factors, molecular recognition, interaction dynamics and synaptic competency, contribute at the moment of synaptic partner choice (Figure 1B)[9,20]. By contrast, Peters' rule can be understood as the sum of all of the preceding development that brought the partners into vicinity prior to synapse formation[6,8]. And finally, initial partner choices ore often modified by pruning or selective stabilization (Figure 1B)[20]. Both Sperry and Peters highlighted important contributors to the development of synaptic specificity. But to understand the outcome, the mechanisms that came to be associated with their names might be better thought of as collaborators that each quantitatively contribute to the beauty of brain development[9], which neither alone could achieve.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Sleep: Hemispheres fight for dominance

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A new study shows that bearded dragons have a peculiar way to coordinate sleep state changes between brain hemispheres. The hemisphere that acts first imposes its activity on the other during their REM sleep-like state.

How do winners win? For an athlete, let's imagine a boxer training for a match, where success could be measured by the hours spent working-out or by maximizing muscle mass, endurance, and speed. However, when there is a second boxer in the ring, then what matters most is being stronger, and faster, than your opponent. A new study published in *Nature* by Fenk *et al.*[1] reveals that, not unlike these athletes locked in competition, there is a night-long fight for dominance between

the two cerebral hemispheres of sleeping bearded dragons (*Pogona vitticeps*) to coordinate state changes. Each hemisphere will win contests, and lose others, but what determines success is who throws the first punch.

Having two sleep states was long thought to be the exclusive purview of birds and mammals[2]. There, sleep states manifest as alternating slow-wave sleep (SWS) and rapid-eye movement (REM) sleep. The processes served by these states is very much an ongoing debate. Evidence implicates SWS in shaping the strength of connections between brain cells, clearing waste generated by waking brain use, and saving energy by reducing metabolic demands. Functions of REM sleep are less clear, but it appears to be involved with maturing the young nervous system, establishing and maintaining sensory-motor maps, and consolidating emotionally rich memories.

At the level of an individual neuron, avian and mammalian SWS is characterized as the slow oscillation of membrane potential between a depolarized up-state with action potentials and a hyperpolarized down-state with neuronal silence. Supported by a uniquely high amount of connectivity between neurons, the oscillation appears as large, slow brain waves when recorded by the electroencephalogram[2]. In both types of animals, SWS is homeostatically regulated, such that losing sleep, or intensifying brain use during prior wakefulness, increases the size and incidence of subsequent slow-waves[3]. In contrast to SWS slow-waves, brain waves during REM sleep are small, fast, and resemble the brain activity of an awake animal. While there is considerable variability in other features of REM sleep physiology across species, most birds and mammals engaged in REM sleep show signs of reduced muscle tone, rapid eye movements, and intermittent twitching[4]. Furthermore, the ability to thermoregulate by shivering (when cold) and panting (when hot) ceases during REM sleep in endotherms. Lastly, brain temperature cools during SWS and warms during REM sleep in both birds and mammals[5].

Our understanding of the evolution of sleep has changed dramatically over the last decade[6]. Two sleep states that in some, but not all, ways resemble mammalian and avian SWS and REM sleep have been observed in fruit flies (*Drosophila melanogaster*), cuttlefish (*Sepia officinalis*) and octopus (*Octopus insularis*), and perhaps also honey bees (*Apis mellifera*), jumping spiders (*Evarcha arcuata*), and zebrafish (*Danio rerio*)[6]. Within non-avian reptiles, two sleep states have been reported in Argentine tegus (*Salvator merianae*), Egyptian rock agama (*Laudakia vulgari*), and bearded dragons (*Pogona vitticeps*)[1,7–10]. However, any evolutionary homologies between sleep states in mammals and other animals have yet to be established[6].

