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Out of thin air: Hyperventilation-triggered seizures

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Abstract

Voluntary hyperventilation triggers seizures in the vast majority of people with absence epilepsy. The mechanisms that underlie this phenomenon remain unknown. Herein, we review observations – many made long ago – that provide insight into the relationship between breathing and absence seizures.

Keywords

Epilepsy; Respiration; Seizure; Circuit; Thalamus; pH

1. Clinical considerations

In 1770, a Swiss physician named Samuel Tissot reported his observations of a young girl who lost consciousness multiple times a day (Tissot, 1770). Although impairment of consciousness was already a known symptom of epilepsy, the lack of any concomitant convulsions led Tissot to conclude that the girl's epilepsy was distinct (Tissot, 1770). Tissot's instincts were correct and he is credited with the coining these events as *petit mal* seizures (Tissot, 1770). But only much later, in 1935, did we learn about the dramatic, highly-stereotyped, electrical activity patterns that likely pulsed within the girl's brain during her brief episodes of unconsciousness. It was Gibbs et al. (1935) who used newly developed electroencephalogram (EEG) recording techniques to provide the first description of the characteristic 3-Hz, spike-and-wave electrical discharge (SWD) now synonymous with absence epilepsy (Fig. 1). Over 80 years later, clinicians still use the electrographic signature of the SWD, accompanied by a loss of consciousness, as diagnostic criteria for absence epilepsy.

In 1989, the International League Against Epilepsy (ILAE) partitioned absence epilepsy into two distinct epilepsy syndromes: *Childhood Absence Epilepsy* (CAE) and *Juvenile Absence Epilepsy* (JAE) (ILAE, 1989). While seizures associated with CAE and JAE are both characterized by impaired consciousness and accompanying 3–4 Hz SWDs, differences between the two syndromes exist. In 2004, Trinka et al. retrospectively examined 163

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Conflict of interest

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patients to identify pyknoleptic absences and non-pyknoleptic absences (Trinka, 2004). While such terminology has generally fallen out of favor, *pyknoleptic absences* refer to seizures that occur in clusters, often hundreds per day, while *non-pyknoleptic absences* occur less frequently (i.e. < 1 per day). Pyknoleptic absences are also associated with an abrupt and severe state of unconsciousness, while the state of unconsciousness associated with non-pyknoleptic absences is often less pronounced.

When the operational distinction between pyknoleptic and non-pyknoleptic absences is applied to patients, absence epilepsy appears to subdivide into two syndromes with differing onset ages (Trinka, 2004). CAE, with a peak onset between 5 and 7 years of age (Matricardi et al., 2014), is primarily associated with frequent, abrupt absences (i.e. pyknoleptic). In contrast, patients with JAE (mean age of onset: 15 years) typically present with infrequent absences (i.e. non-pyknoleptic). Also, relative to CAE, patients with JAE are more likely to present with additional, different seizure types at the time of diagnosis. Specifically, Trinka et al. reported that nearly 95% of JAE patients eventually develop generalized tonic clonic seizures (GTCS), compared to 69% of CAE patients; other reports suggest that GTCS prevalence in the CAE population may be much lower (Shinnar, 2015).

In aggregate, the data indicate that two distinct absence epilepsy syndromes exist. In CAE, relatively young patients present with frequent, abrupt seizures of a singular form that generally subside with age. In JAE, generally older patients present with fewer, less pronounced absence seizures, but also present with other seizure subtypes that, collectively, are less likely to remit. Despite these differences, much overlap between CAE and JAE exists, leading some to argue that absence epilepsy represents a continuum of syndromes primarily characterized by SWDs (Reutens and Berkovic, 1995; Guilhoto, 2017). Moreover, absence seizures are not unique to children and juveniles. Absence seizures occur in adults (Gastaut, 1981), more often in women (Gastaut, 1981; Panayiotopoulos, 1992). Sometimes these seizures recur in patients who had absence seizures in their youth (Michelucci, 1996; Berkovic and Bladin, 1983). Usually, these absence episodes arise in conjunction with other idiopathic generalized epilepsies (IGE) (Marini et al., 2003) or psychoses (Iivanainen et al., 1984). Thus, while CAE represents the prototypical form of the epileptic disorder, absence seizures consisting of SWDs with concomitant impaired consciousness are observed in wide-ranging clinical contexts. Finally, electrographic SWDs and unconsciousness are not the only feature of absence epilepsy; associated comorbidities include attentional problems, depression, anxiety and memory impairments (Tenney and Glauser, 2013).

