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Review

An overview of the phylogeny of cardiorespiratory control in vertebrates with some reflections on the 'Polyvagal Theory'

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ABSTRACT

Mammals show clear changes in heart rate linked to lung ventilation, characterized as respiratory sinus arrhythmia (RSA). These changes are controlled in part by variations in the level of inhibitory control exerted on the heart by the parasympathetic arm of the autonomic nervous system (PNS). This originates from preganglionic neurons in the nucleus ambiguous that supply phasic, respiration-related activity to the cardiac branch of the vagus nerve, via myelinated, efferent fibres with rapid conduction velocities. An elaboration of these central mechanisms, under the control of a 'vagal system' has been endowed by psychologists with multiple functions concerned with 'social engagement' in mammals and, in particular, humans. Long-term study of cardiorespiratory interactions (CRI) in other major groups of vertebrates has established that they all show both tonic and phasic control of heart rate, imposed by the PNS. This derives centrally from neurones located in variously distributed nuclei, supplying the heart via fast-conducting, myelinated, efferent fibres. Water-breathing vertebrates, which include fishes and larval amphibians, typically show direct, 1:1 CRI between heart beats and gill ventilation, controlled from the dorsal vagal motor nucleus. In air-breathing, ectothermic vertebrates, including reptiles, amphibians and lungfish, CRI mirroring RSA have been shown to improve oxygen uptake during phasic ventilation by changes in perfusion of their respiratory organs, due to shunting of blood over across their undivided hearts. This system may constitute the evolutionary basis of that generating RSA in mammals, which now lacks a major physiological role in respiratory gas exchange, due to their completely divided systemic and pulmonary circulations.

1. Introduction

Because of the understandably anthropocentric nature of our society, study of mammalian physiology, as a guide to human physiology and health, remains far in advance of our efforts to understand the physiology of non-mammalian vertebrates. Consequently, we currently know much more about the mechanisms that control visceral function in mammals, compared to the rest of the vertebrates. However, studies on a range of vertebrate species, using neuro-anatomical and electrophysiological techniques, have revealed that the role of the autonomic nervous system (ANS) in control of the heart, is likely to have evolved early in the vertebrate lineage and have been conserved throughout their evolution (Monteiro et al., 2018; Taylor et al., 2014; Taylor et al., 1999; Taylor et al., 2010; Taylor et al., 2010). Thus, the parasympathetic arm of the ANS predominates in both the chronic control of mean heart rate (HR) and the phasic modulation of beat-to-beat variability of HR in all vertebrate groups from sharks to mammals (Monteiro et al., 2018; Taylor et al., 1999, 2014; Taylor et al., 2001). This control is exerted via the X^{th} cranial nerve, the vagus, and we concentrate on vagal control of the heart in this review.

We begin with a very brief account of current knowledge of the regulation of mean HR and heart rate variability (HRV) in mammals, as a

Abbreviations: AB, air-breathing; ABO, air-breathing organs; ANS, autonomic nervous system; CRI, cardio-respiratory interactions; CRS, cardiorespiratory synchrony; CVPN, cardiac vagal preganglionic neurons; DMNX, dorso-medial vagal motor nucleus (as used in PVT); DVN, dorso-medial vagal motor nucleus (presently accepted acronym); HR, heart rate; HF, high frequency; HRV, heart rate variability; LF, low frequency; NA, nucleus ambiguous; PVT, The Polyvagal Theory; R-L shunt, Right to Left intracardiac shunt; RSA, respiratory sinus arrhythmia; VPN, vagal preganglionic motoneurons; PNS, Parasympathetic nervous system; MEF, Myelinated efferent fibres.

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Table 1
List of cited species. List of vertebrate species from which experimental data has been mentioned in the present review, depicting the broad range of animals and groups that provide experimental evidence of the primitive origin of cardiorespiratory interaction. The species are numbered according to the citation order. ID number is shown superscripted in the text.

ID	Popular Name	Species	Class	Order
1	Mouse	*Mus sp*	Mammalia	Rodentia
2	Rat	*Rattus sp*	Mammalia	Rodentia
3	Goat	*Capra aegagrus hircus*	Mammalia	Artiodactyla
4	Miniature swine	*Sus scrofa domestica*	Mammalia	Artiodactyla
5	Cat	*Felis catus*	Mammalia	Carnivora
6	New Zealand White rabbits	*Oryctolagus cuniculus*	Mammalia	Lagomorpha
7	Boa	*Boa constrictor*	Reptilia	Squamata
8	Green iguana	*Iguana iguana*	Reptilia	Squamata
9	Broad nose caiman	*Caiman latirostris*	Reptilia	Crocodilia
10	South American Rattlesnake	*Crotalus durissus*	Reptilia	Squamata
11	Back and White Tegu	*Salvator merianae*	Reptilia	Squamata
12	Indian Python	*Python molurus*	Reptilia	Squamata
13	Ball python	*Python regius*	Reptilia	Squamata
14	Yellow-bellied slider	*Trachemys scripta*	Reptilia	Testudines
15	Tenerife lizard	*Gallotia galloti*	Reptilia	Squamata
16	Sudan plated lizard	*Gerrhosaurus major*	Reptilia	Squamata
17	Nile crocodile	*Crocodylus niloticus*	Reptilia	Crocodilia
18	American alligator	*Alligator mississippiensis*	Reptilia	Crocodilia
19	yellow-lipped sea krait	*Laticauda colubrina*	Reptilia	Squamata
20	Olive-brown seasnake	*Aipysurus laevis*	Reptilia	Squamata
21	Reef shallows seasnake	*Aipysurus duboisii*	Reptilia	Squamata
22	Spine-bellied seasnake	*Lapemis hardwickii*	Reptilia	Squamata
23	Bar-bellied seasnake	*Hydrophis elegans*	Reptilia	Squamata
24	Marine File Snake	*Acrochordus granulatu*	Reptilia	Squamata
25	Caiman	*Caiman sclerop*	Reptilia	Crocodilia
26	Mud Snake	*Farancia abacura*	Reptilia	Squamata
27	Plainbelly water snake	*Natrix erythrogaster*	Reptilia	Squamata
28	Southern water snake	*Natrix fasciata*	Reptilia	Squamata
29	Diamondback water snake	*Natrix rhombifera*	Reptilia	Squamata
30	Grass snake	*Tripoclonotus natrix*	Reptilia	Squamata
31	European adder	*Vipera benis*	Reptilia	Squamata
32	Desert Fringe-toed Lizard	*Uma notata inornata*	Reptilia	Squamata
33	Desert Iguana	*Dipsosaurus dorsalis*	Reptilia	Squamata
34	Zebra-tailed Lizard	*Callisaurus draeonoides*	Reptilia	Squamata
35	River cooter turtles	*Pseudemys concinna*	Reptilia	Testudines
36	Big Bend slider	*Pseudemys scripta*	Reptilia	Testudines
37	Greek tortoise	*Testudo graeca*	Reptilia	Testudines
38	Painted Turtle	*Chrysemys picta*	Reptilia	Testudines
39	Geoffroy's side-necked turtle	*Phrynops geoffroanus*	Reptilia	Testudines
40	Agamid Lizard	*Uromastyx aegyptius*	Reptilia	Squamata
41	Green Turtle	*Chelone mydas*	Reptilia	Testudines
42	Caiman	*Caiman crocodilus*	Reptilia	Crocodilia
43	Monitor lizard	*Varanus salvator*	Reptilia	Squamata
44	Hermann's Tortoise	*Testudo hermanni*	Reptilia	Testudines
45	Softshell turtle	*Trionyx sinensis*	Reptilia	Testudines
46	Red-footed tortoise	*Chelonoidis carbonaria*	Reptilia	Testudines
47	Monitor lizard	*Varanus exanthematicus*	Reptilia	Squamata
48	White Carneaux pigeons	*Columba livia*	Aves	Columbiformes
49	Duck	*Anas boscas*	Aves	Anseriformes
50	Seagull	*Larus argentatus*	Aves	Charadriiformes
51	Great comorant	*Phalacrocorax carbo*	Aves	Suliformes
52	European starlings	Sturnus vulgaris	Aves	Passeriformes
53	Chicken	Gallus gallus domesticus	Aves	Galliformes
54	Streaked shearwater	*Calonectris leucomelas*	Aves	Procellariifromes
55	Mallard duck	*Anas platyrhynchos*	Aves	Anseriformes
56	Tufted duck	*Aythya fuligula*	Aves	Anseriformes
57	Cane toad	*Rhinella marina*	Amphibia	Anura
58	Axolotl	*Ambystoma mexicanum*	Amphibia	Urodela
59	African clawed toad	*Xenopus laevis*	Amphibia	Anura
60	Bullfrog	*Lithobates catesbeianus*	Amphibia	Anura
61	Pepper frog	*Leptodactylus labyrinthicus*	Amphibia	Anura
62	Cururu toad	*Rhinella schneideri*	Amphibia	Anura
63	Human	*Homo sapiens*	Mammalia	Primates
64	West African lungfish	*Protopterus annectens*	Sarcopterygii	Dipnoi
65	South American lungfish	*Lepidosiren paradoxa*	Sarcopterygii	Dipnoi
66	Australian lungfish	*Neoceratodus sp*	Sarcopterygii	Dipnoi
67	African lungfish	*Protopterus aethiopicus*	Sarcopterygii	Dipnoi
68	Dogfish, Catshark	*Scyliorhinus canicula*	Chondrichthyes	Carcharhiniformes
69	Muçum	*Synbranchus marmoratus*	Actinopterygii	Synbrancchiformes
70	Asian swamp eel	*Monopterus albus*	Actinopterygii	Synbrancchiformes
71	Jeju	*Hoplerythrinus unitaeniatus*	Actinopterygii	Characiforme
72	Short-horned sculpin	*Myoxocephalus scorpius*	Actinopterygii	Scorpaeniformes
73	Black cod	*Notothenia angustata*	Actinopterygii	Percciformes
74	Adriatic sturgeon	*Acipenser naccarii*	Actinopterygii	Acipenseriformes
75	Eel	*Anguilla anguilla*	Actinopterygii	Anguilliformes
76	Pacu	*Piaractus mesopotamicus*	Actinopterygii	Characiformes
77	Rainbow trout	*Oncorhynchus mykiss*	Actinopterygii	Salmoniformes
78	Goldfish	*Carassius auratus*	Actinopterygii	Cypriniformes
79	Atlantic cod	*Gadus morhua*	Actinopterygii	Gadiformes
80	Antarctic fish	*Pagothenia bernacchii*	Actinopterygii	Perciformes
81	Antarctic fish	*Pagothenia borchgrevinki*	Actinopterygii	Perciformes

(*continued on next page*)

Table 1 (*continued*)

ID	Popular Name	Species	Class	Order
82	Sea bass	*Dicentrarchus labrax*	Actinopterygii	Perciformes
83	Skipjack tuna	*Katsuwonus pelamis*	Actinopterygii	Perciformes
84	Yellowfin tuna	*Thunnus albacores*	Actinopterygii	Scombriformes
85	Flounder	*Pleuronectes americanus*	Actinopterygii	Pleuronectiformes
86	Spiny catshark	*Squalus acanthius*	Chondrichthyes	Squaliformes
87	Dog	*Canis familiares*	Mammalia	Carnivora

The text uses the English common names of animals to provide a reader-friendly text. These terms may differ according to country or region. The binominal identification and classification of each animal is presented here and identified in the text by their designated superscript number. This review was based on the knowledge produced on many other vertebrate species. This list refers only to those directly mentioned. All species belong to the Phylum Chordata.

