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Role of the locus coeruleus in the emergence of power law wake bouts in a model of the brainstem sleep-wake system through early infancy

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ABSTRACT

Infant rats randomly cycle between the sleeping and waking states, which are tightly correlated with the activity of mutually inhibitory brainstem sleep and wake populations. Bouts of sleep and wakefulness are random; from P2–P10, sleep and wake bout lengths are exponentially distributed with increasing means, while during P10–P21, the sleep bout distribution remains exponential while the distribution of wake bouts gradually transforms to power law. The locus coeruleus (LC), via an undeciphered interaction with sleep and wake populations, has been shown experimentally to be responsible for the exponential to power law transition. Concurrently during P10–P21, the LC undergoes striking physiological changes – the LC exhibits strong global 0.3 Hz oscillations up to P10, but the oscillation frequency gradually rises and synchrony diminishes from P10–P21, with oscillations and synchrony vanishing at P21 and beyond. In this work, we construct a biologically plausible Wilson Cowan-style model consisting of the LC along with sleep and wake populations. We show that external noise and strong reciprocal inhibition can lead to switching between sleep and wake populations and exponentially distributed sleep and wake bout durations as during P2–P10, with the parameters of inhibition between the sleep and wake populations controlling mean bout lengths. Furthermore, we show that the changing physiology of the LC from P10–P21, coupled with reciprocal excitation between the LC and wake population, can explain the shift from exponential to power law of the wake bout distribution. To our knowledge, this is the first study that proposes a plausible biological mechanism, which incorporates the known changing physiology of the LC, for tying the developing sleep-wake circuit and its interaction with the LC to the transformation of sleep and wake bout dynamics from P2–P21.

1. Introduction

Infant mammals repeatedly cycle between the behavioral states of sleep and wakefulness, and bout durations are random with an absence of memory from one bout to the next (i.e., the length of a given sleep or wake bout is independent of the length of prior bouts). Furthermore, sleep and wake bout durations in infants exhibit an exponential distribution – successive sleep bout lengths are exponential independent and identically distributed (i.i.d.) random variables with mean μ_s, while successive wake bout lengths are exponential i.i.d. random variables with mean μ_w. In rats, from birth to about postnatal day 10 (P2–P10), the mean sleep and wake bout lengths μ_s and μ_w increase (μ_s increases from $\sim$ 15 s–$\sim$ 35 s, μ_w increases from $\sim$ 5 s–$\sim$ 10 s), but the two evolve independently of each other and the exponential distribution of bout lengths persists (Blumberg et al., 2005; Gall et al., 2009; Halász et al., 2004; Karlsson et al., 2005; 2004; Kleitman and Engelmann, 1953; Lo et al., 2004; 2002).

Behavioral sleep and wake bouts are tightly correlated with the activity of mutually inhibitory 'sleep-active' and 'wake-active' neuronal populations within the brainstem. During a sleep bout, 'sleep-active' neurons spike and 'wake-active' neurons are inhibited, while the reciprocal activity pattern is observed during a wake bout. Sleep-active populations include the ventrolateral preoptic area, medullary inhibitory area, nucleus pontis oralis, and subcoeruleus, while wake-active populations are divided into the thalamic branch (e.g., laterodorsal tegmentum, pedunculopontine tegmentum) and the hypothalamic branch (e.g., dorsal raphe nuclei, tuberomamillary nucleus) (Blumberg et al., 2005; Karlsson et al., 2005; Schwartz and Roth, 2008). Switching between neonatal sleep-active and wake-active populations in a simplified two-neuron model as well as in a biophysical model of mutually in-

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hibitory sleep-active and wake-active populations is investigated in prior work (Patel, 2015; Patel and Joshi, 2014).

Mathematically, this scenario paints a simple picture of stochastic switching in a bistable system – the behavioral states of sleep and wakefulness, in a dynamical systems setting, can be thought of as two deterministically stable states of the system (one stable state is given by wake neurons firing and sleep neurons being inhibited, while the other stable state is given by the reciprocal activity pattern). In a deterministic setting, the system will approach and perpetually remain in one stable state or the other; if the system is imbued with noise, however, the system will randomly switch between the two stable states (Gardiner, 2009; van Kampen, 2007). Thus, it is possible that in early infancy switching between the sleep and wake states is driven primarily by noise within the system; the distinct states of sleep and wakefulness (i.e., the inability of sleep and wake populations to be active concurrently) arise as a consequence of strong reciprocal inhibition between sleep and wake populations, and alternations between the sleep and wake states may be driven by noise.