2. Etiology

The causes of absence epilepsy are complex and varied, but primarily involve genetic mutations. While many rodent studies highlight potential mechanisms underlying absence epilepsy (Depaulis and Charpier, 2017; Depaulis et al., 2016; Felix, 2002; Cortez et al., 2016; Coenen and Van Luijtelaa, 2003), herein we primarily focus on human genetic mutations associated with the disorder. To date, identified human mutations include genes encoding for specific subunits of (1) the primary ionotropic receptor for γ -aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, and (2) the low threshold, T-type calcium channel. The primary ionotropic receptor for GABA, also called the A-type GABA

(GABA_A) receptor, is a pentameric structure, wherein each of the 5 subunits corresponds to one of four subunit subtypes: α , β , δ , γ (Jones-Davis and Macdonald, 2003; Macdonald et al., 2010; Rudolph et al., 2001). Identified, CAE-associated mutations have been localized to the $\gamma 2$ (Tan, 2007); $\alpha 1$ (Cossette, 2002; Lachance-Touchette, 2011; Maljevic, 2006) and $\beta 3$ (Huntsman et al., 1999; Roden et al., 2010; Holopainen, 2001) subunits of the GABA_A receptor.

While more studies are required, the aforementioned GABA_A receptor subunit mutations generally appear to reduce the capacity of the receptor to traffic to the plasma membrane of neurons (Berkovic and Bladin, 1983). For example, mice heterozygous for the R43Q point mutation in the $\gamma 2$ subunit produce SWDs (Berkovic and Bladin, 1983). Cortical neurons in these mice receive reduced GABAergic inhibition, an effect attributed to reduced surface expression of the receptor; GABAergic inhibition was largely spared in other brain structures involved in SWD generation. Similar to the R43Q mutation in the $\gamma 2$ subunit, $\alpha 1$ subunit mutations are also associated with both increased SWDs (Cossette, 2002; Maljevic, 2006) and reduced GABA_A receptor expression at the cell membrane (Lachance-Touchette, 2011; Maljevic, 2006). Finally, mutations in the $\beta 3$ subunit of the GABA_A receptor are also associated with SWDs. And again, the emerging picture indicates that $\beta 3$ subunit mutations reduce the number of functional GABA_A receptors and, generally, reduce inhibition (Jones-Davis and Macdonald, 2003; Huntsman et al., 1999; Roden et al., 2010).

In contrast to the aforementioned, loss-of-function mutations in the GABA_A receptor, T-Type Ca²⁺ channel mutations associated with absence epilepsy lead to a gain of function. Chen et al. originally identified missense mutations in *CACNA1H*, the gene encoding the $\alpha 1H$ subunit of the T-type channel complex, in a Han Chinese cohort (Chen, 2003). Subsequent studies on other, non-Chinese populations confirm that *CACNA1H* mutations are associated with CAE (Heron, 2007). Consistent with these observations, several studies have demonstrated that CAE-associated *CACNA1H* mutations generally lead to greater calcium influx through the channel following activation (Khosravani, 2004; Vitko, 2005; Peloquin, 2006). Greater Ca²⁺ influx, in turn, is thought to support robust low-threshold Ca²⁺ spikes that sustain SWDs (see below). The induction of absence seizure-like SWDs in otherwise normal rats by the introduction of the human-associated, C456S, gain-of-function *CACNA1H* mutation (Wang, 2015) supports this hypothesis. However, this conclusion warrants a word of caution. Epilepsy-associated variants in *CACNA1H* are also observed in *unaffected* individuals (Heron, 2007), suggesting that T-Type Ca²⁺ channel mutations appear to increase CAE susceptibility, but alone do not cause CAE. Indeed, the emerging paradigm is that most epilepsies are complex disorders that do not arise from a single, clear biological origin (Heron, 2007; Staley, 2015). Instead, most epilepsies are multifactorial disorders that likely involve mutations in several proteins (i.e. polygenic), and are disorders often influenced by the environment, a recurring theme within this *Special Issue*.