template for subsequent comparison with the other vertebrate groups. We then expand on some ideas examined in previous reviews that have contributed to a debate on the 'Polyvagal Theory' (PVT), which claims unique properties for the vagus nerve in mammals, both in cardiac control and a range of high-order behavioural strategies, characterized as social engagement (Grossman & Taylor, 2007; Monteiro et al., 2018; Porges, 1995, 2021; Taylor et al., 2014). Because PVT rests on the claim that there are critical differences in the mechanisms modulating HR and HRV between mammals and reptiles, we begin our comparative analysis with reptiles, the diverse vertebrate group (turtles, lizards, snakes and crocodiles) that gave rise separately to both early mammals and birds. We then consider birds, a group that share with mammals the high metabolic rate associated with endothermy, having seemingly evolved it along a separate evolutionary line that contains crocodilians and the extinct dinosaurs. The review then considers the amphibians (frogs, toads and salamanders) and air-breathing fishes, some of which sit at the base of the evolution of the air-breathing, 4-legged tetrapods. We then consider the aquatic water–breathing bony fishes, that have proliferated in the seas and freshwater to represent the vast majority of vertebrate species. Finally, we describe our work on cardio-respiratory interactions (CRI) in sharks and rays, a primitive group in which the vagus is solely responsible for neural control of the heart, as it lacks sympathetic innervation. This study culminated in characterisation of individual cardiac vagal preganglionic neurons (CVPN), using central recordings from dual locations in the brainstem, giving us a better understanding of this aspect of control than for any vertebrate group, other than mammals (Taylor & Butler, 1971, 1982; Taylor, 1992). These data suggest that the nature of vagal control of the heart evolved early in vertebrate phylogeny, showing some adaptive changes at the advent of air-breathing.

Although the nature and location of central interactions are known only for mammals and sharks, it has been possible to observe that the fundamental neuroanatomical and physiological features of the control of CRI seem common to all groups of vertebrates. These include: two or more locations for CVPN plus fast conducting, myelinated efferent fibres, which together with a fast and transient effect of the cholinergic influence over the cardiac pacemaker, introduce a respiration-related component into HRV. These factors are critical for tonic plus phasic, beat-to-beat, respiration-related control of HR. The diverse CRI shown by vertebrates and the fundamental similarities shown by the control systems involved obviate the need to postulate any "smart" moves during their evolution.

We understand that psychology, by its very nature, is anthropocentric and consequently out of our remit, so we do not pretend to have anything useful to say in this review on the possible roles of a 'social engagement system' in humans that may in some way involve parasympathetic input via the vagus nerve. However, we urge students of psychology to read this brief synopsis of the phylogeny of vagal control of the heart in vertebrates as they may benefit from putting their studies of human behaviour into the context supplied by study of modern examples of our vertebrate ancestors. These indicate that our control systems and their responses to environmental change evolved progressively, so that mammals are not set apart from the rest of the vertebrates, in this regard at least, as implied by some statements arising from biomedical and psychological studies.

This review draws on experimental studies on a wide range on vertebrate species, which for ease of comprehension we have identified by their common names, each accompanied by a superscript number. The species, genus and grouping of each animal are identified against these numbers in Table 1.

2. Mammalia (mammals)

Autonomic regulation of cardiac function has been studied in many species of mammals, with in-depth physiological studies performed on captive-bred mice[1], rats[2], goats[3] and miniature swine[4]. These studies revealed that the ANS exerts a tonic control over mean HR, overriding the rhythm generated by the intrinsic pacemaker. This is constituted of an excitatory, adrenergic tone, exercised by the sympathetic arm of the ANS, of between 5% and 30% and an inhibitory, cholinergic tone varying from 15% to 100%, exercised by the parasympathetic arm of the ANS and acting as the principal determinant of routine mean HR (Taylor et al., 2014). Many changes in mean HR in response to discontinuous stimuli are determined by changes in vagal tone rather than sympathetic tone, although the latter can play an important role in controlling both HR and peripheral blood flow in stressful conditions.

Importantly, the vagus is also largely responsible for modulating instantaneous, beat-to-beat changes in HR. The heart in healthy, fit mammals accelerates during inspiration and slows during exhalation. Power spectral analysis of HRV reveals a peak at a relatively high frequency, which is respiration-related and characterised as respiratory sinus arrhythmia (RSA) (Bootsma et al., 1994; Grossman & Taylor, 2007; Taylor et al., 1999, 2014). Although influenced by feedback from pulmonary stretch receptors, RSA has a clear central origin. Efferent activity in the cardiac branch of the vagus arises from cardiac vagal preganglionic neurons (CVPN) that innervate ganglia positioned at the pacemaker region on the sinoatrial node (Taylor et al., 1999, 2014). CVPN are distributed in two major locations in the mammalian brainstem, the dorsomedial vagal motor nucleus (DVN) and the ventrolateral nucleus ambiguus (NA). The NA is the site for the vagal preganglionic motoneurons (VPN) supplying axons to the heart and lungs (Agostoni et al., 1957; Taylor et al., 1999). While 70% of VPN are located within the DVN (Ranson et al., 1993), cell bodies of pulmonary and CVPN are concentrated in the NA, with up to 70% of pulmonary neurons and 80% of CVPN located together in the NA in the cat[5] (Jordan & Spyer, 1987; Taylor et al., 1999). Anterograde tracing studies on the rat cardiac vagus revealed that both the DVN and NA project CVPN to ganglia on the rat[2] sino-atrial node. This is indicative of a chronotropic influence and confirmed that vagal control of HR has a curious dual central representation. Projections from the NA consisted of larger (presumptive myelinated) axons than those from the DVN, with greater divergence at the cardiac ganglion cells (Cheng et al., 1999; Cheng & Powley, 2000).

Detailed analysis of the firing pattern of CVPN located in the NA, reveals that they fire during expiration and are inhibited during inspiration, a pattern that is identical to that recorded from post-inspiratory neurons (Gilbey et al., 1984; Spyer, 1994). Activity in post-inspiratory neurons is gated by descending fibres from the Kolliker-Fuse nucleus, which is thus essential for proper pattern formation and phase control within the respiratory network (Dutschmann & Herbert, 2006) and may have a similar overriding influence on the generation of RSA. The NA is anatomically very close to the ventral respiratory group, including the Pre-Bötzinger complex, the primary area for respiratory rhythmogenesis in mammals. CVPN in the NA have been shown to receive direct inhibitory inputs from these neighbouring inspiratory neurons (Jordan

& Spyer, 1987; Jordan et al., 1985; Taylor et al., 1999). Activity in CVPN is also affected indirectly by input from lung stretch receptors, entering via the nucleus of the solitary tract (NTS) that gate activity from baroreceptor afferents (Spyer, 1994). Inspiratory inhibition of CVPN activity ensures that any stimulus that enhances inspiration actively increases heart rate while inputs, peripheral or central, that suppress ventilation or prolong expiration lower heart rate (Daly, 1985). Respiratory activity during inspiration accordingly silences the discrete population of CVPN in the NA, so that they are inactive during inspiration and do not respond to baroreceptor stimulation (Davidson et al., 1976). Their inhibitory input to the heart is consequently withdrawn, causing cardiac acceleration during inspiration (Jordan & Spyer, 1987; Jordan et al., 1985; Taylor et al., 1999). So, the respiration-related fluctuations in instantaneous HR, identified as RSA, are initiated by fluctuations in inhibitory input from the brain to the heart through the vagus nerve in response to both centrally generated (feed-forward) influence from respiratory neurons and afferent input from pulmonary stretch receptors (feed--back) that gate baroreceptor inputs (Spyer, 1990). Consequently, CVPN in the NA fire with respiration-related and cardiac-related rhythms. The central interactions affecting activity in CVPN are instantaneous (Spyer, 1994). Both are relayed to the heart, causing virtually instantaneous changes in HR, because they travel in rapidly conducting, myelinated efferent axons leaving the CVPN in the NA. These are classified as B-fibres on the basis of their high conduction velocities (Grundfest, 1939). This high conduction velocity from the NA is considered essential for the beat-to-beat modulation of instantaneous HR that generates RSA.

The smaller proportion of CVPN located within the DVN are activated by stimulation of pulmonary C-fibres, but are unaffected by stimulation of arterial baroreceptors or the respiratory cycle (Jones et al., 1995, 1998; Jordan et al., 1985). These neurons show regular activity, but this is not rhythmic. Their efferent axons supplying the heart lack myelin sheaths and are classified as C-fibres based on their slow conduction velocities. They have relatively minor, slowly developing effects on HR that may provide some tonic control of baseline HR (Jones et al., 1995; Jones, 2001).

Peripheral stimulation of the cardiac vagus in the cat[5], rat[2], and rabbit[6] clearly showed the enhanced degree of control exerted on the heart by activity in myelinated fibres from CVPN located in the NA, when compared with the activity in slow fibres from CVPN in the DVN (Jones et al., 1995). It remains possible that a rhythmical respiratory input conveyed by fast B-fibres, and a tonic input conveyed by slow C-fibres, interact at the level of the cardiac ganglia. This combination of inputs may attenuate the respiratory modulation otherwise seen when only the B-fibres are utilised in cardio-inhibitory reflexes (Jones, 2001). Therefore, the two CVPN populations may exert distinct modulatory effects on HR. In mammals, these have been identified by their different locations and their functional properties, including their afferent connections, the conduction velocity of their efferent axons, their efferent activity, and the consequent effects on HR (Daly & Kirkman, 1989; Jones et al., 1995; Jones, 2001).

Thus, the generation of RSA in mammals seems reliant on the following anatomical and physiological factors:

1) VPN, including CVPN, in two major locations in the brainstem, the dorsomedial DVN and ventrolateral NA where they receive different afferent connections and generate very different efferent activities.
2) Instantaneous effects of central respiratory drive on activity in CVPN in the NA cause them to be active during expiration and inactive during inspiration. This latter effect seems to originate as inhibition from inspiratory neurons in a ventral group close to the NA, though pontine modulation of post-inspiratory activity is clearly involved. The resultant respiration-related activity modulates HR, acting as feed-forward control, generating RSA.
3) Rapid conduction (3−15 m sec^{-1}) of activity from CVPN within the NA, via myelinated, efferent axons (B-fibres), together with the transient nature of cholinergic influence over the cardiac pacemaker, enables instantaneous, beat-to-beat control of the HR.
4) CVPN in the DVN do not show respiration-related activity and innervate the heart via unmyelinated, slow C-fibres. Their influence on HR is relatively minor and remains contentious.
5) Activation of pulmonary stretch receptors during inflation provides a feedback signal, gating the baroreceptor response.

Other factors may contribute to the generation of RSA:

6) Modulation of respiratory activity from chemoreceptors responding to changes in the respiratory gases, CO_2 and O_2 (Taylor et al., 1999).
7) A GABAergic inhibitory input from the hypothalamic defence area (Jordan & Spyer, 1987).
8) Mechanical effects on the heart and associated blood vessels due to ventilatory movements of the thoracic cavity, which can also stimulate mechanoreceptors (Taylor et al., 1999).

