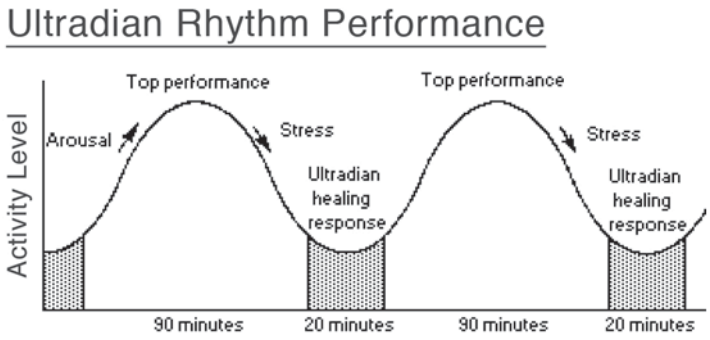
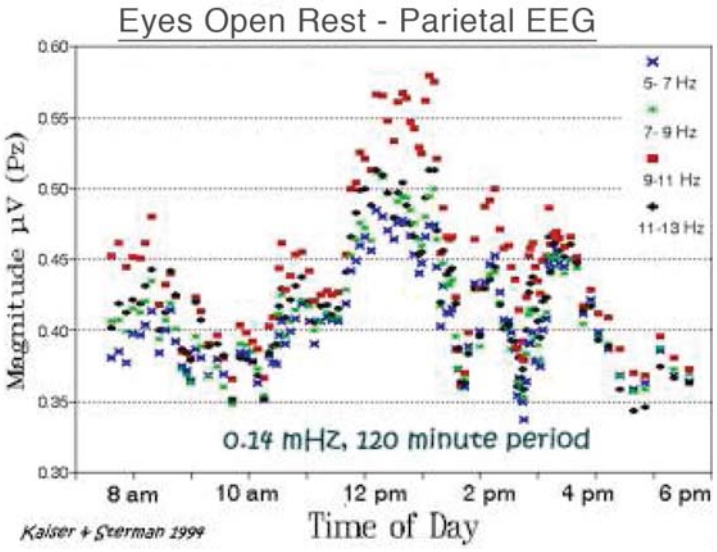
Infra-Low Frequencies and Ultradian Rhythms