Outside of birds and mammals, the two sleep states of dragons have received a lot of attention. Scientific focus on this unassuming animal has arisen following its initial, high-impact description[7], which revealed peculiar clockwork precision of the alternation between states. In humans, the time to cycle through sleep states is often said to be 90 minutes, but anyone with sleep-tracking technology regularly gains insight into the considerable variation in the length of a 'sleep cycle'. Similar variability is found in other mammals and birds. Conversely, dragons alternate between sleep states

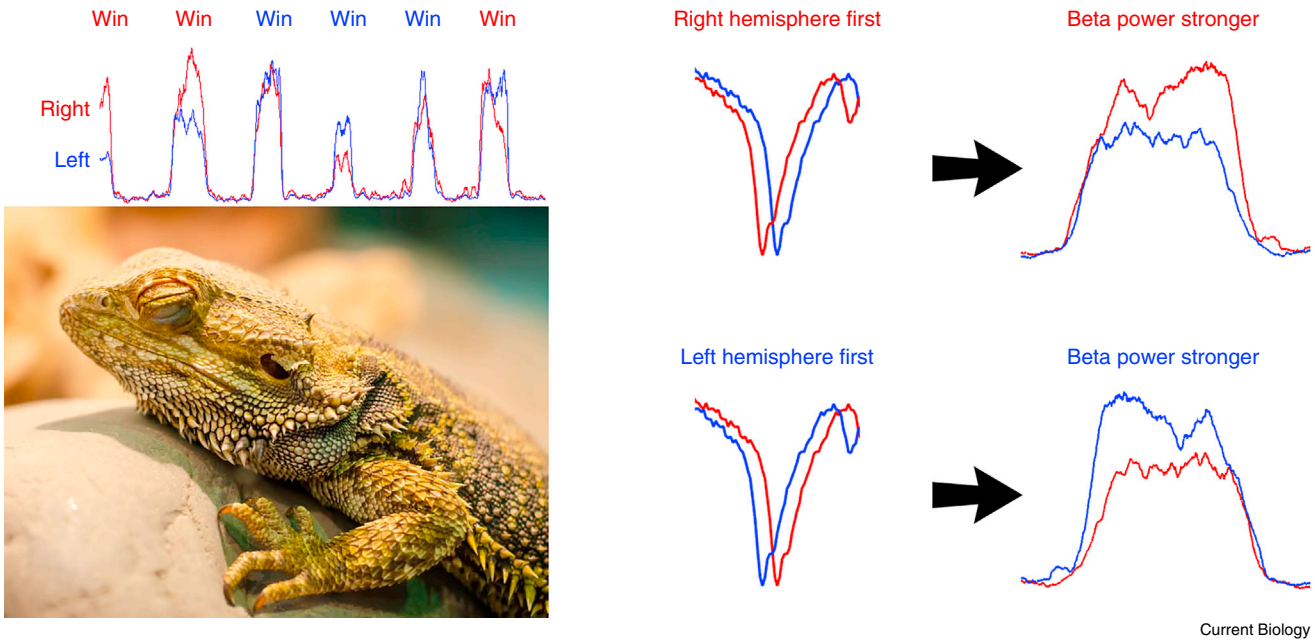

Figure 1. Hemispheres compete to impose their activity on the other during the REM sleep-like state of bearded dragons.
Photograph of a sleeping bearded dragon (*Pogona vitticeps*). Above its head is shown the variation of brain activity (20 Hz beta power) for the right (red) and left (blue) hemisphere, recorded over 8 minutes. The alternation of dominant beta power reflects the 80-second cyclicity between slow-wave sleep (little activity) and rapid-eye movement sleep (high activity). To the right of the photograph is shown the 20 millisecond lag between the sharp negative wave during REM sleep illustrating that the leading hemisphere drives stronger beta power in the ipsilateral hemisphere. Bearded dragon image used with permissions by artas/Getty images. Signals were adapted from recordings by P-A.L. from *P. vitticeps*.

with a remarkably regular period of (about) 80 seconds[7,8].