3. The Polyvagal theory

The Polyvagal Theory (PVT) proposes that modulation of HR in mammals differs fundamentally from all other vertebrates and is associated with uniquely mammalian physiological and behavioural traits. It states that: whilst retaining the "*primitive vegetative vagus*", which they inherited from their reptilian ancestors, the mammals are advantaged by the novel evolutionary appearance of a "*smart vagus*". This '*smart vagus*' is described as arising from a '*special medullary centre'* that coordinates its cardiopulmonary functions with: '*calming'* (enhancing cardiac vagal tone to slow the heart and calm the body, which is also dependent of concomitant reduction of sympathetic excitation); '*communication'* (vocalisation, facial expressions and rotation of the head); plus visceral functions, such as the ingestion of food and, vomiting. The NA is credited with being this centre, containing a '*vagal system*' that serves as the origin of the '*smart vagus'* (Porges, 2011).

These statements imply that mammals evolved a unique vagal nucleus in the NA that has a particular association with visceral efferent nerve fibres supplied by a combination of cranial nerves. It was also stated that the generation of RSA was dependent on the CVPN in the NA having myelinated efferent fibres, with a high conduction velocity that are unique to mammals, stating that: "*only mammals have a myelinated vagus"* (Porges, 2009, 2011).

In developing PVT, the author identifies separate functional roles for two discrete branches of the vagus (Porges, 2011): one "*branch"* arising in the DVN and innervating smooth and cardiac muscle fibres, regulating reflexive vegetative functions; the other originating in the NA, where it combines a wide range of functional roles, including the generation of RSA. This description may have been introduced to aid understanding of these relatively complex relationships, however, it is not literally the case. VPN located separately in either the DVN or the NA both supply axons to mixed nerves (see above). For example, the cardiac branch of the vagus nerve in mammals contains both myelinated and non-myelinated efferent fibres, derived from either nuclei, plus very large numbers of afferent/sensory fibres, providing feedback on the condition of the heart to the brainstem. To separate the functional properties of the two efferent fibre types, it is necessary to use robust and specific electrophysiological techniques, such as 'anodal block' (Jones et al., 1995).

To clarify what constitutes the 'vagus', it is worth reminding ourselves that the X^{th} cranial nerve (the vagus or the pneumogastric nerve) in mammals supplies the heart, the lungs, soft palate, larynx, pharynx, and esophagus (generating peristalsis) as well as multiple organs caudal of the diaphragm that do not concern the present discussion. A branch of the vagus is the recurrent laryngeal nerve innervating the larynx and pharynx that controls vocalisation, which is virtually unique to mammals and thus merits attention from PVT.

We also need to define the nature of the mammalian NA, which extends throughout the ventrolateral medulla. Rostrally, it extends from the level of the facial nucleus, while its caudal limit extends to the first

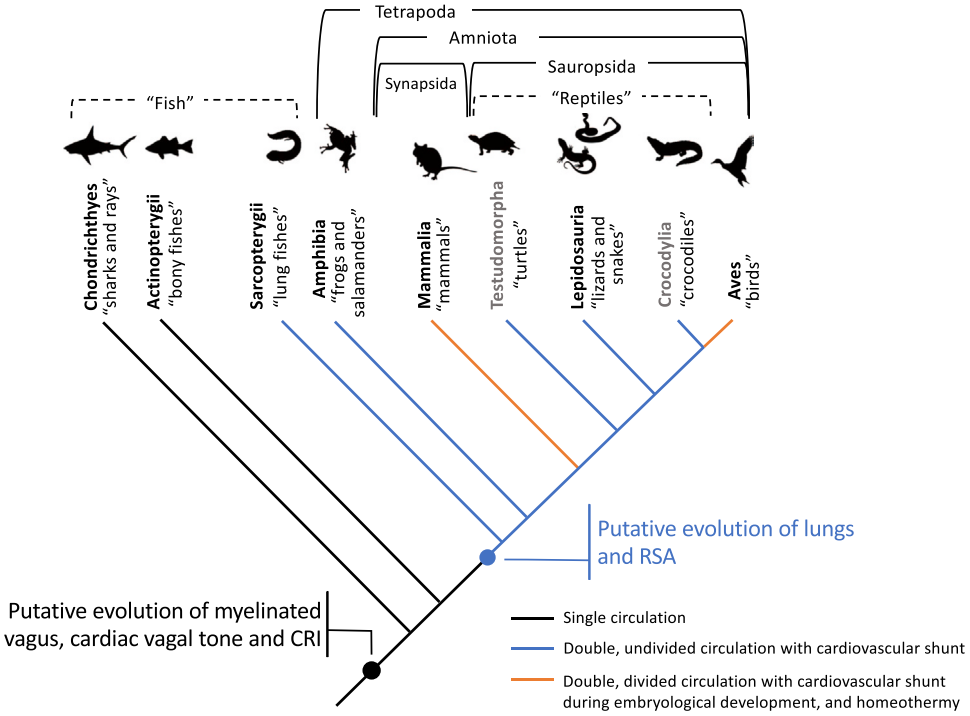

Fig. 1. A simplified cladogram of the vertebrate group, which indicates the relationships between organisms. This provides a parsimonious analysis of the evolution of morpho-functional traits. The black filled-circle indicates the putative evolutionary origin of both: a myelinated vagus and cardiorespiratory interactions (CRI), initially in aquatic vertebrates with a single circulation (black line). The blue filled-circle indicates the putative evolutionary origin of lungs for air-breathing together with CRI resembling Respiratory Sinus Arrhythmia (RSA) in vertebrates with a double, undivided circulation, enabling vascular shunting (blue line). The orange line denotes endothermic groups with double and completely divided circulations (with a cardiovascular shunt during embryological development). CRI have not yet been investigated in Testudomorpha and Crocodylia (in grey). The groups (fish and reptiles) indicated by divided lines refer to popular divisions.

cervical segment of the spinal column. A dorsal division of the NA provides somatomotor innervation from the vagus to the pharyngeal and thoracic viscera, while the ventral division is comprised of parasympathetic preganglionic neurons. The majority of VPN innervating the heart and lungs (78% and 68% respectively in the cat[5]) are in the NA. In addition to the heart and lungs, neuron cell bodies in the NA also innervate muscles of the soft palate, larynx, and pharynx by contributing motor fibres from three cranial nerves: the glossopharyngeal (IXth), vagus (Xth), and spinal accessory (XIth).

PVT states that the viscerotropic organisation of the "*vagal system*" becomes more complex in mammals during "*phylogenetic development*" by incorporating pathways from other cranial nerves, including the trigeminal, facial, accessory, and glossopharyngeal. By this device, PVT includes integration of functions such as head rotation, mastication, and salivation into the "*vagal system*" thus creating a "*smart vagus*" and the consequent naming of PVT. However, as stated above, several of the functions described are not mediated by the vagus nerve, but by other cranial nerves with separate motor origins and distinct functions, some with their nuclei located outside of the NA. Because PVT states that the NA forms the '*special medullary centre*' that is the origin of the '*smart vagus*' it implies that the NA incorporates groups of neurons (nuclei) that provide axons to cranial nerves other than the vagus. As stated above, this is, in part, the case but several of these cranial nerves have separate functions, some under conscious control, and do not project from the NA. Consequently, it seems invalid to refer to this as a "*vagal system*" or to postulate the existence of a "*smart vagus*".

A more coherent description of the combined actions of these cranial nerves was provided by reference to them as "*the social engagement system*" (Porges, 2007a, 2009). This described a somatomotor component, innervating facial muscles (VIIth - the facial cranial nerve), plus the muscles of mastication (Vth - the trigeminal cranial nerve), head-turning (XIth - the accessory cranial nerve), and those supplying muscles of the larynx, pharynx (Xth - the vagus) plus the middle ear (Vth - the mandibular cranial nerve). In addition, the XIIth (the hypoglossal cranial nerve) supplies somatic efferent fibres to the intrinsic and extrinsic muscles of the tongue, while a conjoint spinal nerve (C1) supplies the geniohyoid muscle, which inserts on the hyoid bone and aids swallowing. These nerves were discriminated from the visceromotor component, innervating the bronchi and heart via a myelinated vagus, largely originating in the NA. This description of a complex system may indeed govern important aspects of social engagement in mammals, though PVT should probably address the role of areas in the forebrain in calming and the conscious control of behaviour.

As we will illustrate below, elements of the system generating CRI and even RSA in particular, have been described in non-mammalian vertebrates. So, it is not useful to regard mammals as unique in this and many other respects. This tendency of some workers to stress the special nature of mammals often betrays an anthropocentric bias that may enrapture students of psychology and even some areas of biomedical science. This subjectivity can seem short-sighted to comparative physiologists, who strive to uncover the evolution of function, such as neural control of the cardiovascular system, by studying extant species from a range of vertebrate groups (see Table 1).

3.1. *Sauropsida - "Reptiles" (turtles, lizards, snakes and crocodilians)*

Many of the arguments advanced in support of PVT claim that mammals show unique brain structures and functions compared with reptiles: "*Since our interests are in mammals and specifically humans, this paper will focus on the evolution of vagal regulation of cardiac function from reptiles to mammals*" (Porges, 1995). This emphasis on reptiles versus mammals has classic undertones, reminiscent of historical zoological texts that contrasted the "advanced" mammalian against the "primitive" reptilian brain. A more recent publication (Porges, 2021) takes a stronger line in considering the phylogenetic transition from reptiles to mammals, stating that the ANS was: "*repurposed to suppress defensive strategies in order to support and express sociality… …with capacities to self-calm, to spontaneous socially engage others, and to mitigate threat reactions in ourselves and others through social cues.*". We have argued above that this grand vision is not explained by phylogenetic changes in the specific roles of the vagus nerve and its central connections. It describes the functional roles of the so-called '*vagal system*' invoked by PVT that incorporates aspects of control exerted by several cranial nerves arising from different areas of the brainstem. Behaviours that can be described as 'social engagement' are also likely to include inputs from 'higher centres' in the forebrain, responsible for conscious responses. Although

the assertions made by PVT expand enormously outside of the established roles of the vagus nerve in controlling HRV and RSA they should not be taken by its supporters as rendering our comparative survey of these particular functions in all vertebrate groups as outside of their professional and intellectual interests. We would consider this a short-sighted response, as PVT incorporates these features into its assertions about the stated primacy in psychological terms of mammals over reptiles. As physiologists interested in the evolution of function, we remain convinced of the importance of a consideration of the evolving role of the vagus, at its singular level of function in cardiac control, throughout the vertebrate groups. We suggest that this should be of interest to anyone speculating over the primacy of mammals, in terms of neural control of survival strategies at any level. The limitations claimed for the reptiles are of particular concern, as their antecedents occupy a key position in the evolution of mammals.

Consequently, given the importance of the reptile-mammal transition to the arguments advanced in development of PVT, we begin our examination of the phylogeny of cardiac control in vertebrates with this anatomically diverse and fascinating group of ectothermic amniotes. It is of immediate importance to stress that the term 'reptile' covers a diverse group of primarily terrestrial animals, broadly described as having dry, scaly skin, laying soft-shelled eggs and having a body temperature that varies with the external environment. However, this description ignores a complex phylogeny. The term 'reptile' represents a 'paraphyletic' group of organisms, the turtles, squamates (lizards and snakes) and the crocodilians, which have descended from a common ancestral group, but is not inclusive of all its descendants. A cladistic analysis of the group indicates that it comprises all amniotes except synapsids (the mammals and their extinct relatives). The reptiles evolved from a sauropsid stock, which includes the extinct dinosaurs and the crocodilians that are more closely related to the birds than they are to the other living reptiles. So, a proper phylogenetic description of the reptiles would include birds. These relationships are illustrated in Fig. 1. To aid the likely readership of this article we have retained the traditional Linnaean classification for this synopsis, considering the reptiles together and treating birds as a separate group.

