeminal ganglia and for the trunk skin in the spinal cord [30, 31]. A single AP in one or two sensory neurons can initiate swimming. Their peripheral axons carry action potentials into the CNS where their central axons project to distribute excitation longitudinally.

(2) Sensory pathway neurons are excited by sensory neurons and distribute sensory signals in the brain on both sides [24, 31]. Single sensory neurons excite many sensory pathway neurons and in this way the sensory signal is amplified [28]. Trigeminal sensory pathway neurons are only excited by head skin stimuli and make direct connections to level 4 reticulospinal neurons [24].
(3) Sensory processing neurons are a new and important proposal for the movement initiation pathway [26]. They are excited by sensory pathway neurons and excite reticulospinal neurons. The evidence and definition of these neurons is preliminary but suggests that they extend firing (possibly by mutual re-excitation) and introduce noise and variability. They transform the short and nearly synchronous firing in sensory pathway neurons (<30 ms) into longer lasting and variable firing (~ 1000 ms) which is different in each neuron of their population. This firing acts as a sensory memory of any brief sensory stimulus to the skin.
(4) Reticulospinal neurons lie in the hindbrain and project to the spinal cord. They sum the input from different sensory pathways and modalities like skin touch and light [32]. It is here that excitation from sensory processing neurons builds up noisily and can reach firing threshold. It is these reticulospinal neurons that effectively make the decision to swim because, when they fire, the first flexion of swimming is initiated. During swimming they generate the rhythm by firing once on each cycle.
(5) Motoneurons and **reciprocal inhibitory neurons** are excited strongly by the reticulospinal neurons so they fire once on each cycle of swimming [33]. Motoneuron firing leads to muscle contraction and flexion of the body. The alternation of firing with the neurons on the opposite side is organised by reciprocal inhibition [34]. Alternation is re-enforced by post-inhibitory rebound firing organised by this reciprocal inhibition [22, 35]. The result is alternating waves of contraction and swimming.

Figure 2

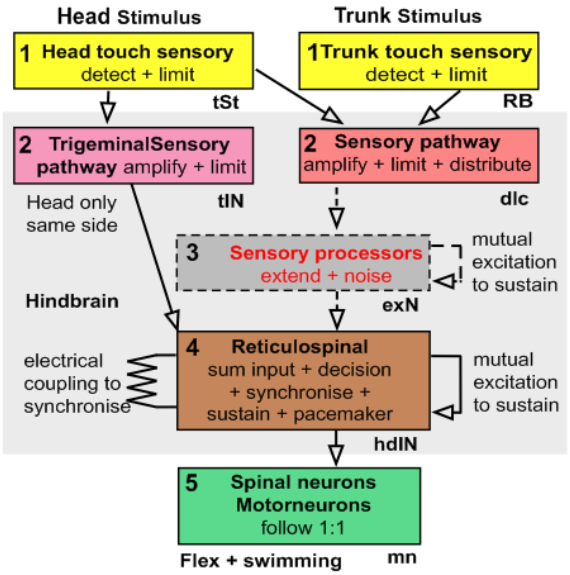

Figure 2. Organization of neuronal pathways from head and trunk skin stimulation to swimming in the hatchling frog tadpole. The boxes represent populations of similar excitatory neurons in the 5 functional levels between a skin stimulus and a motor response. Arrows show direct excitatory synaptic connections established by recording from pre- and post-synaptic neurons. Dashed boxes and arrows are populations and

connections proposed to explain current evidence. For simplicity, the pathways are only shown for one side of the body and inhibitory neurons are omitted. Letters near boxes are the abbreviations of neuron names they contain.

4. Evidence on the operation of the tadpole touch sensory system

Sensory neurons innervate the skin in all vertebrates with fine unspecialised "free" nerve endings which wrap around the skin cells. Tadpole sensory neurons (tSt) for head skin lie in the trigeminal ganglia and their central axons reach the brain in the 5th cranial nerve [30]. The trunk skin has similar endings coming from sensory Rohon-Beard (RB) neurons in the spinal cord [31, 36]. There are up to 100 of each type on each side. Recordings from sensory neurons showed that they fire 1 to 3 spikes when stimulated in their receptive field.