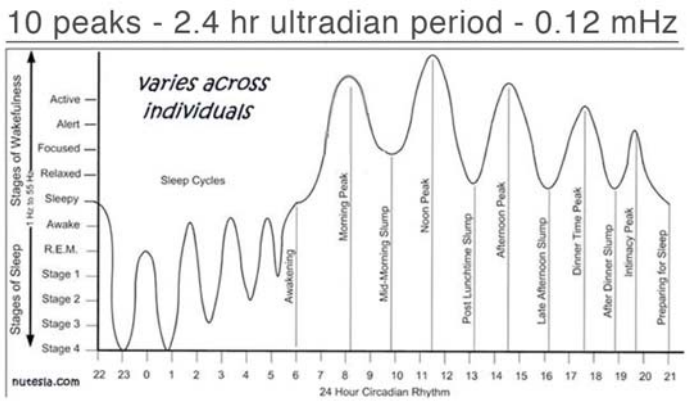
By David Kaiser PhD - April 10, 2013

Ultradian rhythms are present in every aspect of biology. Ultradian means many times a day, and we have many habits that we perform regularly across the day. We eat three times a day, brush our teeth once or twice a day, take breaks periodically, and we have newer rhythms in our behavioral repertoire like checking Facebook or our email twice a day or every half-hour. Ultradian rhythms are observed in our daily behavior and in the brain. Our brain is autorhythmic and demonstrates amazing stability over a vast array of rhythms spanning multiple time frames. In the brain we find periodicities ranging from a few milliseconds to several minutes and hours (Hughes et al., 2012). We observe ultradians in neuronal firing rates, in brainwave activity, in sleep arousals, sleep spindles, and even for epileptic seizures (Aladjalova, 1957; Leopold et al 2003; Staba et al, 2002, Steriade et al., 1993). Ultradian rhythms correspond to infra-low frequencies, those below 0.1 Hz and usually those of interest are well below 0.1 Hz, down at the milli-Hz (mHz) range. Infra-low frequencies (ILF) correspond to multiple minute periods or rhythms. For instance 1 mHz corresponds to a 17-minute ultradian rhythm, 0.18 mHz to a 90-minute cycle and 0.14 mHz to 2 hours. The latter two periods encompass the range of our Basic-Rest- Activity-Cycle, how we tend to rest and work in two-hour increments (Kleitman, 1982; Rossi & Kleitman, 1992)This cycle exists in us because it is the brain's timebased management (or cycle) of cortical excitability. This cycle of cortical excitability followed by inactivity continues onward through the night as REM and non-REM sleep cycles. Brain plasticity cycles with the same periodicity (Ribeiro et al 2008; Rossi & Lippincott, 1992). Arousal cycles are apparent in the EEG. Activity peaks every 2 hours or so in all frequencies (Kaiser & Sterman, 1994; Aeschbach et al 1999; Hayashi et al 1994;



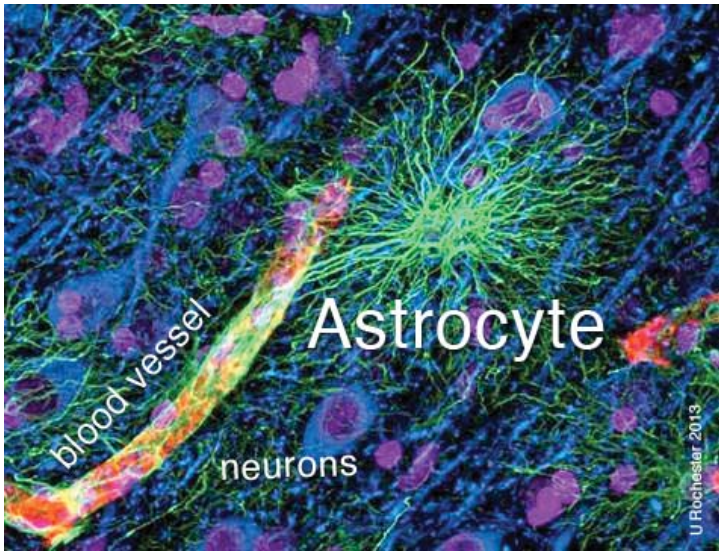
Adapted from: Rossi, EL: The 20 Minute Break. Tarcher-Putnam, New York, 1991, p.12





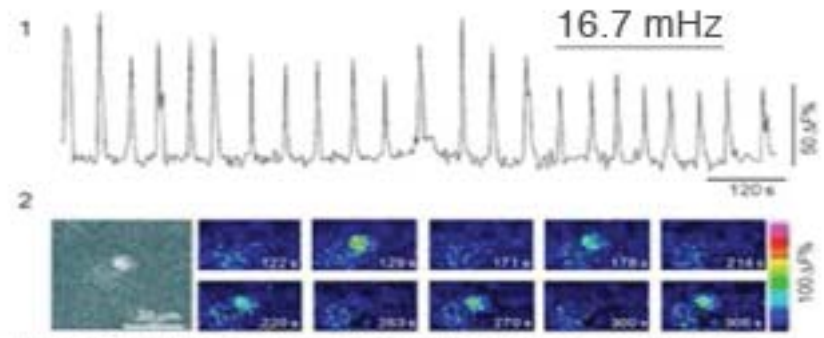
Chapotot et al., 2000; Meneses & Corsi Cabrera , 1990) All of these frequencies (0.1 Hz to 100+ Hz) follow the phase of an infra-low fluctuation, which reflects the excitability dynamics of a cortical network (Vanhatalo et al., 2005; Vanhatalo et al, 2003; Vanhatalo et al., 2004).