PVT characterises the control of the reptilian heart as reliant on the "*primitive vagus*", located in the DVN, supplying unmyelinated vagal efferent axons to the heart. These are described as generating a bradycardia associated with "orienting" or "freezing" of motor activity, in response to stimuli such as the presence of a predator or prey, which in mammals would cause arousal, increased physical activity and tachycardia. Thus, reptiles are characterized as showing: "*low ambient vagal tone and transient increases in vagal tone in response to environmental challenges*" (Porges, 1995, 2021). This implies that reptiles do not exhibit a 'fight or flight' response, being depicted as: "*under-powered*" with "*no vagal brake*" on the heart as it would "*further reduce energy production during unchallenged situations*". In contrast to "*underpowered reptiles*", PVT describes the "*supercharged mammals*" as supplying myelinated vagal efferent fibres to the heart from the NA as a persistent brake to inhibit the metabolic potential of their "*high-powered system*". It describes the high vagal tone in mammals, generated in the NA, as keeping them from "*literally, bouncing off the walls"* (Porges, 2011).

Based on a small number of early studies (e.g. Belkin, 1964; Jacob & McDonald, 1976), PVT considers the vagal, inhibitory modulation of the heart in reptiles to be restricted to behavioural freezing or diving, with virtually no regulation during periods of intermittent lung ventilation and physiologically relevant situations such as muscular exercise or digestion. This assumption is immediately contradicted by consideration of our work with snakes[7]. When engaged in physical activity or threatened by the immediate presence of the investigator Boidae[7] snakes did not "*freeze*". When handled, they struck at and bit the masked hand of the investigator. During this vigorous response, HR doubled and this increase was largely due to withdrawal of an inhibitory cholinergic tone, plus a less marked rise in sympathetic tone (Taylor et al., 2001). Subjective responses to working with reptiles have convinced us that they cannot be described as '*under powered*'. Adult green iguanas[8] and even juvenile caiman[9] have to be handled with great care, including thickly gloved hands. They fight or flee!.

On the basis of large numbers of studies published over more the course of more than 50 years (see for example Burnstock, 1969; Hedberg & Nilsson, 1975), we consider the view of autonomic regulation of the reptilian heart advanced by PVT to be erroneous. As in mammals, well conducted studies on undisturbed reptiles, clearly demonstrate that HR operates under a high level of vagal modulation and that the excitatory sympathetic innervation is of little importance in inactive, undisturbed animals[7,8,10,11,12,13,14] (Campbell et al., 2006; Enok et al., 2012; Taylor et al., 2014; Taylor, Andrade et al., 2009; Wang & Warburton, 2001; Wang, Taylor et al., 2001). Thus, when HR is measured in an undisturbed reptile, the variations in its mean values are primarily due to differences in cardiac vagal tone. The parasympathetic role in determining mean HR can be revealed by injection of atropine, an antagonist to muscarinic, cholinoreceptors on the heart, while injection of the β-receptor antagonist, propranolol reveals adrenergic tone (Duran et al., 2020; Sanches et al., 2019). In undisturbed *boas*[7] the average cholinergic tone on the heart, calculated from cardiac intervals using equations given in a previous study (Campbell et al., 2006), was 65% while adrenergic tone was 20%. There was a very clear inverse relationship between changes in parasympathetic tone and mean HR, including following a meal (Wang & Warburton, 2001; Wang et al., 2021; Wang, Taylor et al., 2001). With regard to control of HR in rattlesnakes[10], held undisturbed in our laboratory, adrenergic tone on the heart was 40% while cholinergic tone was 120%, which implies that mean HR doubled after cholinergic blockade (Campbell et al., 2006). In two species of lizards (green iguana[8] and black and white tegu[11]) adrenergic tone was 25% while cholinergic tone varied between 30% and 70% (Sartori et al., 2015; Taylor et al., 2014). There are many other examples showing the primacy of cholinergic tone (Overgaard et al., 2002; Sartori et al., 2015; Taylor & Wang, 2009; Taylor et al., 2014). Accordingly, the reptiles studied to date can be characterised as possessing a predominant cardiac vagal tone, with any increase in mean HR during disturbance or activity being largely due to withdrawal of this inhibitory vagal tone, although there may be a short-term increase in sympathetic activity (Taylor et al., 2014).

PVT clearly states that RSA is not observed in reptiles, quoting a study investigating spectral components of HRV that failed to identify oscillations in HR associated with ventilation (Gonzalez & Porcell, 1988). On the basis of power spectral analysis of HRV on two species of lizards[15,16] (Gonzalez & Porcell, 1988; Porges et al., 2003), it was concluded that there was no spectral component associated with ventilation in the HRV signal from either species and consequently, for reptiles. However, it is only possible to detect RSA when HR is at least twice as fast as ventilation, a relationship termed the Nyquist criterion, which was covered in some detail in a previous review (Grossman & Taylor, 2007). Data presented in the tables and figures of these articles on lizards clearly indicate that the respiration rate approximated the HR (i.e. was greater than 0.5 the cardiac frequency). Thus, 'aliasing' would have occurred during measurement rendering detection of CRI by spectral analysis impossible (Grossman & Taylor, 2007). It is also probable these animals had a reduced vagal tonus on the heart due to conditions imposed by experimentation, causing a high and unvarying HR. Incomplete recovery from anaesthesia, the effects of instrumentation or handling; even the mere presence of the experimenter, are all factors that potentially can blunt physiological responses, including levels of autonomic control of visceral functions. This could cause a reduction in vagal modulation and increasing sympathetic influence over the heart. Such imbalances are incompatible with respiratory modulation generating RSA, which is generated via the parasympathetic NS, though evidence of RSA is not an index of the extent of cardiac vagal tone, as determined by efferent activity emanating from the NA (Grossman & Taylor, 2007). Studies on a range of reptilian species including snakes[10], lizards[11] and crocodiles[17] (Bertelsen et al., 2021;

Campbell et al., 2006; Duran et al., 2020; Sanches et al., 2019; Stegmann et al., 2017) showed that mean HR remains elevated for several hours following experimental manipulation and respiratory modulation of the cardiovascular system, including HRV, is only restored when resting HR is re-established by a normal high vagal tone.

It is also a potential problem that analysis of spectral components in HRV is confusing in vertebrates having relatively low metabolic rates as these are often matched by reduced rates of ventilation and episodic breathing. At low rates of ventilation, the associated peak in spectral analyses of HRV is likely to overlap other peaks at low or even over very low frequencies (LF and VLF peaks, Duran et al., 2020; Monteiro et al., 2018; Sanches et al., 2019). Also, when breathing is episodic, the observable peak in spectral analyses is less prominent and can be embedded with other peaks (Duran et al., 2020; Sanches et al., 2019).

In rattlesnakes[10] HR is about five times higher than ventilation, which in settled animals shows long periods of regular activity. Using data-loggers to monitor HR in unrestrained rattlesnakes enabled us to observe clear HRV in these settled, recovered animals. We recorded a respiratory component in the power spectrum of HRV from these snakes that developed as HR fell following disturbance and varied with diurnal changes in activity levels (Campbell et al., 2006). In a later telemetric study on remotely monitored rattlesnakes, animals with low settled HR showed ventilation-related HRV. This was shown to vary with the alterations in ventilation that followed temperature change (Sanches et al., 2019). These variations were respiration-related, with instantaneous HR slowing upon expiration and increasing during inspiration (Campbell et al., 2006). This pattern of variation is similar to that recorded from conscious, unrestrained mammals and characterised as RSA (Berntson et al., 1993). This relationship was abolished in rattlesnakes[11] by injection of atropine, indicating that it is controlled by muscarinic receptors innervated by the parasympathetic arm of the ANS, via the vagus nerve (Campbell et al., 2006).

Inactive reptiles show very large changes in instantaneous HR during intermittent ventilation of their lungs. Thus, as in mammals, there is a very pronounced interaction between the cardiovascular and respiratory systems. A tachycardia during bouts of ventilation is characteristic of species belonging to all major groups of reptiles[18–34] (e.g. Andersen, 1961; Heatwole, 1977; Huggins et al., 1970; Jacob & McDonald, 1976; Pough, 1969; Johansen, 1959). Additionally, spontaneous changes in HR are most pronounced on surfacing after a dive in aquatic species and an early description of the tachycardia during ventilation in turtles[35], which spend prolonged periods submerged, even suggested that bradycardia during breath-hold represent the normal state (Belkin, 1964). In both the slider turtle[36] and the tortoise[37], the onset of lung ventilation following breath-hold, was closely accompanied by a tachycardia (Burggren, 1972). These changes in instantaneous HR with ventilation disappear upon pharmacological blockade of the ANS[10] (Taylor & Wang, 2009; Taylor, Andrade et al., 2009). Although activity from lung stretch receptor afferents have been recorded from the vagus nerve of reptiles[10,12,38,39] (Sundin et al., 2001) and a functional role for lung stretch receptors was established for a lizard[40] (Al-Ghamdi et al., 2001), experimental stimulation of pulmonary stretch receptors, arterial chemoreceptors and baroreceptors or water receptors was without obvious effect on heart rate. Thus, we concluded that the tachycardia at the onset of ventilation most likely resulted from central interactions between respiratory and cardiac neurons in the medulla (Taylor & Wang, 2009).

In addition to modulating instantaneous HR, the vagus nerve also regulates pulmonary arterial resistance. Injection of atropine increased both mean HR and pulmonary blood flow in all species studied[10] (Taylor & Wang, 2009). Changes in blood flow to the lung are possible due to a cardiac shunt operating across the undivided ventricle of the reptilian heart. Efferent activity in the vagus nerve innervating the pulmonary artery, causes vasoconstriction, increasing its resistance and redirecting blood flow into the systemic circulation. This change is termed a right to left cardiac shunt[10]. Section of relevant vagal branches cancels control of pulmonary blood flow and increases lung perfusion[10] (Filogonio et al., 2020; Filogonio et al., 2016; Leite et al., 2014; Leite et al., 2013; Taylor, Andrade et al., 2009).

PVT correctly emphasises the importance of the NA in the generation of RSA in mammals, but also claims that the presence of this ventrolateral nucleus in the brainstem and its functional role are unique to this group, claiming that the heart in reptiles is supplied solely with unmyelinated axons from the DVN. However, PVT has accepted that separation of the vagal motor nucleus into a dorsal nucleus (the DMNX or DVN) and a ventrolateral nucleus (the NA) "*is first seen in reptiles*" (Porges, 2011). In chelonians[41], the two nuclei are "connected" but in a crocodilian[42] and a lizard[43] "*the separation between DVN and NA is as complete as it is in mammals*". This observation agrees with our neuroanatomical studies. Turtles and tortoises[44–46] (the anapsids) have a large proportion of VPN (40–50%) in ventrolateral nuclei that could form an equivalent of the NA (Cruce W.L.R, 1974; Leong et al., 1984; Taylor et al., 2014). Crocodilians such as the broad nose caiman[9] have the majority of VPN in the DVN but there is a discrete lateral cell group outside the DVN, containing about 12% of VPN and designated as a putative NA (Taylor et al., 2010). Although a previous study showed a clearly defined NA in the brainstem of a lizard[47] (Barbas-Henry & Lohman, 1984), in the squamate reptiles (lizards and snakes) we observed a relatively sparse distribution of VPN outside of the DVN. In an agamid lizard[40] and an iguana[8], the majority of VPN were located in the DVN with a small proportion (2–6%) scattered ventrolaterally (Taylor et al., 2014). In the rattlesnake[10] 95% of VPN were in the DVN while ~4% of VPN were located in scattered ventrolateral locations outside the DVN (Campbell et al., 2006). However, in the rattlesnake[10] a proportion of the neuron cell bodies located outside of the DVN were CVPN plus VPN supplying the pulmonary artery (Campbell et al., 2006; Filogonio et al., 2020), providing possible sites for central interactions between CVPN and pulmonary artery VPN that could govern cardiorespiratory integration, including cardiac shunting.