Spinal sensory pathway neurons are excited by glutamatergic synapses from the longitudinal axons of skin sensory neurons. In the spinal cord, recordings from pairs of neurons, show that the RB neurons directly and strongly excite two types of sensory pathway neuron. These neurons only fire very briefly (Fig. 3a; [28, 37, 38]).

Figure 3

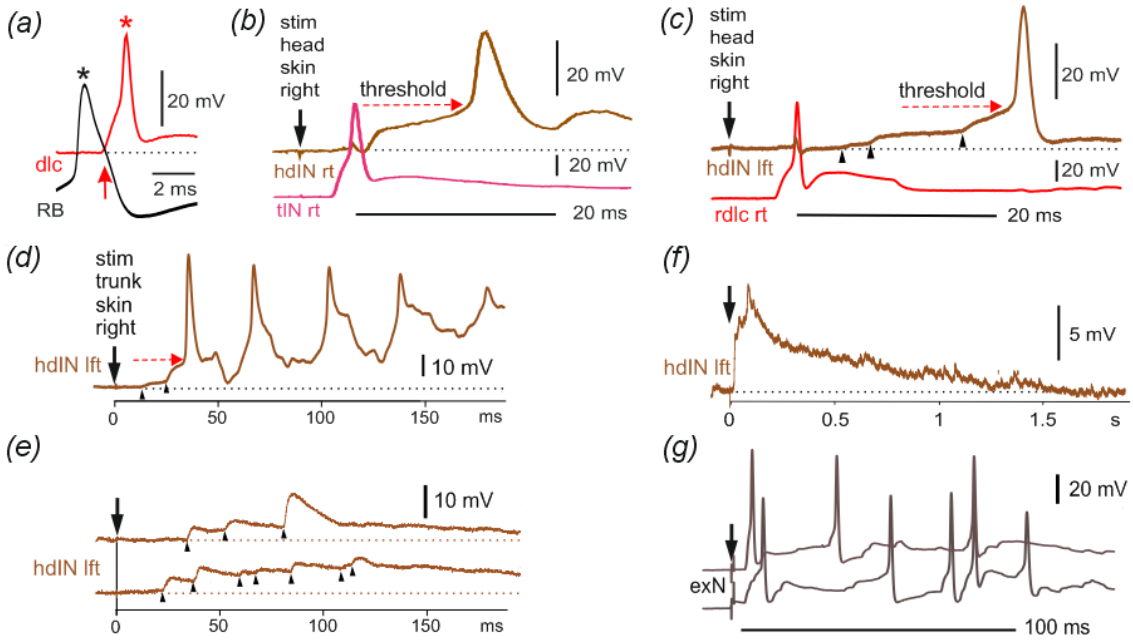

Figure 3. Recordings show the activity and connections of neurons in the swimming response pathway: (a) Current injection into a sensory RB neuron leads to an action potential (peak at black *) and direct excitation of a sensory pathway dlc neuron (Excitatory Postsynaptic Potential EPSP starts at red arrow) and then produces an action potential in the dlc (red *). ***(b - c)*** Paired recordings showing responses to a 1 ms head skin current stimulus which evoked swimming. ***(b)*** A sensory pathway tIN (pink) responds with a single spike. The excitation from this and other tIN spikes excites the hdIN on the same side (brown) which depolarises smoothly to threshold (dashed arrow) and fires a spike. ***(c)*** A rostral dlc on the right side also fires a single spike (red) but this cannot explain the slow, noisy build-up of excitation (arrowheads) to threshold (dashed

red arrow) and firing in the hdIN on the opposite side. ***(d - f)*** Trunk skin stimulation also leads to variable excitation of hdINs. ***(d)*** A stronger stimulus leads to 2 jumps (arrowheads) hdIN which reach threshold (red arrow) and firing is followed by rhythmic firing during swimming. ***(e)*** Two examples of responses subthreshold for swimming show noisy excitation (arrowheads) summing but not reaching firing threshold. ***(f)*** The long duration of subthreshold excitation in hdINs is revealed by averaging 5 recordings at a slower time-scale. ***(g)*** Two examples of responses of a possible sensory processing neuron (exN) in the hindbrain to a trunk skin stimulus (at arrow). Each record shows an early spike and variable later firing.