In dragons, SWS-like brain activity is characterised not by slow-waves, but sharp-waves[1,2,7,8]. Whereas slow-waves occur continuously during SWS, sharp-waves in dragons are intermittent spikes. Nonetheless, slow- and sharp-waves share similar aspects, such that sharp-waves in reptiles might be an evolutionary precursor to avian and mammalian slow-waves[2,11]. Notably, similar to avian and mammalian slow-waves, reptilian sharp-waves tend to increase following sleep loss[8] and travel through the brain as a propagating wave[11]. As a result, slow- and sharp-waves occur throughout much of the brain, and both waves respond similarly to pharmaceutical manipulation[2]. SWS in dragons alternates with a sleep state that in some ways resembles REM sleep in birds and mammals[7–9]. Notably, REM sleep in dragons is also characterized by wake-like brain activity and eye movements under closed eyelids. However, unlike REM sleep in furry and feathered animals, eye movements are fewer and slower during REM sleep in dragons, the limbs do not twitch, muscle atonia is not clear, and the brain does not warm[5,7–9]. When one state gives way to the other, this information must be coordinated between the hemispheres. But how?

In their paper, Fenk *et al.*[1] described a new type of wave occurring in a region of the brain likely to be homologous to the claustrum. In mammals, the claustrum is a thin region located deep in the cortex, but one that sends and receives connections to nearly all areas of the cortex. In mammals[12] and dragons[13], the claustrum is involved in the genesis of slow-waves and sharp-waves, respectively. This structure also plays a role in interhemispheric infighting during the REM sleep-like state in dragons[1]. Here, the claustrum generates another type of wave during sleep — a sharp negative field potential (SNs). During the SWS-like state, sharp-waves are uncoordinated between the left and right claustra. During REM sleep, sharp-waves disappear, and the claustrum generates SNs. These sharp, negative waves occur *almost* synchronously, but with a 20 millisecond lag between the appearance of the downward potential in one claustrum relative to the other (Figure 1). One hemisphere leads, and the leader can flip within and, albeit more rarely, across episodes. The claustrum that leads also shows stronger activity (20 Hz beta power); the hemisphere with stronger beta power imposes its activity on the other. This between-hemisphere competition is initiated 30 milliseconds before by a bilateral cluster of neurons located retrogradely to the claustrum that may be homologous to the avian isthmi pars magnocellularis (Imc). Unilateral lesion of the cluster favours dominance of the contralateral brain hemisphere across the entire night. Taken together, Fenk *et al.*[1] described a hitherto unknown winner-take-all mechanism for the interhemispheric coordination of REM sleep in dragons.

Whether this neuronal mechanism is an idiosyncratic feature of REM sleep in dragons, or is also found in other lizards[8–10], birds and mammals[3,4], or animals more broadly[6], is unknown. It is interesting to speculate that this pathway might sustain a basic mechanism of sleep states, including REM sleep in birds. Accordingly, the avian Imc has been implicated in bottom-up attention and gaze control[14], raising the possibility that REM sleep in dragons is involved in visual attention re-processing. The results by Fenk *et al.*[1] might also relate to unihemispheric slow-wave sleep exhibited by some marine mammals[15] and birds[16]. Sleeping with one-half of the brain at a time allows the animal to maintain vigilance using the one eye that remains open[16]. Sharp-waves in dragons are uncoordinated between the two hemispheres, revealing that brain asymmetries can exist during sleep in reptiles, restricted to one sleep state. And while the closing of only one eye — the behavioural correlate of unihemispheric sleep in marine mammals and birds — has been observed in resting reptiles, it remains unclear whether they too can sleep with one-half of their brain at a time[17]. Nonetheless, interhemispheric infighting in dragons involves attentional and visual pathways[1], perhaps an underlying mechanism for the sustained vigilance permitted by sleeping unihemispherically.

A new mechanism for the coordination of between-hemisphere activity in dragons highlights the unending need for comparative sleep research. The hundreds of species already studied by sleep scientists have revealed inspiring diversity in the form of sleep[4,6], and elegant adaptations to permit sleep in the most unlikely ways and places[15,16,18,19]. And so, the millions of species that have gone unstudied represent an untapped opportunity for discovery[20]. It is in these species we will learn what else is possible for sleep. The endeavour will never be completed, but the journey will enhance our understanding of sleep in unbounded, and unrecognizable, ways.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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