Both the rattlesnake[10] and the tegu lizard[11] display a clear respiration-related power spectrum component in their HRV. This is developed at relatively low HR and can be abolished by atropine. Accordingly, this component was designated as reptilian RSA (Duran et al., 2020; Sanches et al., 2019). To what extent this relationship is generated centrally or as a result of peripheral reflexes remains to be investigated, though evidence from study of the generation of a tachycardia at the onset of a bout of ventilation strongly suggests an important contribution from central interactions (see above). Neither can we yet determine which group of CVPN generates RSA in these reptiles. This requires central recordings from identified sites in the CNS and would necessarily include location of respiratory neurones, which also remains to be done. However, our neuranatomical studies have revealed that several species of lizards, snakes and crocodilians have VPN both within the DVN and in ventrolateral groups that may represent a reptilian NA (reviewed by Taylor et al., 2001; Taylor et al., 2010; Taylor, Leite, McKenzie et al., 2010; Taylor et al., 2014). Together, these experimental data are robust enough to refute the proposition that centrally controlled cardiorespiratory interactions, generated from VPN in dual locations in the brainstem, are restricted to mammals, as propounded in the background to PVT (Porges et al., 2003; Porges, 2009, 2011).

The declaration that: "*Only mammals have a myelinated vagus.*" (Porges, 2009, 2011) also defies decades of descriptions of myelinated fibres in branches of the vagus nerves from a wide range of vertebrates. Recently we have presented electron micrographs that identified myelinated fibres in the cardiac branch of the vagus in rattlesnakes[10] (Sanches et al., 2019) and tegu lizards[11] (Duran et al., 2020). We are at present examining the ultrastructure of the vagus nerve in a range of other species in combination with measurements of conduction velocity (Taylor et al., 2014).

As described earlier, reptiles show cardiac shunting, with flow to the lungs controlled by changes in the peripheral resistance of the pulmonary artery, which is under vagal control[10] (Filogonio et al., 2020).

Accordingly, an increase in HR at the onset of a breathing bout, when combined with shunt control, both due to withdrawal of an inhibitory vagal tonus, may be highly effective in increasing oxygen uptake during bouts of air-breathing. This provides a directly relevant function for centrally controlled, respiratory modulation of the cardiovascular system, which is likely to have been retained during phylogenetic evolution. Mammalian RSA, which does not have a clearly defined physiological role, would seem to be rooted in their reptilian ancestry.

As an afterthought it may be worth noting that some reptiles do 'express sociality' by providing parental care of offspring. Female crocodiles await the hatching of their clutch of eggs then protect the hatchlings from predation and starvation while some female pythons surround their clutch and warm it, raising their body temperature by shivering thermogenesis, with blood flow through the heart temporarily directed separately to the systemic and pulmonary circuits, showing pressure separation as in mammals and birds (Alexander, 2018; Brazaitis & Watanabe, 2011; Doody et al., 2021; Harlow & Grigg, 1984; Slip & Shine, 1988; Vergne et al., 2009).

3.2. Aves (birds)

Birds are grouped with crocodilians as Archosaurs (see Fig. 1), a group that also included the extinct dinosaurs, but differ from crocodilians by being endotherms that maintain high stable body temperatures (around 42 °C). As in mammals, the high rates of metabolism required for endothermy are supported by a completely divided heart with ventricular pressure separation, high HR as well as high systemic blood pressures and high blood flows. Having evolved from separate groups of reptilian ancestors, the endothermy in birds and mammals are a striking example of convergent evolution (but see below) leading to very similar cardiovascular physiologies. PVT gives scant attention to birds and yet, like mammals, birds are fast-reacting, alert animals showing a wide and varying range of complex behaviour patterns, including courtship, nesting and parental care, often supported by apparently monogamous relationships; migration, use of tools and communication, including mimicry. Birds 'sing' using the syrinx, which is located at the base of a trachea. Some of the muscles in the syrinx insert on the sternum and produce sounds without the vocal folds of mammals, using vibrating membranes at the entrance to the bronchi, with some species able to produce two tones concurrently. Bird calls are specifies-specific and serve to hold flocks and nestlings together and to establish territories. These abilities are similar or often superior to those shown by many mammals and emphasised by PVT, which refers to the "*supercharged mammals*". Flying birds can support their body weight while hovering, diving to catch prey or traversing continents, so can certainly be described metaphorically as: "*bouncing off…* or over!. *the walls*".

Birds breathe continuously and rhythmically to supply their high metabolic rate. They lack a diaphragm and through-ventilate the lungs into air sacs. Gas exchange occurs over the parabronchi that do not change volume during ventilation. Intrapulmonary chemoreceptors in birds are extremely sensitive to intrapulmonary CO_2, but relatively insensitive to lung stretch (Maina, 2006; Scheid & Piiper, 1986). As in reptiles and mammals, the reflex effects of central chemoreceptor stimulation appear to predominate over all other receptor inputs. However, there is evidence of feed-forward central control of cardiorespiratory interactions dependent upon vagal efferent control of HR (Taylor et al., 1999). Birds have dual autonomic innervation of the heart but the inhibitory parasympathetic control dominates as in mammals. Bilateral vagotomy tripled HR in the pigeon[48], duck[49] and seagull[50], while in the cormorant[51], the adrenergic tone was at about 30%, and the inhibitory vagal tone was far higher at 240%, implying that mean HR increased 2.4-fold following cholinergic blockade (Taylor et al., 2014; Yamamoto et al., 2009).

HRV has been recorded in several bird species. Similar to mammals, due to their high ventilatory frequency, there are distinguishable low and high frequency components (LF and HF) on the power spectrum signal calculated from the inter-beat intervals. LF oscillations appear to be related to thermoregulation and are altered by stress, while the HF component relates to ventilation in birds[52–54] (Carravieri et al., 2016; Cyr et al., 2009; Khandoker et al., 2004; Kjaer & Jørgensen, 2011). The mechanisms generating the HF component in HRV are unknown, and may be affected by the ventilatory mechanics of bird lungs that involve air sacs rather that changes in lung volume (Maina, 2006; Scheid & Piiper, 1986). The nature of cardiorespiratory interactions in birds has been elucidated to some extent by studying the responses to submersion of diving species. Clear indications of respiration-related oscillations in HR, similar to the RSA described in mammals, were recorded in spontaneously breathing ducks[55] with denervated lungs. The peaks of the accelerations in HR were clipped off when water was poured down an orally facing tracheal cannula, suggesting that they were generated centrally by interactions with the respiratory rhythm generator and lost during stimulation of receptors that normally respond to submersion by inducing apnoea (Butler & Taylor, 1983). This implies that inhibitory activity in CVPN is modulated by respiratory activity. As this modulation reduces vagal tone, it is likely inspiratory neurons inhibit CVPN as in mammals (see above). There was a slight increase in instantaneous HR on surfacing from forced submersion in the ducks[55] with denervated lungs, which was interpreted as further evidence for central interactions between inspiratory neurones and CVPN (Butler & Taylor, 1983). A ground-breaking study remotely recorded respiration-related HRV from shearwaters[54], using ECG data-loggers. This revealed clear high frequency peaks in the power spectrum at a frequency which matched the respiratory rate (Carravieri et al., 2016). Injection of antagonists to the ANS revealed that control of HRV was predominantly from the parasympathetic arm. As such, this pattern of HRV resembles mammalian RSA.

In addition to these similarities in HRV, birds may also possess the equivalent of a mammalian NA with respect to the distribution of CVPN. VPNs in the pigeon[48] are localised in the DVN and in an area identified as the avian homologue of the reticular formation (Katz & Karten, 1985). In the tufted duck[56] VPNs are located predominantly in the DVN with only 3% of cell bodies in a putative NA and a diffuse area identified as the reticular formation. However, while 77% of CVPNs were located in the ventral subnucleus of the DVN, 21% were in the NA and 2% in the reticular formation (L. Blogg, P. J. Butler & E. W. Taylor, unpublished observations – cited by Taylor et al., 2014). This distribution represents a relative concentration of CVPN into areas outside of the DVN as the mean number of CVPNs in the DVN represents only about 3% of the total population of VPNs; whereas, in the NA, CVPN represent about 30% of total VPN. This disproportionate distribution of CVPN outside of the DVN suggests that birds may have evolved a similar functional separation of CVPN to that described in mammals and as a consequence have the central connections enabling the generation of avian RSA. This remains to be investigated (Taylor et al., 2001).

There is clear evidence of myelination of the vagus nerve in birds[53] (Abdalla & King, 1979) as observed in MEV analyses[48] (Schwaber & Cohen, 1978). In general, the observed HRV has been attributed to fast-conducting myelinated vagal nerves (Stauss, 2003; Taylor et al., 2014).

On the basis of the criteria listed above, it seems realistic to postulate that birds show CRI that can be characterized as an avian version of RSA, very similar to that in all respects with described in mammals. This could be regarded, along with homeothermy, as an example of convergent evolution from their separate reptilian ancestors. However, this is likely to be an overly simplistic interpretation of the data. To assume that we have witnessed a completely independent, mimetic evolution of these fundamental processes in these two groups could be to misunderstand the nature of phylogenetic evolution, which posits that relatedness among taxa follows a tree-like structure (Page, 2003). A recent detailed review (Grigg et al., 2021), observed that there is a considerable similarity between the processes driving non-shivering thermogenesis

between birds and mammals. These authors framed the hypothesis that whole-body endothermy is homologous in the two groups and did not originate by independent, convergent evolution as distinct processes. This suggested homology was supported by compelling evidence, gained from palaeontological studies, for the widespread occurrence of whole-body 'tachymetabolic' endothermy among numerous extinct dinosaurs from both the synapsid and sauropsid stocks, very early in each clade's family tree. These clades are respectively the antecedents of mammals and birds. So, endothermy can be described as a plesiomorphic trait, distinguishing both mammals and birds. Therefore, it is parsimonious to suggest that the characteristics of vertebrate CRI are similarly homologous between mammals and birds. Thus, mammalian and avian RSA likely evolved from a common ancestral, likely reptilian stock that showed similar characteristics in CRI to both groups (see Fig. 1).

3.3. Amphibia (toads, frogs and salamanders)

Amphibians represent the transition from aquatic to terrestrial life within vertebrates. Their aquatic, gill-breathing larvae (tadpoles) metamorphose into amphibious adults, inhabiting both terrestrial and aquatic habitats. In adult anurans (frogs and toads) respiratory gas exchange is bimodal as they use both the structurally simple lungs, force ventilated by muscles in the buccal cavity, as well as the well-perfused skin (Gargaglioni & Milsom, 2007). Amphibians characteristically have two ventilatory rhythms, an oscillatory gular pump, ventilating the buccal cavity and a positive pressure pump, driving periodic lung inflation. Like reptiles, amphibians have an undivided ventricle with the possibility of cardiac shunting (see above). Bouts of lung ventilation are accompanied by a rapid and instantaneous tachycardia and increased perfusion of the pulmonary circuit[57] (Taylor et al., 1999, 2010; Wang, Taylor, et al., 1999a; Wang & Taylor, 1999).