Trigeminal sensory pathway neurons form a small trigeminal nucleus of around 25 neurons (tINs) on each side of the hindbrain and have descending axons [24]. Head skin sensory neurons directly excite tINs and more rostral spinal sensory pathway neurons [25].

Sensory pathway neurons: distribute signals from skin sensory neurons to targets on both sides of the brain; amplify sensory signals so one or two spikes in a few sensory neurons elicit a single spike in many pathway neurons (the number firing may depend on the number of sensory neurons firing and crudely code the stimulus strength); set a limit on the excitation reaching the brain because there is a fixed number of them.

5. Evidence on the activation of the swimming control system

Movements of the body and limbs in vertebrates are thought to be controlled by reticulospinal neurons in the hindbrain which project to the spinal cord [39-43]. Tadpole swimming starts when a population of hindbrain reticulospinal neurons (hdINs) becomes active [21, 24, 25, 33]. These neurons are electrically coupled [44], so when a few fire, the whole population on one side is recruited and they all fire once in synchrony [45]. They then play a critical role in driving swimming [22, 46]. As well as exciting motorneurons and other spinal neurons, these electrically coupled neurons excite each other chemically by releasing glutamate [33]. Mutual activation of their own NMDA receptors turns on pacemaker properties and sustains their own regular, rhythmic firing and swimming [45, 47-49].

It was therefore surprising when recordings from these reticulospinal hdINs showed that the only sensory pathway neurons to make strong and direct synaptic connection to them were the hindbrain (tINs) excited by head skin stimulation (Fig. 3b). This pathway could evoke hdIN firing and swimming starting on the stimulated side at relatively short latencies (hdINs: median delay of 12 ms; motor nerve: median 25 ms; [25]. To our knowledge, this is the first simple, non-giant neuron pathway for the initiation of locomotion defined in the vertebrates.

How does a stimulus to one side lead to swimming starting on the opposite side? Spinal sensory pathway dlc neurons carry excitation to the opposite side when the head or trunk skin is stimulated. Surprisingly, recordings from these neurons and hdINs on the opposite side showed no direct, short latency excitation (Fig. 3c; [25]) but revealed a very variable pattern of longer latency excitation [26]. This could build up over time to reach the hdIN threshold so they fired at long and variable latencies (Fig. 3c, d; median 57 ms). The response times of the first hdIN firing matched the delays to the start of swimming in motor nerve recordings (Fig. 1d).

What are the characteristics of the variable pattern of excitation recorded in reticulospinal dINs following a brief skin stimulus? Even when the stimulus was too weak to evoke swimming, hdINs on each side of the body received long-lasting excitation seen as EPSPs occurring for many hundreds of ms after the stimulus (Fig. 3e - f) [26]. This pattern of EPSPs could not be produced directly by the single nearly synchronous spikes fired early by sensory pathway dlc neurons. The EPSPs must be generated by unidentified neurons firing irregularly for some time after skin stimulation. We obtained information about the timing of the APs in these unidentified neurons by measuring the timing of the EPSPs they evoked in hdINs following skin stimulation (Fig. 3e). The major and critical conclusion was that the sensory pathway neurons must excite undefined populations of sensory processing neurons on each side of the brain whose function was to extend sensory firing for about 1 second, act as a sensory memory of brief stimuli, and produce variable excitation of the hdINs to initiate swimming. We call them extension neurons (exNs) and have some recordings of hindbrain neurons with suitable prolonged and variable firing to skin stimulation (Fig. 3g).

6. A model of sensory memory to extend brief sensory firing

How could sensory pathway neuron firing and excitation be extended by sensory processing exN neurons in the hindbrain? A simple proposal is that exN neurons excite each other to form a small recurrent network and sustain their own activity for a short time [11]. To test this idea, we built a network of 30 model exN neurons excited by brief excitation from sensory pathway dlc neurons. The exNs were connected to a model hdIN [49] to monitor the synaptic excitation they produced. With variability in the synaptic strength of all excitatory synapses in the network, the variable patterns of exN firing it generated could be qualitatively matched to the data on the timing of EPSPs in hdINs. These results show that it is simple to prolong firing in a small model network of unspecialised neurons if there is variable and weak recurrent excitation among them even without any inhibition [26]. If such a network was connected to hdINs in a model swimming network it should start swimming after variable and unpredictable delays.