What is responsible for the ILF signal we record from the scalp? What in the brain is cycling so slowly, as slow as our 2-hour daily rhythm of rest and activity? We might expect a single mechanism to be responsible, or alternatively our behavioral and cortical rhythms may be the interplay of multiple contributors. Cortical excitability fluctuates every 90 to 120 minutes, and these fluctuations are the recorded ultradian rhythm at one level of description. But what entity or mechanism is responsible for turning cortical excitability off and on, facilitating it for an hour and dampening it for another hour. Is there a governing system, neurotransmitter, or subcortical nucleus that cycles every 2 hours (or 90 minutes to 2.4 hours, see figure above) and produces an increase and decrease in cortical activity accordingly?

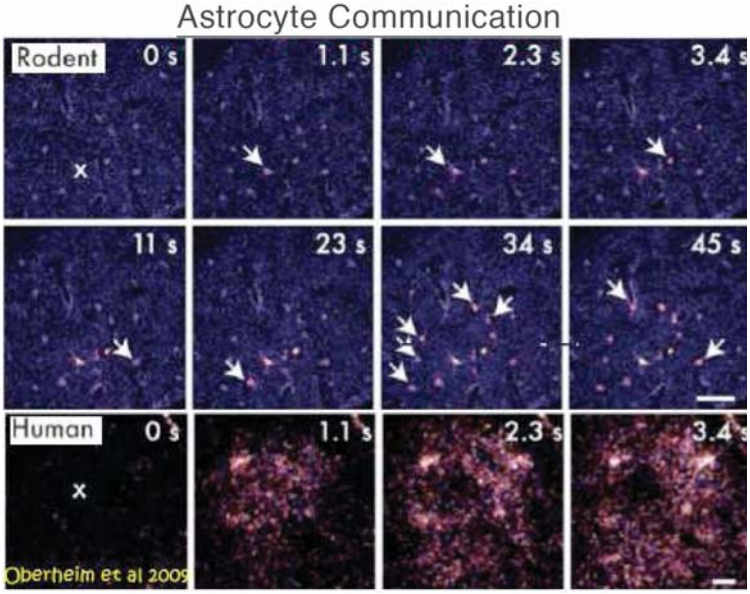


Most mammalian cells and tissues express circadian rhythms (Yoo et al., 2004; Kowalska and Brown, 2007). Our EEG reveals a circadian peak in the early afternoon, poking above the ultradian peaks, as shown in Figure 2. Circadian rhythms are regulated by clock genes, and are life's response to cycles of light and darkness. Even under free-running conditions, these rhythms are remarkably stable. Ultradian rhythms, those lasting from half an hour to a few hours, are not an evolutionary adaptation to the earth's rotation but rather a response to basic metabolic challenges. A waxing and waning of the brain's energy state is adaptive, and common to homeodynamic systems, those maintaining homeostasis in an energetically-variable environment. eneration of infra-slow frequency waveforms may involve multiple intracranial structures and mechanisms, notably glial cells and the blood-brain barrier (Vanhatalo et al., 2003). Infralow frequencies between 0.1 and 1 Hz correspond to the default mode cycles, brief periods of activity and rest, a weaving on and off of our default mode and the taskpositive networks, mediated by the salience network. Fluctuations in the 0.01– 0.1 Hz range in EEG activity are relevant to cognitive task performance (Monto et al, 2008), as they reflect network dynamics, competition among the default mode, central executive, and the salience networks, all modulated by endogenous mechanisms. The thalamus consistently shows oscillations at < 0.1 Hz in animal research and may be a source of ILF signals (Hughes et al., 2011). Nuclei in the dorsal thalamus express rhythms as slow as 0.005 Hz in vitro. (Lorincz et al., 2009). However we are interested in an even slower ILF than 5 mHz. We are most interested in the 0.001 to 0.0001 Hz range, 1 to 0.1 mHz, the ILF frequency range for which we find much therapeutic impact. Astrocytes are known to modulate cortical slow oscillations and may be responsible for even lower ILFs (Fellin et al., 2009). Thalamic astrocytes generate spontaneous and often highly rhythmic intracellular calcium oscillations as slow as 0.003 Hz (Parri & Crunelli 2001). As the astrocyte network manages energy and excitability in the thalamus, this dynamic resonates through the thalamus and includes thalamocortical