Similar to other vertebrate groups, amphibians typically have a dominant cholinergic tonus as the major autonomic influence over mean HR[58–62] (Longhini et al., 2017; Taylor et al., 1999, 2014; Zena et al., 2017). However, experiments on adult amphibians have reported diverse levels of cholinergic tonus on the heart[59,60] (Claësson et al., 2015; Ihmied & Taylor, 1995; Taylor et al., 2014). Adult bullfrogs[60], when routinely active, were reported to have negligible vagal tone on the heart and moderate levels of adrenergic tone (Taylor et al., 2012), while the African clawed toad[59] shows a very high level of inhibitory vagal tonus on the heart, which increases with temperature and during hypoxia (Taylor & Ihmied, 1995; Taylor et al., 2012). Neither of these studies made observations of HRV. However, a recent, unique power spectral analysis of HRV in the cururu toad[62] identified a well-marked peak in the HRV spectral signal that matched the frequency of the lung inflation cycle. These cardiorespiratory interactions were shown to be under parasympathetic control (Zena et al., 2017). An electron microscopic study of the cardiac branch of the vagus nerve in this species identified myelinated axons (C.A.C. Leite – *unpublished observation*). The sum-total of these data likely identify our first example of RSA in an amphibian.

There is likely to be a central component influencing these cardiorespiratory interactions in many amphibians, linked with the fact that 30% of VPN supplying the larynx, heart, lungs and viscera in the African clawed toad[59] lie in a ventral nucleus outside of the DVN that may represent an amphibian NA (Wang, Taylor, et al., 1999a). Increases in heart rate and pulmonary blood flow during bouts of fictive breathing in decerebrated, paralyzed and through ventilated toads[57] were indicative of central control of cardiorespiratory interactions (Wang & Taylor, 1999). Also, denervation of pulmonary stretch receptors in the African clawed toad[59] did not abolish the increase in heart rate associated with lung inflation, again implying a role for central interactions (Taylor et al., 1999). The low levels of cardiac vagal tone recorded from inactive, adult bullfrogs may relate to the fact that all of their VPN are located within the DVN, though no observations of HRV were made in this study[60] (Taylor et al., 2012).

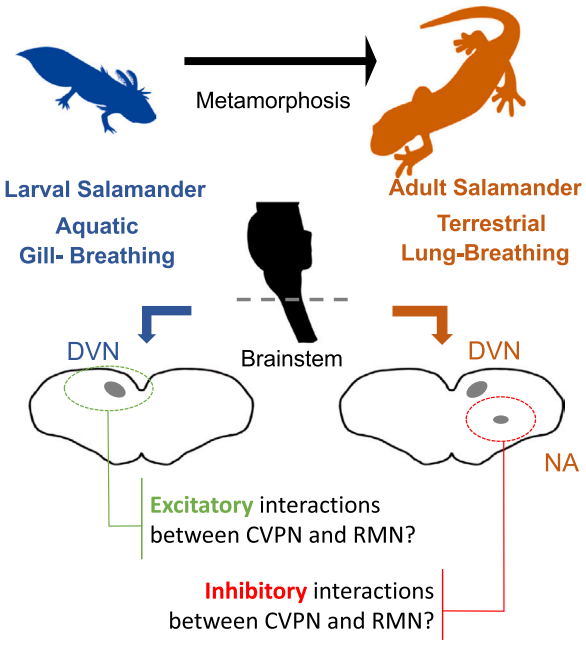

Fig. 2. Cartoon of putative changes accompanying metamorphosis in amphibians. The larval salamander is an aquatic gill-breather which metamorphoses into an adult terrestrial lung-breather, losing its gills and ventilating lungs. During this change the number of vagal preganglionic neurons increases and some (15% in axolotl) migrate from the dorsal motor column of the vagus (DVN) into a ventrolateral *nucleus ambiguous* (NA) (Ihmied & Taylor, 1992a; Taylor et al., 2001). The heart, lungs and larynx are innervated from both nuclei in adult *Xenopus,* with 30% in the NA (Ihmied & Taylor, 1992b; Wang et al., 1999a; 1999b). This redistribution of vagal preganglionic neurons may signify a change from excitatory to inhibitory interactions between cardiac vagal preganglionic motoneurons (CVPN) and respiratory motoneurons (RMN).

As amphibians metamorphose from an aquatic larval stage to air-breathing adults, they provide the ideal model for testing the hypothesis that the ventrolateral location of VPN in vertebrates may be somewhat related to the development of lung-breathing (Taylor, 1993). Neuroanatomical studies of the neotenous axolotl[58] showed that in the pre-metamorphosed, aquatic adult the VPN are concentrated in the medial DVN. Following induced metamorphosis, when the animal migrated onto land and switched to air-breathing, VPN almost doubled in number and about 15% of them were relocated into a ventrolateral position (Taylor et al., 2001) (Fig. 2). This change was accompanied by an increase in HRV (Aruna Narshi, *unpublished observations*). The ventrolateral migration of neuron cell bodies from the DVN to form the NA occurs during embryonic development in mammals[5] (Windle, 1933). Although currently discredited, the theory that "ontogeny recapitulates phylogeny" would support the suggestion that the DVN is more 'primitive' than the NA. But fish species with a long heritage contradict this theory (see below). Once again, comparative studies reveal mechanisms in 'lower' vertebrates that mimic those described for mammals[63] (Taylor & Gee, 2021).

3.4. Sarcopterygii (lungfishes)

Air-breathing in fishes is epitomised by the lungfishes (Order - Dipnoi), which represent the earliest vertebrate group with an air-breathing organ (ABO) that can be considered, on both anatomical and functional criteria, as a true lung. This group of lobe-finned fishes (subclass Sarcopterygii – see Figs. 1 and 4) arose in the Devonian period around 400 million years ago, together with early tetrapods, with which they share many plesiomorphic features, including limb and jaw structure, paired lungs and a pulmonary circulation[64–66] (Biscotti et al., 2016; Graham,

1997; Nogueira et al., 2016). The lungs are inflated by means of a buccal pressure pump that forces air into the lungs by raising the floor of the closed mouth, using muscles inserted on the pectoral girdle and innervated by the hypobranchial nerves (Taylor et al., 1996; Taylor et al., 1999). Expiration is brought about by elastic recoil of the lungs[64–66] (Graham, 1997; Moraes et al., 2005). A similar mechanism operates in amphibians, so it can be postulated that these features were fully evolved in the ancestral lobe-finned fishes whose ancestors crawled onto land and evolved into the Tetrapoda, initiating the vertebrate terrestrial invasion. The circulatory system is specialized for air-breathing, with separate pulmonary and systemic circulations anticipating the amphibian system[64–66] (Burggren & Johansen, 1986). Both heart rate and pulmonary blood flow increase during air-breathing[65] (Monteiro et al., 2018). Lungfishes are endowed with pulmonary stretch receptors as well as both central and peripheral chemoreceptors that provide feedback supporting these responses[64,65] (DeLaney et al., 1983).

The South American lungfish[65] rises to the surface at regular intervals to ventilate the lungs and can survive for long periods in burrows during drought (Amin-Naves et al., 2004; Sanchez et al., 2001). Each air-breathing episode is accompanied by an immediate and marked increase in instantaneous HR, due solely to cholinergic parasympathetic modulation (Axelsson et al., 1989; Monteiro et al., 2018). Power spectral analysis of this HRV showed a clearly defined peak at each individual breathing frequency, these CRI resemble mammalian RSA, though, because of the low surfacing rates of lungfish, these peaks were located at relatively “very low frequencies”, according to mammalian criteria (Malik et al., 1986). The immediacy of the cardiac response was attributed to the measured conduction velocity of cardiac vagal fibres, some of which matched mammalian B-fibres and, like them, have myelin sheaths[65] (Monteiro et al., 2018) (see Fig. 3). The presence of RSA-like HRV in lungfish was shown to be effective in improving oxygen uptake per breath[65] (Monteiro et al., 2018). It is of interest to the present debate that this unique experimental evidence of a role for ‘RSA’ was observed in this primitive lung breathing vertebrate (see Fig. 1).

Mechanisms for central control of air-breathing (AB) in lungfish are unknown, but our recent study on the piramboia[65] revealed that CVPN have multiple locations in the brainstem, both within the DVN and ventrolateral to it (Monteiro et al., 2018). This suggests that control of the heart and possibly the pulmonary arterial supply by the parasympathetic vagus nerve has diverse influences from within the CNS, resulting in their observed integration with AB (Bayley et al., 2019; Fritsche et al., 1993). It has been suggested that the African lungfish[64] possesses two separate central rhythm generators, one for gill ventilation and the other for air-breathing[64,65,67] (Fishman et al., 1985). It seems possible that the former innervates the jaws and branchial innervation via the V^{th}, VII^{th}, IX^{th}, and X^{th} cranial nerves generate gill ventilation, while the latter supplies the hypobranchial complex via occipital and anterior spinal nerves, generating AB[68] (Taylor et al., 2006). These nerves are the morphological equivalent of the hypoglossal nerve innervating the muscles of the tongue in reptiles, birds and mammals that is utilized in suckling by infant mammals, an activity thought to require its own central oscillator (Taylor et al., 1999).

The aquatic environment is prone to hypoxia, particularly in tropical habitats. This selective pressure has resulted in the evolution of diverse, species, from several Orders and Sub-orders of typical water-breathing fish that resort to AB. These animals use a wide range of different ABO, associated with the bucco-opercular cavity, extensions of the gut, or body surface. All species studied to date exhibit a pronounced tachycardia when air-breathing at the surface[64–67,69,70] (Graham, 1997; Graham et al., 1995; Monteiro et al., 2018; Randall et al., 1981; Skals et al., 2006). Expiration is typically associated with a bradycardia, followed by a marked tachycardia upon inspiration that is associated with large increases in cardiac output and increased perfusion of the ABO[65] (Axelsson et al., 1989; Johansen, 1966; Skals et al., 2006). This increase in HR is generated by the release of a predominant inhibitory vagal tonus to the heart, resulting from stimulation of stretch receptors associated with the ABO, plus central chemoreceptors[65] (Axelsson et al., 1989; Johansen, 1966; Skals et al., 2006), as is the case for mammals (Jordan & Spyer, 1987; Taylor et al., 1999). Although AB is often discontinuous and arrhythmic in fish (Graham, 1997; Randall et al., 1981), it has been proposed that the associated variations in HR are homologous to RSA in mammals[71] (Graham et al., 1995; McKenzie et al., 2007). After each AB, these fish typically return to the HRV pattern of a water-breathing fish, indicating that the two patterns are separately controlled[69] (Graham, 1997).

3.5. *Water-breathing fishes*

3.5.1. *Actinopterygii (bony-skeleton fishes)*

Vertebrates first evolved as fish, breathing water which is much more viscous and denser than air and holds less oxygen per unit volume. Gases also diffuse much more slowly through water and hypoxia is a frequent environmental challenge in aquatic environments. Consequently, water-breathing fish have to work relatively hard to obtain sufficient oxygen to fuel aerobic metabolism. The efficiency (work done for unit uptake) of their consumption is increased by an effective counter-current flow of blood and water over the gills. Deoxygenated blood is pumped directly from the heart to the gills, flowing within the gill lamellae in the opposite direction to a flow of water entering via the mouth to exit through the operculum (Hughes & Shelton, 1962; Taylor, 1992, 1998). Like mammals, fish blood contains red blood cells that increase its oxygen carrying capacity. Consequently, to ensure blood leaving the gills is saturated with oxygen, the rates of flow of blood and water across the counter-current are matched according to their oxygen capacity. Water flows may vary, and they can be around ten times faster than blood flow in normoxia, rising to 40 times in hypoxic water (Hughes & Shelton, 1962; Piiper & Scheid, 1977; Taylor, 1992, 1998).