7. Discussion

All animals have to make decisions about whether to respond to sensory stimuli. Studying simpler animals, can uncover the detailed neuronal pathways for decisions to initiate simple movements, like swimming [29]. In crayfish and fish escape responses, sensory neurons directly excite giant neurons, bringing them rapidly to firing threshold. They fire a single spike, and the first flexion of swimming is initiated at a short and constant latency by the direct excitation of motorneurons [17, 18].

In hatchling tadpoles, tracing the neuronal pathway from a brief skin touch to the initiation of swimming, has revealed two ways in which populations of non-giant reticulospinal neurons (hdINs) can control the first flexion of swimming (Fig. 2). Stronger head skin stimulation excites tIN neurons on the same side of the hindbrain [24] and they directly excite the hdIN population and swimming follows at fairly short and constant latencies [25]. This pathway provides a simple and direct way to initiate locomotion. Weaker stimuli to the head or trunk have revealed unexpected complexity. Instead of a simple reflex-like pathway, we propose that small populations of sensory processing neurons (exNs) in the hindbrain are excited by sensory pathway neurons and extend firing nearly 1 second (see Fig. 2 level 3; [26]. This process introduces noise into the sensory signal in the brain and then provides prolonged, excitation to the reticulospinal

hdINs to bring them to firing threshold, so swimming is initiated after variable delays on either side of the body. The exNs therefore combine two functions: they hold a roughly 1 second sensory memory of recent stimuli and generate a noisy “decision signal” to brainstem hdINs. Their firing is the “decision” which initiates the first flexion of swimming after variable delays.

What is the significance of extending sensory excitation and inserting delay and noise into the movement initiation pathway?

(1) Integration of sensory inputs is made possible by the long duration excitation exNs produce in reticulospinal hdINs. If an initial stimulus does not lead to a motor response, then this excitation remains present and could sum with excitation from other later stimuli to the same location (temporal summation) or to any other part of the body (spatial summation). In addition, other sensory modalities like water currents [50] and light dimming [32] can initiate swimming. Extended excitation in hdINs acts as a sensory memory and could sum with other sensory inputs if they occur within the 1 second time window. Neurons with extended excitation can therefore act as integrators for a range of sensory inputs so, responses are “considered” in the context of stimuli reaching the animal.

(2) Motor coordination is essential for the production of effective movements. When stimulated, the tadpole must decide whether or not to make the first body flexion of swimming, and which side flexes first. This is a very organised process in response to head skin stimulation [25]. The hdIN firing on each side falls into discreet alternating time windows, so synchronous firing of the two sides is avoided. It is very likely that reciprocal inhibition is important here [34, 51] . However, in *Xenopus* immobilised preparations synchronous firing of both sides can occur [52, 53] as in simple model networks with reciprocal inhibition [35, 54]. Slowing down hdIN excitation and making it noisy, probably reduces the chance of hdINs reaching firing threshold simultaneously on both sides, reducing the probability of synchronous firing.

(3) Introducing variability into responses may make responses less predictable and help animals to avoid predation [55]. The slowly rising excitation in hdINs following skin stimulation introduces variability into: the delay before hdINs reach their firing threshold and swimming starts; the side which fires first to gentle stimulation; and the direction of swimming. There is one exception to this general picture. Stronger stimuli to the head skin lead to short latency and predictable flexion towards the stimulated side [25] and the biological significance of this behaviour is not clear.

8. Overview of a simple decision to move

Can the complete neuron-to-neuron pathway from a sensory stimulus to a coordinated motor response be defined? At present the only examples are those specialised for fast responses [17, 18, 24]. The latencies to most skin stimuli in tadpoles are long and variable, like eye movements and other coordinated motor responses in adult animals [3]. Our new evidence on tadpole swimming initiation is still incomplete but has a surprising new sensory processing stage (Fig. 2). The neurons at this stage extend and add noise to the signal reaching the brainstem reticulospinal neurons which drive swimming. The evidence supports the basic proposals from studies on eye movements where variable excitation leads to long and variable response times. The evidence for extension neurons producing variable excitation is strong but

characterisation of the neurons involved is at present weak. Our expectation is that neurons performing this extension or sensory memory function will be a fundamental component of movement initiation pathways in most animals. The slowing down of responses allows animals to integrate multiple sensory inputs and to make “considered” rather than “rash” responses!