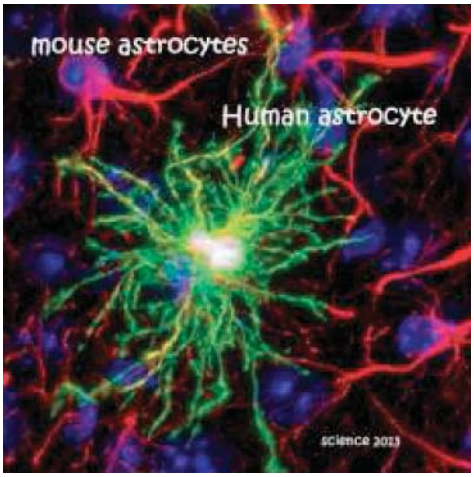
neurons, providing a tone for their firing, which transfers into the overall dynamic of the thalamocortical network and allows detection of the ILF at the scalp. Astrocytes are glial cells, a very common type of glia. Early neuroscientists debated glia's classification, morphology, and role in the nervous system. The term "glia" is the Greek word for glue, reflecting the standard view that glia served as passive support for the neuronal system. Glia -- and astrocytes in particular -- are now recognized as active participants in brain function and thought processes, with direct roles in modulating neuronal interactions, which has implications for local network segregation and global functional complexity. Glia interact with neurons both at the synapse and at the axon. Astrocytes assist synaptogenesis and plasticity, and oligodendrocytes, another type of glia, speed information exchange between neurons by insulating select axons.



Rhythmic Ca^{2+} oscillations and intra- and intercellular Ca^{2+} waves in thalamic astrocytes. (a) Rhythmic intracellular $[Ca^{2+}]_i$ oscillations recorded from an astrocyte in a rat VB slice (1), corresponding raw images (2) (modified from Parri et al., 2001).

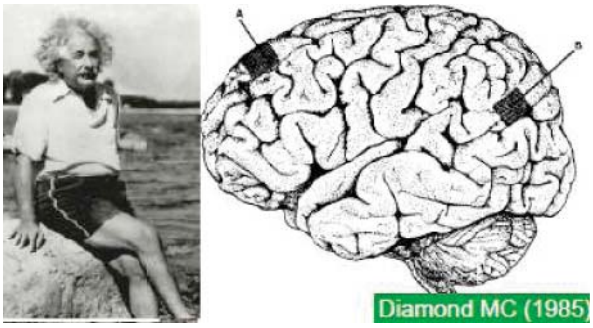


Glia take up the most space of any element of our brain, taking up as much as 90% of our cortex, 80% of the cortex of our genetic relative the chimpanzee, 60% of rodents, and 20% of fruit flies (Laming et al., 1998). Across species, astrocytes increase in prevalence proportionally with the complexity of the brain. The astrocyte–neuron ratio is 1:25 in the leech, 1 in 6 for the round worm, 1 in 3 for rats and mice, and approximately 3 astrocytes to 2 neurons in the human and 7 to 1 in the neocortex (Oberheim et al, 2009). Advances in glia specific to humans including size and complexity of astrocytes has also occurred in addition to the general pattern associated with larger brains. Astroctyes in humans are 2.6 times larger, with 10 times as many processes, and signal 10 times faster than those of rodents.