Since the flow of both water and blood across the gill lamellae is markedly pulsatile (Hughes & Shelton, 1962), a close, beat-to-beat temporal relationships between heart beat and ventilation, termed cardiorespiratory synchrony (CRS), has long been hypothesised as being important for the optimisation of respiratory gas exchange in fish (Hughes, 1970; Satchell, 1960; Taylor, 1992). However, clear evidence of a functional role in optimizing respiratory gas exchange has been elusive (Taylor, 2011). A subtle modulation of HRV by respiratory activity was demonstrated by power spectral analysis of cardiac intervals in the sculpin[72] and termed cardiorespiratory *integration*. It mirrored a progressive recovery of rate of oxygen uptake following experimental manipulation, more closely than the progressive reduction in HR [68,72] (Campbell et al., 2004). Abolition of this integration by cardiac vagotomy affected oxygen uptake,[73] demonstrating that the parasympathetic arm of the ANS mediates these relationships, and that such modulation plays an identifiable role in respiratory gas exchange. Later re-examination of these data, using anti-aliasing techniques, revealed that HRV in the sculpin included a component synchronous with ventilation rate, indicating CRS is indeed a factor optimizing respiratory gas exchange in this species (Taylor et al., 2006).

Typical bony fishes (Actinopterygii) have dual, cholinergic and adrenergic innervation of the heart, but a cholinergic tonus predominates[68–71,73–84] (Taylor et al., 2014). The adrenergic tone is often low or virtually absent[71,71,74,76,78,80–84] (Taylor et al., 1999, 2010, 2014; Taylor, 2011). An extreme example of this dominance is the flounder[85]. When inactive, it had a cholinergic tonus of 26% while adrenergic tonus was negative. In that species there was no evidence that catecholamines supported cardiac function, even after an exhaustive chase (Mendonça & Gamperl, 2009). CRS in bony fishes is generated by moderate hypoxia that causes a bradycardia, with mean HR slowing to matching ventilation rate (Randall & Smith, 1967; Taylor, 1992). The bradycardia is generated by stimulation of both chemoreceptors and mechanoreceptors on the branchial arches and is abolished by cardiac vagotomy or injection of atropine, indicating it is under cholinergic, vagal control[76] (Leite et al., 2009; Taylor & Leite, 2009).

In bony fish, it was observed that bursts of respiration-related activity recorded from the cardiac vagus in moderately hypoxic fish were generated centrally by feedforward interactions, reinforced by feedback reflexes[76] (Leite et al., 2009; Taylor & Barrett, 1985; Taylor & Leite, 2009). When the cardiac vagus was stimulated peripherally by bursts of electrical activity, mimicking the efferent activity recorded during hypoxia, it paced heartbeats over a wide range of frequencies, both higher and lower than the intrinsic cardiac frequency. Atropine injection blocked such HR entrainment indicating that CRS is modulated by acetylcholine release via the vagus activity, denoting its parasympathetic nature (Leite et al., 2009; Taylor & Leite, 2009; Taylor et al., 2006).

Further experimental evidence obtained by electrical stimulation of respiratory and cardiac nerves (Vth, VIIth, IXth and Xth) in pacu[76] indicate that these CRI would be processed by excitatory interactions between respiratory motoneurons and CVPN in the DVN (Leite et al., 2009; Taylor, Leite, Florindo, et al., 2009b). The mechanisms underlying these interactions were discussed elsewhere (Taylor & Leite, 2009b; Taylor, Leite et al., 2009). Those experiments identify the vagus as the primary route for control of effective and fast cardiorespiratory interactions in vertebrates, most likely evolved from their early piscine ancestors. After the evolution of air-breathing, excitatory interactions in the DVN were substituted by inhibitory interactions between respiratory and cardiac motoneurons in the NA in the lung-breathing vertebrate lineages, due to lateral migration of CVPN and RMN (see Fig. 2).

3.5.2. *Chondrichthyes (cartilaginous-skeleton fishes - sharks and rays)*

The sharks and rays are an ancient group with a fossil record extending back about 500 million years (Frey et al., 2019). Like the bony fishes, they employ unidirectional gill ventilation with a counter-current of blood against water over the gills, having septal pumps over each gill slit, rather than an operculum (Milsom & Taylor, 2015). In this group of fishes, the sympathetic arm of the ANS does not extend into the oropharyngeal region, and therefore the heart and branchial circulation receives only parasympathetic innervation, supplied by the vagus nerve. A series of experiments on the catshark[68] revealed a unique dual cardiac innervation from the vagus nerve, with efferent, motor fibres travelling chiefly in the branchial branch that is an extension of the 4th branchial branch of the vagus and afferent, sensory fibres travelling chiefly in the visceral branch[68] (Short, Butler, & Taylor, 1977; Taylor, 2011). Despite the lack of sympathetic innervation, there is evidence of a role for circulating noradrenaline in the modulation of vagal control of the heart in the spiny catshark[86] (Agnisola et al., 2003; Butler et al., 1978).

Tonic control of HR in the catshark[68] is present in normoxia, varies with temperature, increases during hypoxia, and is abolished by hyperoxia (Taylor, 1992; Taylor et al., 1977). Hypoxia induces a reflex bradycardia mediated by increased activity in the vagus nerve[68] (Butler & Taylor, 1971, 1975; Taylor et al., 1977). The role of this hypoxic bradycardia is under debate. It may serve to improve the effectiveness of respiratory gas exchange over the gills or to protect the heart[79,68] (McKenzie et al., 2009; Taylor, 1992). It is termed the primary response in contrast to the secondary tachycardia recorded from hypoxic mammals, which is a response to stimulation of lung receptors by hyperventilation[87] (Daly & Scott, 1962). In cartilaginous fishes the "*metabolic output*" is not simply adjusted by changes in mean HR during hypoxia, as suggested by PVT (Porges, 1998). Both HR and oxygen uptake, which is a measure of the rate of aerobic metabolism, are unchanged during moderate hypoxia down to a critical oxygen partial pressure. Below this level, a hypoxic bradycardia is compensated by increased stroke volume so that cardiac output is effectively unchanged down to lower levels of oxygen availability[68] (Butler & Taylor, 1975; Taylor et al., 1977; Taylor, 1992).

It was experimentally observed that when catsharks[68] held at 23 °C were undisturbed and had recovered from instrumentation, they showed long periods of 1:1 synchrony between HR and ventilation rate. This relationship was abolished by injection of atropine and lost whenever the fish was disturbed (Taylor, 1992). So, the CRS presented by cartilaginous fishes is typical of routinely active fish in well aerated water and corresponds to the observation that these animals are relatively inactive in their natural habitat of the shallow seas during the day, with activity levels rising at night. This contradicts the statement that these fish lack the ability to "*self-sooth or calm*" (Porges, 1998) and implies that CRS is generated by central feedforward control without the reflex reinforcement provided by mild hypoxia, as reported for bony fishes. These data show that CRS in sharks is observed when cardiac vagal tone is relatively low in inactive, undisturbed fish. Changes in spontaneous activity or experimental manipulation, abolish CRS (Taylor, 1992, 2011).

A detailed neurophysiological study of sharks[68], using the decerebrated, force-ventilated catshark (Barrett & Taylor, 1985a, 1985b, 1985; Taylor & Butler, 1982) established that there was tonic efferent activity in the branchial cardiac branch of the vagus nerve, supplying the heart in normoxic fish. This was separable into low levels of continuous activity plus regular burst of activity that were respiration-related. The nerves had conduction velocities typical of mammalian B-fibres (Barrett & Taylor, 1985b), which relates to a previous description of myelinated nerve fibres in the cardiac vagi of the catshark[68] (Short et al., 1977). This reveals an ancient origin for myelination of cardiac vagal efferent fibres, conferring high conduction rates, as described above in the lungfish[65].

Our neuroanatomical study of the catshark[68] brainstem revealed that although 90% of VPN are located in the DVN there is a small group (10%) of ventrolaterally located cells. These proved to be solely CVPN and represent about 45% on the total population of CVPN, with the rest in the DVN (Barrett & Taylor, 1985b, 1985). Central recordings from CVPN in the 2 locations, using microelectrodes, revealed that the respiration-related activity in cardiac nerves originated from CVPN in the DVN, where they are co-located with respiratory motor neurons (Barrett & Taylor, 1985b, 1985; Taylor, 1992). Activity in the ventrolateral group of CVPN was continuous but not respiration-related and experimentation revealed that they are responsible for reflex changes in HR, for example during hypoxia[68] (Taylor & Butler, 1982) and exposure to capsaicin[68] (Jones & Young, 1993). The fact that respiratory rhythmicity is confined to CVPN in the DVN is simply explained by their colocation with respiratory motor neurons. This does raise the interesting possibility that the primordial NA was composed of CVPN released from a respiratory drive and able to affect tonic control of mean HR with reference to oxygen availability, temperature and activity levels.

Physical stimulation of gill arches, a response conducted centrally by afferent fibres in the respiratory branches of the vagus nerve, caused activity in both groups of CVPN[68] (Barrett & Taylor, 1985a, 1985; Taylor, 2011), which led to recorded efferent activity in the branchial cardiac branches causing a marked bradycardia. This response is opposite in kind to the mammalian response to stimulation of lung stretch receptors. This is in part what separates the primary and secondary responses to hypoxia in vertebrates, as described above. As described for bony fish, experimental studies revealed that phasic, peripheral electrical stimulation of the cardiac vagus in the catshark[68] could entrain HR at rates both below and above its intrinsic rate (Taylor et al., 2006). Also, physical stimulation of gill arches or central stimulation of a respiratory branch of the vagus generated phasic activity in the cardiac vagus[68] (Barrett & Taylor, 1985a; Taylor et al., 2006). The accumulated evidence suggested that there is central feed-forward control of HR in cartilaginous fishes, as represented by the catshark[68], operating in inactive fish in normoxia that can be influenced by peripheral mechanoreceptor and chemoreceptor inputs. This controls HR on a beat-by-beat basis in sharks and can generate CRS by recruiting heartbeats. The mechanisms that could underly this direct recruitment of heart beat by respiration-related activity in the cardiac vagus have been discussed elsewhere (Taylor, Leite et al., 2009). Although this system differs in important respects from the mammalian system, it shares important attributes, including dual locations for CVPN,