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References

1. Pilianidis T., Mantzouranis N., Kasabalis A. 2012 Start reaction time and performance at the sprint events in World Athletic Championships. *Int J Perf Anal Spor* **12**(1), 112-118.
2. Helmholtz H. 1850 Vorläufiger Bericht über die Fortpflanzungsgeschwindigkeit der Nervenreizung. *Archiv für Anatomie, Physiologie und Wissenschaftliche Medicin*, 71-73.
3. Noorani I., Carpenter R.H. 2016 The LATER model of reaction time and decision. *Neurosci Biobehav Rev* **64**, 229-251. (doi:10.1016/j.neubiorev.2016.02.018).
4. Eaton R.C. 1984 *Neural Mechanisms of Startle Behaviour*. Berlin, Springer.
5. Korn H., Faber D.S. 2005 The Mauthner cell half a century later: a neurobiological model for decision-making? *Neuron* **47**(1), 13-28. (doi:10.1016/j.neuron.2005.05.019).
6. Edwards D.H., Heitler W.J., Krasne F.B. 1999 Fifty years of a command neuron: the neurobiology of escape behavior in the crayfish. *Trends Neurosci* **22**(4), 153-161.
7. Sillar K.T., Picton L.D., Heitler W.J. 2016 *The neuroethology of predation and escape*. Oxford, Wiley-Blackwell.
8. Smith P.L., Ratcliff R. 2004 Psychology and neurobiology of simple decisions. *Trends Neurosci* **27**(3), 161-168. (doi:10.1016/j.tins.2004.01.006).
9. Schall J.D. 2003 Neural correlates of decision processes: neural and mental chronometry. *Curr Opin Neurobiol* **13**(2), 182-186.
10. Hanes D.P., Schall J.D. 1996 Neural control of voluntary movement initiation. *Science* **274**(5286), 427-430.
11. Goldman-Rakic P.S. 1995 Cellular Basis of Working Memory. *Neuron* **14**, 477 - 485.
12. Durstewitz D., Seamans J.K., Sejnowski T.J. 2000 Neurocomputational models of working memory. *Nat Neurosci* **3 Suppl**, 1184-1191.
13. Wang D., Grillner S., Wallén P. 2013 Calcium dynamics during NMDA-induced membrane potential oscillations in lamprey spinal neurons – contribution of L-type calcium channels (CaV1.3). *The Journal of Physiology* **591**(10), 2509-2521. (doi:10.1113/jphysiol.2012.248526).
14. Carpenter R.H., Williams M.L. 1995 Neural computation of log likelihood in control of saccadic eye movements. *Nature* **377**(6544), 59-62. (doi:10.1038/377059a0).