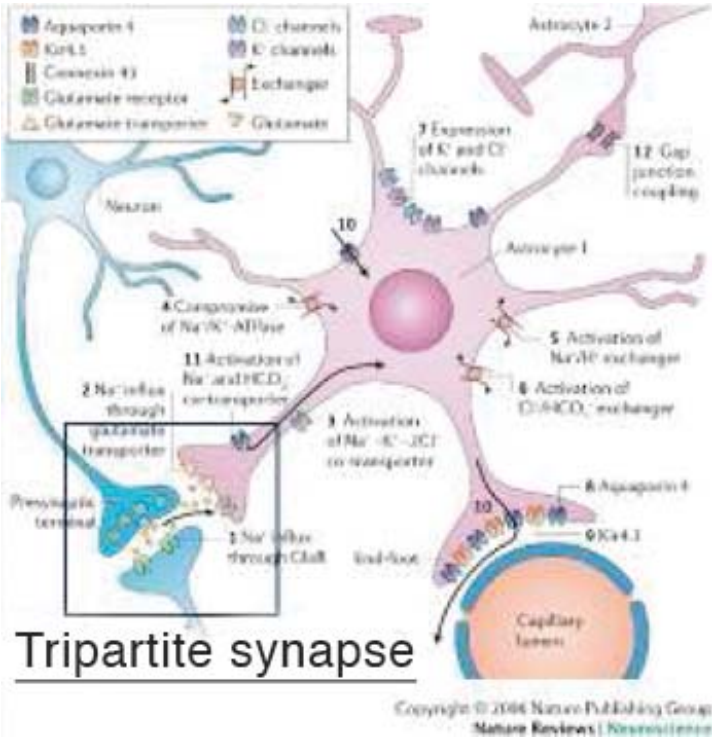


The evolution of the astrocyte-neuron partnership is responsible for our mental supremacy on earth. Einstein's brain was found to have much higher glia/neuron ratios than other men his age in the left parietal lobe (Brodmann area 39), an area involved in symbol representation and calculation, and the additional energetic support (higher glia ratio) likely supported his mental excellence (Diamond

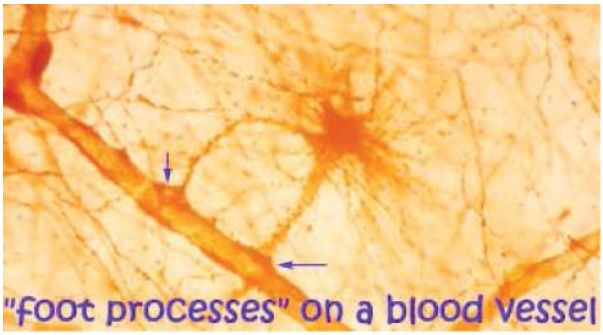
et al, 1985). The human astrocytic network complexity and diversity permits the increased functional competence of our brain compared to other mammals and even other primates (Oberheim et al, 2009).