Sleep and wake bout lengths, as mentioned above, exhibit an exponential distribution throughout the P2–P10 epoch, though the mean bout times μ_s and μ_w increase throughout this period (μ_s rises from $\sim$ 15–$\sim$ 35 s and μ_w rises from $\sim$ 5–$\sim$ 10 s in rats). During the P10–P21 period, however, a remarkable *qualitative* change is observed – while sleep bouts remain exponentially distributed (with μ_s increasing from $\sim$ 35 s to $\sim$ 70 s in rats), the distribution of wake bout lengths gradually and strikingly transforms from exponential to power law (with μ_w concurrently increasing from $\sim$ 10 s to $\sim$ 25 s in rats) (Blumberg et al., 2005; Gall et al., 2009; Karlsson et al., 2005; 2004; Kleitman and Engelmann, 1953). Moreover, there is strong experimental evidence that the locus coeruleus (LC), a small population of noradrenergic neurons, interacts in a pivotal manner with sleep and wake populations and is responsible for the transformation of the wake bout distribution from exponential to power law that is seen during the P10–P21 epoch (e.g., lesion experiments establish that if the LC is ablated prior to P10, then the wake bout distribution fails to shift from exponential to power law from P10-P21, and instead remains exponential with a rising mean) (Aston-Jones and Bloom, 1981; Berridge et al., 2012; Gall et al., 2009; Saper et al., 2001; Takahashi et al., 2010). Experimental investigations, however, have not yet determined the nature of the interaction between sleep/wake populations and the LC.

It is well known that the LC diffusely innervates many brainstem areas crucially involved in the mammalian sleep-wake system and hence plays an important role in sleep and arousal behavior (Gall et al., 2009), particularly through early postnatal development. Interestingly, and in step with the remarkable changes in sleep-wake behavior observed through early rat infancy, the rat LC simultaneously exhibits drastic shifts in its physiology and dynamics. In infant rats, experiments have shown that LC neurons display synchronized subthreshold membrane potential oscillations (and synchronized spiking), a tendency which diminishes and finally disappears as the animal ages. From P2–P10, LC dynamics are stable, and the LC exhibits a synchronized network oscillation with relatively large amplitude (up to 15 mV) and low frequency ($\sim$ 0.3 Hz). From P10 to P21, LC dynamics change substantially – the LC network gradually desynchronizes as the amplitude of synchronized subthreshold oscillations decreases while the oscillation frequency increases (up to $\sim$ 3 Hz), while at P21 and beyond LC-wide network synchrony is rarely observed. Evidence suggests that synchrony across LC neurons in infants may be due to extensive (but weak) dendro-dendritic gap junctions throughout the entire LC network coupled with slow intrapopulation synaptic inhibition, and from P10 to P21 gap junction connectivity diminishes, leading to less synchronization and higher oscillation frequencies, while at P21 and beyond gap junction connectivity is eliminated or insufficient to synchronize LC neurons under normal physiological conditions (Christie, 1997; Christie and Jelinek, 1993; Christie et al., 1989; Coyle and Molliver, 1977; Groves and Wilson, 1980; Ishimatsu and Williams, 1996; Travagli et al., 1995; Williams and Marshall, 1987). A biophysical model of the LC, in which gap junction pruning yields the increase in network oscillation frequency and decline in oscillation amplitude observed experimentally during the P10 to P21 period, is developed in prior work (Patel and Joshi, 2015).

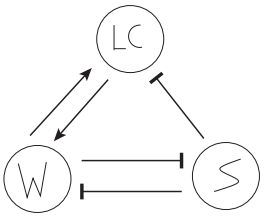

Fig. 1. Circuit diagram for the three-population circuit consisting of a sleep-active population (S), wake-active population (W), and the locus coeruleus (LC). Arrow line heads indicate excitatory synpatic input, while bar line heads indicate inhibitory synaptic input.

The stark temporal concordance during P10–P21 of changing LC dynamics and the transformation of the wake bout distribution from exponential to power law, along with the experimental evidence indicating that the LC is required for the P10–P21 transformation of the wake bout distribution, suggests that the observed changes in LC functioning may underlie the ability of the LC to modify and influence the physiological behavior of infant sleep-active and wake-active populations. However, to our knowledge, this possibility has not been investigated, and no models have yet been proposed for the interaction of the LC with sleep-active and wake-active populations during the critical P10-P21 epoch.

In this work, we construct a physiologically based coarse-grained three-population model of the interaction of the LC with sleep and wake populations during P2–P10 as well as during the pivotal P10–P21 epoch. We model each population using a Wilson Cowan-type equation; the circuit diagram for the model is shown in Fig. 1. We show that strong reciprocal inhibition between the sleep and wake populations, coupled with noisy external excitation supplied to each population, allows random switching in the activity of the two populations, yielding random bout durations and exponential sleep and wake bout distributions. We show that mean sleep and wake bout lengths can be independently controlled by inhibition – modifying sleep to wake inhibitory strength allows modulation of the mean sleep bout length, without affecting the mean wake bout length (and vice versa). Moreover, we show that excitatory feedback between the LC and wake population allows the LC to transform the wake bout distribution from exponential to power law – specifically, we show that the change from exponential to power law wake bouts from P10 to P21 arises as a consequence of the LC shifting from an oscillatory mode to a nonoscillatory mode. Additionally, we show that a slow time scale in the feedback between the LC and wake population is necessary to bring about the transformation of the wake bout distribution, and we argue that it is likely that this slow time scale is present in wake to LC excitation, rather than in LC to wake excitation.

2. Results

The model consists of a sleep population, a wake population, and a LC population modeled using a Wilson Cowan-style formalism. The sleep and wake populations each receive noisy external excitation and strongly inhibit each other, resulting in random