15. Gold J.I., Shadlen M.N. 2007 The neural basis of decision making. *Annu Rev Neurosci* **30**, 535-574. (doi:10.1146/annurev.neuro.29.051605.113038).
16. Brody C.D., Hanks T.D. 2016 Neural underpinnings of the evidence accumulator. *Curr Opin Neurobiol* **37**, 149-157. (doi:10.1016/j.conb.2016.01.003).
17. Herberholz J., Marquart G.D. 2012 Decision Making and Behavioral Choice during Predator Avoidance. *Front Neurosci* **6**, 125. (doi:10.3389/fnins.2012.00125).
18. Fetcho J.R. 1991 Spinal network of the Mauthner cell. *Brain Behav Evol* **37**(5), 298-316. (doi:10.1159/000114367).
19. Kimura Y., Satou C., Fujioka S., Shoji W., Umeda K., Ishizuka T., Yawo H., Higashijima S. 2013 Hindbrain V2a neurons in the excitation of spinal locomotor circuits during zebrafish swimming. *Curr Biol* **23**(10), 843-849. (doi:10.1016/j.cub.2013.03.066).
20. McLean D.L., Dougherty K.J. 2015 Peeling back the layers of locomotor control in the spinal cord. *Curr Opin Neurobiol* **33**, 63-70. (doi:10.1016/j.conb.2015.03.001).
21. Li W.-C. 2011 Generation of Locomotion Rhythms Without Inhibition in Vertebrates: The Search for Pacemaker Neurons. *Integrative and Comparative Biology* **51**(6), 879-889. (doi:10.1093/icb/icr021).
22. Roberts A., Li W.-C., Soffe S.R. 2010 How neurons generate behaviour in a hatchling amphibian tadpole: an outline. *Frontiers in Behavioral Neuroscience* **4**. (doi:10.3389/fnbeh.2010.00016).
23. Roberts A., Conte D., Hull M., Merrison-Hort R., al Azad A.K., Buhl E., Borisyuk R., Soffe S.R. 2014 Can Simple Rules Control Development of a Pioneer Vertebrate Neuronal Network Generating Behavior? *Journal of Neuroscience* **34**(2), 608-621. (doi:10.1523/Jneurosci.3248-13.2014).
24. Buhl E., Roberts A., Soffe S.R. 2012 The role of a trigeminal sensory nucleus in the initiation of locomotion. *J Physiol* **590**(10), 2453-2469. (doi:10.1113/jphysiol.2012.227934).
25. Buhl E., Soffe S.R., Roberts A. 2015 Sensory initiation of a co-ordinated motor response: synaptic excitation underlying simple decision-making. *J Physiol* **593**(19), 4423-4437. (doi:10.1113/JP270792).
26. Koutsikou S., Merrison-Hort R., Buhl E., Ferrario A., Li W.C., Borisyuk R., Soffe S.R., Roberts A. 2018 A simple decision to move in response to touch reveals basic sensory memory and mechanisms for variable response times. *J Physiol*. (doi:10.1113/JP276356).
27. Boothby K.M., Roberts A. 1995 Effects of site and strength of tactile stimulation on the swimming responses of Xenopus laevis embryos. *J Zool (Lond)* **235**, 113-125.
28. Li W.-C., Soffe S.R., Roberts A. 2003 The spinal interneurons and properties of glutamatergic synapses in a primitive vertebrate cutaneous flexion reflex. *J Neurosci* **23**(27), 9068-9077.
29. Kristan W.B. 2008 Neuronal decision-making circuits. *Curr Biol* **18**(19), R928-932. (doi:10.1016/j.cub.2008.07.081).
30. Roberts A. 1980 The function and role of two types of mechanoreceptive 'free' nerve endings in the head skin of amphibian embryos. *J comparative Physiology A* **135**, 341 - 348.

31. Clarke J.D.W., Hayes B.P., Hunt S.P., Roberts A. 1984 Sensory physiology, anatomy and immunohistochemistry of Rohon-Beard neurones in embryos of Xenopus laevis. *J Physiol (lond)* **348**, 511-525.
32. Jamieson D., Roberts A. 1999 A possible pathway connecting the photosensitive pineal eye to the swimming central pattern generator in young Xenopus laevis tadpoles. *Brain, Behavior and Evolution* **54**(6), 323-337.
33. Li W.-C., Soffe S.R., Wolf E., Roberts A. 2006 Persistent Responses to Brief Stimuli: Feedback Excitation among Brainstem Neurons. *J Neurosci* **26**(15), 4026-4035. (doi:10.1523/jneurosci.4727-05.2006).
34. Dale N. 1985 Reciprocal inhibitory interneurones in the Xenopus embryo spinal cord. *J Physiol (lond)* **363**, 61-70.
35. Ferrario A., Merrison-Hort R., Soffe S.R., Li W.C., Borisyuk R. 2018 Bifurcations of Limit Cycles in a Reduced Model of the Xenopus Tadpole Central Pattern Generator. *J Math Neurosci* **8**(1), 10. (doi:10.1186/s13408-018-0065-9).
36. Roberts A., Hayes B.P. 1977 The anatomy and function of 'free' nerve endings in an amphibian skin sensory system. *Proc R Soc Lond B Biol Sci* **196**(1125), 415-429.
37. Clarke J.D.W., Roberts A. 1984 Interneurones in the Xenopus embryo spinal cord: sensory excitation and activity during swimming. *J Physiol (Lond)* **354**, 345-362.
38. Roberts A., Sillar K.T. 1990 Characterization and Function of Spinal Excitatory Interneurons with Commissural Projections in Xenopus laevis embryos. *Eur J Neurosci* **2**(12), 1051-1062.
39. 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 research reviews* **57**(1), 183-191. (doi:10.1016/j.brainresrev.2007.07.019).
40. Orlovsky G.N., Deliagina T.G., Grillner S. 1999 *Neuronal Control of Locomotion*. Oxford, OUP; 322 p.
41. Viana Di Prisco G., Pearlstein E., Robitaille R., Dubuc R. 1997 Role of Sensory-Evoked NMDA Plateau Potentials in the Initiation of Locomotion. *Science* **278**(5340), 1122-1125.
42. Daghfous G., Green W.W., Alford S.T., Zielinski B.S., Dubuc R. 2016 Sensory Activation of Command Cells for Locomotion and Modulatory Mechanisms: Lessons from Lampreys. *Front Neural Circuits* **10**, 18. (doi:10.3389/fncir.2016.00018).
43. Deliagina T.G., Zelenin P.V., Orlovsky G.N. 2002 Encoding and decoding of reticulospinal commands. *Brain research reviews* **40**(1-3), 166-177.
44. Li W.-C., Roberts A., Soffe S.R. 2009 Locomotor rhythm maintenance: electrical coupling among premotor excitatory interneurons in the brainstem and spinal cord of young *Xenopus* tadpoles. *Journal of Physiology (London)* **587**(8), 1677-1693.
45. Hull M.J., Soffe S.R., Willshaw D.J., Roberts A. 2015 Modelling the Effects of Electrical Coupling between Unmyelinated Axons of Brainstem Neurons Controlling Rhythmic Activity. *PLoS Comput Biol* **11**(5), e1004240. (doi:10.1371/journal.pcbi.1004240).
46. Soffe S.R., Roberts A., Li W.-C. 2009 Defining the excitatory neurons that drive the locomotor rhythm in a simple vertebrate: insights into the origin of