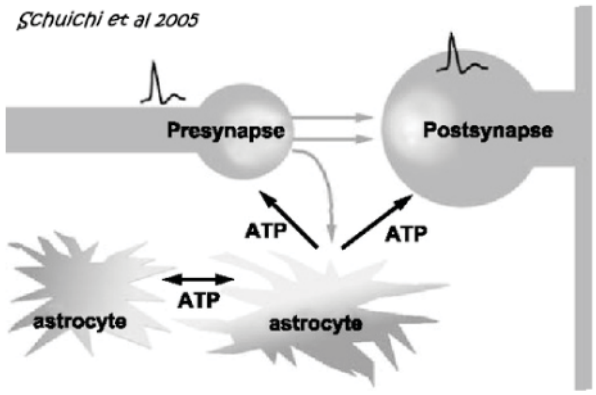
Neurons and glia interact dynamically to process information and organize behavior. Astrocytes play a critical role in plasticity. The synapse is not just an interaction of two neurons but rather is typically an interplay between neurons and their astrocytes (i.e., Tripartite synapse model; Kang et al. 1998; Araque et al. 1999; Carmignoto 2000). Astrocytes release neurotransmitters in response to synaptic activity, and in so doing provide a feedback loop on synaptic transmission. Astrocytes are able to modulate and likely integrate the activity of adjacent neurons by releasing neurotransmitters (Parpura et al. 1994; Bezzi et al. 1998; Innocenti et al. 2000). Astrocytes release neurotrophic signals that strongly promote CNS neuron survival (Banker, 1980). In fact, in vivo astrocyte survival is necessary for cortical neuron survival (Wagner et al., 2006). Astrocytes might promote neuron survival simply by inducing CNS neurons to form synapses. Astrocytes can also release both vasoconstrictors and vasodilators through direct connection with capillaries via “foot processes” (Zonta et al., 2003; Metea and Newman, 2006; Gordon et al., 2007). Astroglia play a causal role in regulating synchronized activation of neuronal ensembles (Poskanzer & Yuste, 2011) and likely segregate and coordinate cortical networks. Mammalian astrocytes regulate neuronal networks through the reuptake and release of glutamate and other neurotransmitters (Halassa and Haydon, 2010). When cultured with astrocytes, the synaptic activity of retinal ganglion cells increases by nearly 100-fold over ganglion cells cultured without astrocytes (Barres 2008). Hence, through a variety of mechanisms astrocytes are integral to brain function.



Astrocytes produce long-term fluctuations in ATP release (energy), synaptic plasticity, as well as glutamate and calcium availability, jointly constituting a multi-faceted capability of regulating cortical excitability and plasticity (Fellin et al, 2007). Astrocytes possess many of the same molecules of the neuronal synaptic machinery and are thus able to influence synaptic strengthening and depression; however, they are not electrically excitable. The rate of synaptic plasticity adjustments by astrocytes is an ILF, occurring only slowly and coordinating slowly through calcium waves. Astrocyte calcium waves generally do not propagate to other astrocytes in vivo, providing evidence that these can respond as individual cells, much like neurons, with their own unique response

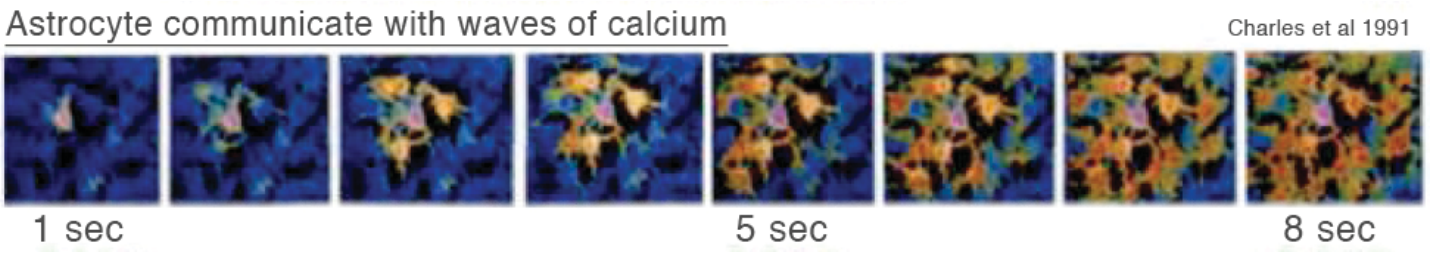


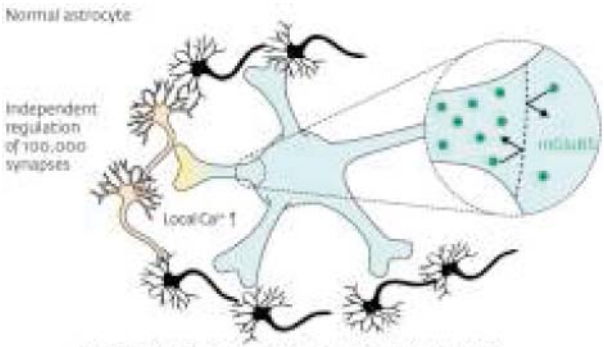
patterns (Schummers et al., 2008). Astrocytic networks intercommunicate with neuronal networks and process information on this slower time-scale, 0.1 to 0.001 Hz. This regulation of cortical synapses via calcium waves is observed as slow cortical oscillations in the EEG (Lorincz et al 2009), effectively cycles of cortical excitability. Astrocyte networks influence an even slower arousal cycle, the sleep-waking cycle. They control sleep pressure accumulation in part by inhibiting awake-state-promoting cholinergic neurons in the basal forebrain (Halassa et al, 2009; 2010).