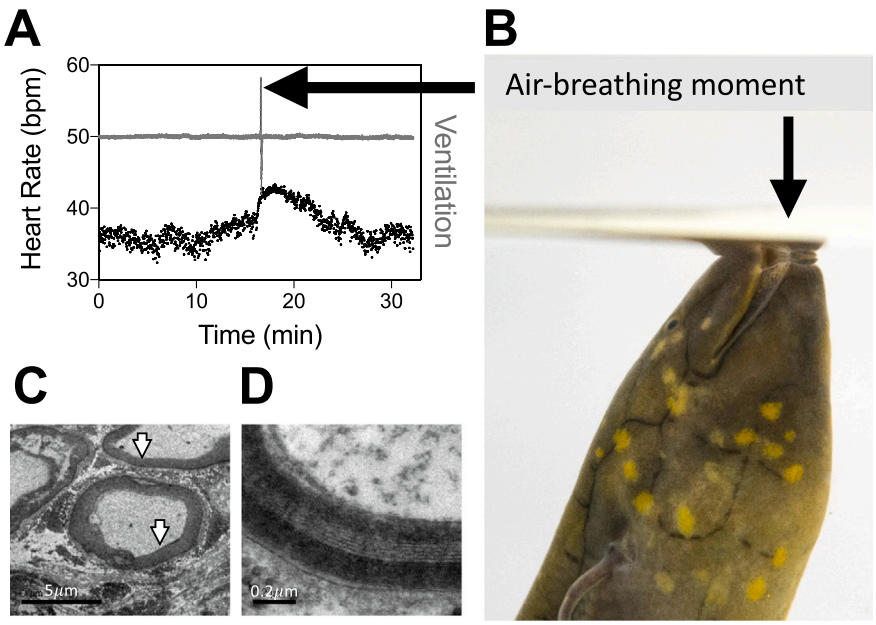

Fig. 3. Air breathing in a lungfish, *L. paradoxa*. The panels are: (A) cardiorespiratory recordings showing one air breath (ventilation – grey) and heart rate (bpm – black); (B) lungfish (260 g) photographed taking an air-breath at the water surface; (C) transmission electron micrograph obtained from cross sections of the cardiac vagus, in which myelinated axons are clearly observable (arrows point to myelinated fibres); (D) detail of typical layering of the myelin sheath. Scale bars: 5μm in C and 0.2μm in D. Photography by G. Oda (2018). Original data discussed in Monteiro et al. (2018).

myelinated fibres in the cardiac vagi, with evidence that this includes fibres originating in the DVN, and vagal control of instantaneous HR that generates not RSA but CRS in the inactive animal. These data are available as comprehensive reviews (Taylor & Wang, 2009; Taylor et al., 1999; Taylor, 1992; Taylor, Leite et al., 2009) or more recent condensed reviews (Milsom & Taylor, 2015; Taylor, 2011).

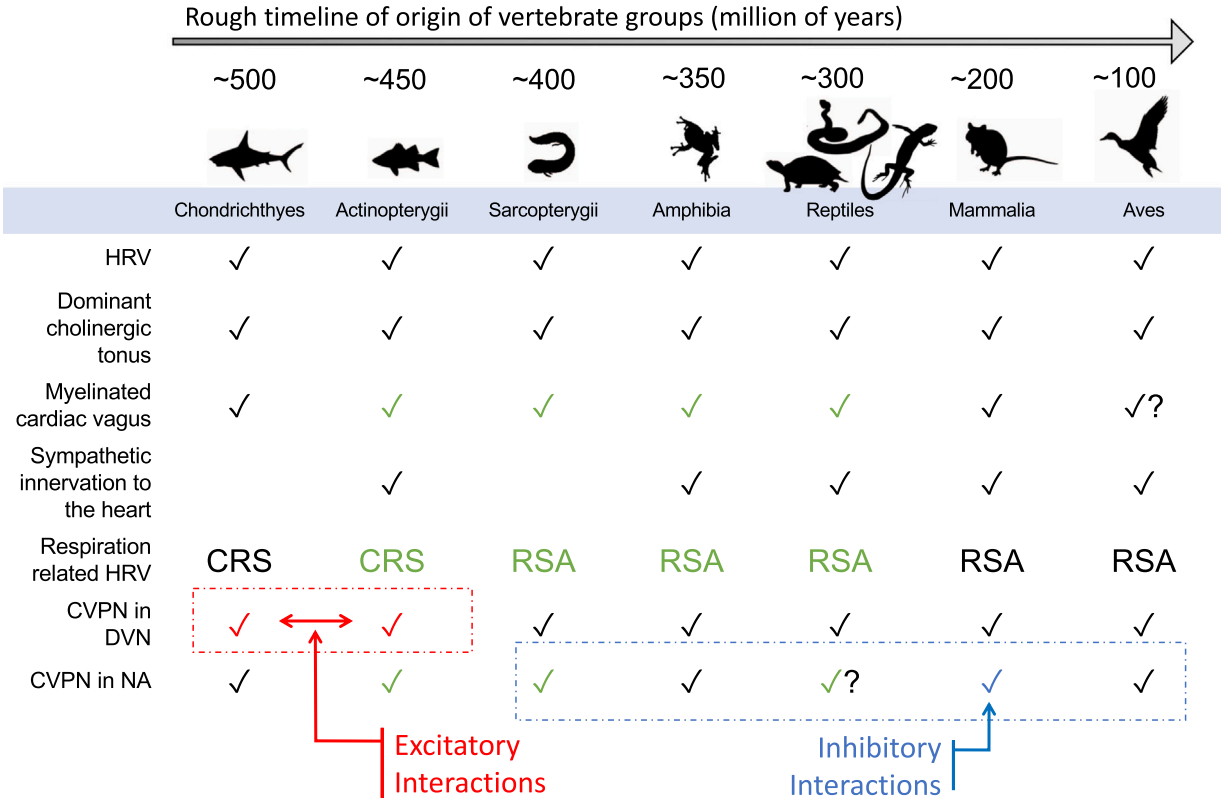

Fig. 4. Autonomic structures and functions that generate cardiorespiratory modulation in vertebrates. The central interactions which modulate respiration-related heart rate variability (HRV) are likely generated by the activation of CVPN in the DVN in water breathing vertebrates (fish and amphibian tadpoles), as described for the catshark. The lung breathing vertebrates (lungfish, adult amphibians, reptiles, birds and mammals) show RSA-like HRV, possibly generated by inhibition of ventro-lateral CVPN in the NA, as clearly demonstrated in mammals. The dotted squares indicate the putative location of central nervous interaction for respiratory related HRV. The red ✓ indicate experimental evidence of excitatory neuronal interactions between respiratory neurons and CVPN. The blue ✓ indicates experimental evidence of inhibitory neuronal interactions between respiratory neurons and CVPN. The green text denotes recent experimentally validated information. CRS – Cardiorespiratory Synchrony; RSA – Respiratory Sinus Arrhythmia; CRI – Cardiorespiratory Interactions. '?' Indicates current investigations.

4. Conclusion

The anatomical and physiological mechanisms described as necessary to generate cardiorespiratory interactions, termed RSA in mammals, have been shown to be dispersed, in various forms, across vertebrate phylogeny (Table 1, Figs. 1 and 4). Consequently, they are likely to have evolved early in vertebrate ancestry (Monteiro et al., 2018; Page, 2003; Taylor et al., 2014).

5. Final considerations

The central conclusions of this synopsis regarding parasympathetic control of the heart in vertebrates can be listed as follows and are illustrated in Fig. 4.

1. Representatives of all vertebrate groups, when relatively inactive and undisturbed by external factors such as imposed experimentation, show an inhibitory tonus on the heart, imposed by the parasympathetic arm of the ANS, via the cardiac branch of the Xth cranial nerve, the vagus (Fig. 4). Recorded changes in heart rate are most often due to changes in the degree of this inhibitory vagal tonus.
2. Heart rate is also modulated by phasic activity in the ANS, communicated via the vagus nerve to generate HRV, with an important component being CRI. These have been recorded from representatives of all classes of vertebrates, as phasic, respiration-related, efferent activity arising from CVPN supplying a cardiac branch of the vagus nerve, which generates instantaneous changes in HR coordinated with respiratory cycles.
3. CVPN have been identified in two or more locations, the DVN and discrete locations outside of the DVN, within the brainstem of all major groups of vertebrates from sharks to mammals (Fig. 4). This latter group is characterised as the NA in mammals and contains 80% of CVPN, while in the phylogenetically distant sharks CVPN are equally distributed between the DVN and a ventro-lateral group composed solely of CVPN, which can be considered as a primordial NA, dedicated to control of the heart (see Figs. 1 and 4).
4. CRI are generated by a combination of central interactions between CVPN and neighbouring respiratory neurons and feedback from peripheral receptors in the respiratory and cardiovascular systems. The nature of these interactions varies from fish to mammals (Fig. 4).
5. In water-breathing vertebrates such cartilaginous and bony fishes CRI can take the form of cardiorespiratory synchrony (CRS), with the phasic counter-current of water and blood flows over the gills matched according to their capacity to transport oxygen. Present evidence suggests that CRS is generated by excitatory, central interactions between respiratory neurons and CVPN in the DVN, plus feedback from peripheral chemo- and mechanoreceptors (Fig. 4).
6. The evolution of air-breathing led to cardiac intervals being matched to the relatively slow ventilatory movements shown in air-breathers, as shown by mammals. This form of CRI, characterised in mammals as RSA is driven by changes in inhibitory control of the heart exercised by CVPN in the NA, which respond to an inhibitory input from neighbouring inspiratory neurons, generating the respiratory rhythm.
7. CRI similar to RSA has been identified, on the basis of a range of physiological plus neuroanatomical factors, to be present in other air-breathing vertebrates, such as birds, snakes, lizards, toads and in the lungfish (Fig. 4).
8. Myelinated, fast conducting, efferent fibres, identified as B-fibres, have been described and characterized in the cardiac vagus of a shark, a bony fish, a lungfish, birds and mammals. These are likely to be present in all vertebrate groups, as they are a necessary component of instantaneous control of heart rate (Figs. 1, 3 and 4).
9. Air-breathing, ectothermic vertebrates with incompletely divided hearts often show episodic breathing. These episodes are linked to surface air breathing in lungfishes, amphibians and diving reptiles. In terrestrial reptiles they may relate to marked changes in metabolic rate, occurring during locomotion or following a meal. The onset of each bout of air breathing is accompanied by an immediate tachycardia, due largely to withdrawal of an inhibitory vagal tonus, and is accompanied by cardiac shunting, which improves lung perfusion and the resultant effectiveness of oxygen uptake. Accordingly, it is clear that these CRI serve a clear respiratory role. CRI are conserved in mammals (and birds) as RSA, but do not show such a clear physiological role, though they may provide potential for optimal levels of performance. This apparent lack of a substantial role relates to their inability to perform cardiac shunting across their completely divided circulations. As such, RSA could represent a relic of a system evolved in ancestral reptiles or at the origins of the tetrapods, as exemplified by the lungfishes (Figs. 1 and 2).

In formulating PVT, elements of the ANS that originate in the NA have been included together with other nuclei in the brainstem, to constitute a “vagal system” in mammals that affects “social engagement” responsible for behavioural functions, such as ‘calming’ and ‘socializing’. As stated in our introduction, we have not addressed the evidence of a role for the vagus nerve in “social engagement”. We accept that the vagus nerve subserves many important functions, some presently being explored by biomedical physiologists (e.g. Borovikova et al., 2000). We recognise PVT as a theory, or perhaps more properly a hypothesis, which deserves proper examination by workers in the field it occupies. Our engagement has been limited to its excursions into a particular aspect of comparative physiology, which is our field. We consider that every ‘theory’ must expect regular examination. This, of course, has remained the case for Charles Darwin’s theory, which proposed, on the basis of wide-ranging observations, that natural selection explains the origin of species. His theory (Darwin, 1859) has survived intact for over 150 years, despite thorough examination by workers studying population genetics, the structure and functions of DNA, genomics and even epigenetics. The progenitor of the Polyvagal Theory makes clear in his publied work (e.g. Porges, 2011) that he shares our respect for Darwin’s theory. It will be interesting to see how PVT evolves in response to present and future examination by a range of scientists and clinicians.

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