reticulospinal control. *The Journal of Physiology* **587**(20), 4829-4844. (doi:10.1113/jphysiol.2009.175208).
47. Li W.-C., Roberts A., Soffe S.R. 2010 Specific Brainstem Neurons Switch Each Other into Pacemaker Mode to Drive Movement by Activating NMDA Receptors. *The Journal of Neuroscience* **30**(49), 16609-16620. (doi:10.1523/jneurosci.3695-10.2010).
48. Ferrario A., Merrison-Hort R., Soffe S.R., Borisyuk R. 2018 Structural and functional properties of a probabilistic model of neuronal connectivity in a simple locomotor network. *Elife* **7**. (doi:10.7554/eLife.33281).
49. Hull M.J., Soffe S.R., Willshaw D.J., Roberts A. 2016 Modelling Feedback Excitation, Pacemaker Properties and Sensory Switching of Electrically Coupled Brainstem Neurons Controlling Rhythmic Activity. *PLoS Comput Biol* **12**(1), e1004702. (doi:10.1371/journal.pcbi.1004702).
50. Roberts A., Feetham B., Pajak M., Teare T. 2009 Responses of hatchling Xenopus tadpoles to water currents: first function of lateral line receptors without cupulae. . *J exp Biol* **212** 914 - 921
51. Messina J.A., St Paul A., Hargis S., Thompson W.E., McClellan A.D. 2017 Elimination of Left-Right Reciprocal Coupling in the Adult Lamprey Spinal Cord Abolishes the Generation of Locomotor Activity. *Front Neural Circuits* **11**, 89. (doi:10.3389/fncir.2017.00089).
52. Kahn J.A., Roberts A. 1982 The central nervous origin of the swimming motor pattern in embryos of Xenopus laevis. *J Exp Biol* **99**, 185-196.
53. Li W.C., Merrison-Hort R., Zhang H.Y., Borisyuk R. 2014 The generation of antiphase oscillations and synchrony by a rebound-based vertebrate central pattern generator. *J Neurosci* **34**(17), 6065-6077. (doi:10.1523/JNEUROSCI.4198-13.2014).
54. Wang X.-J., Rinzel J. 1992 Alternating and synchronous rhythms in reciprocally inhibitory model neurons. *Neural Comput* **4**, 84 - 97.
55. Domenici P., Blagburn J.M., Bacon J.P. 2011 Animal escapology I: theoretical issues and emerging trends in escape trajectories. *The Journal of Experimental Biology* **214**(15), 2463-2473. (doi:10.1242/jeb.029652).