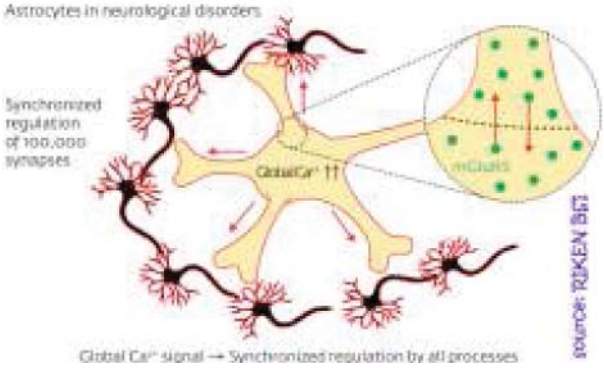


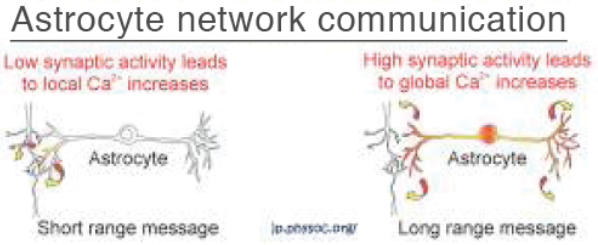
Astrocytic ATP has an essential role for the formation of the intercellular Ca2+ wave, and in turn functions as a feedback signal to modulate synaptic transmission in adjacent neurons.

Astrocytes release ATP through hemichannels (Cotrina et al., 1998), vesicle-dependent mechanisms (Pascual et al., 2005), and other means. It is this release of ATP that provides the tone for faster neural operations, based on energy availability (Parri and Crunelli, 2002, Parri et al., 2001, Parri and Crunelli, 2001). The ATP release cycle emerges as the scalp ILF. In other words the ILF signal we measure at the scalp is likely information generated by astrocytic spatio-temporal dynamics. No other system in the brain appears to regularly change state or activate in this time frame. The next task will be to prove that by altering ILF signal via neurofeedback or magnetic stimulation, we alter astrocyte-neuronal dynamics.









Given the ubiquity of the astrocytes in our nervous system, it is no surprise that astrocyte dysfunction is associated with many brain-based disorders ranging from ADHD to epilepsy and mood disorders. Diminished astrocytic uptake of glucose from capillaries, its conversion to lactate, and storage as glycogen can explain many of the symptoms of ADHD (Todd and Botteron, 2001). Astrocytes are known to be responsible for the rapid improvement in mood in depressed patients after acute sleep deprivation (Hines et al 2013). Healthy astrocytes send separate signals through each process but astrocytes will send synchronous signals to their entire network when failing or ill (Arizono et al, 2012). Because of their ubiquity, there is no central nervous system disease or dysfunction that does not substantially involve astrocytes (Banaclocha, 2007). Some believe that astrocyte activity may contribute to conscious modulation of brain rhythms in neurofeedback (Pereira & Furlan, 2010). As astrocytes generate ILF signals that can propagate through the cortex and be measured at the scalp, we are provided a vast opportunity to impact astrocyte functionality with ILF training and address basic energy cycle issues in health and sleep. We may be able to coordinate ultradian rhythms across the brain and in so doing synchronize individuals to resting states and improve sleep.

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