3. Outcome & treatment

As remission often occurs by early adulthood, absence epilepsy is frequently described as a benign disorder. Such a designation requires reconsideration (Tenney and Glauser, 2013). *First*, reported remission rates are variable and generally not as high as commonly perceived.

Several studies report that approximately 60% of subjects remit by 20 years of age (Trinka, 2004; Loiseau et al., 1983; Wirrell et al., 1996), although the number of seizure-free subjects no longer requiring medication is likely lower (Sillanpää et al., 1998). *Second*, prior to possible remission, a cocktail of anti-seizure drugs (ASDs) – ethosuximide, valproic acid and lamotrigine – is sometimes recommended to manage seizures (Glauser, 2013). While ASD cocktails are at times effective, the treatment strategy also often contributes to additive and intolerable side-effects (Matricardi et al., 2014). Moreover, little is known regarding the effects of such a blunt pharmacological strategy on the developing brain. *Third*, long-term cognitive and psychosocial problems are prominent in absence patients. Comorbidities include social anxiety disorder, depression, attention deficit disorder and behavioral/linguistic problems (Tenney and Glauser, 2013; Wirrell, 1997; Caplan, 2008; Caplan, 2015). Considering remission rates, available treatment methods and comorbidities, labeling absence seizures as *benign* appears ill-suited.

4. Hyperventilation triggers absence seizures

SWDs are triggered by voluntary hyperventilation in over 90% of patients with absence epilepsy (Glauser, 2013; Wirrell, 1997; Caplan, 2008, 2015; Panayiotopoulos, 1999), a phenomenon initially documented in the early 20th century (Waternberg, 2015; Giannakodimos et al., 1995). The use of hyperventilation to unequivocally and quickly diagnose patients with absence epilepsy is now commonplace, and largely obviates the need for a protracted EEG recording procedure to capture spontaneous seizures (Adams and Leuders, 1981). The effectiveness of this diagnostic tool even provides fodder for Holowach and O’Leary’s suggestion that a diagnosis of absence epilepsy “*should be seriously questioned [if one] does not have an attack on hyperventilation.*” (Holowach et al., 1962).

Hyperventilation elicits high-amplitude, slow and rhythmic brain activity even in *nonepileptic* individuals (Nims et al., 1940; Lum et al., 2002). This phenomenon, known as *Hyperventilation-Induced, High-Amplitude Rhythmic Slowing* (HIHARS), is often confused with SWD activity in the EEG. HIHARS and SWDs are both observed on most cortical recording electrodes, reflecting a generalized EEG pattern. HIHARS also evokes many of the automatisms – staring, eye opening/eyelid fluttering, yawning – observed during absence seizures (Lum et al., 2002). Electrographically, however, HIHARS and seizure-associated SWDs are distinct EEG events. HIHARS consists of slow (2–5 Hz), high-amplitude (>100 mV) electrical activity reminiscent of delta waves observed during slow-wave sleep (Khosravani, 2004). In contrast, spontaneous and hyperventilation-triggered SWDs observed in absence patients consist of the canonical 3 Hz, high-amplitude, nearly sinusoidal EEG wave that is punctuated by an abrupt and rapid spike during each cycle of the oscillation (see Fig. 1). Thus, while hyperventilation can clearly alter brain activity in healthy individuals, it is also clear that such rapid breathing evokes distinct electrical activity patterns in absence patients.

5. Physiological response to hyperventilation

To understand how hyperventilation alters EEG patterns, it is important to understand the relationship between breathing and blood pH, a relationship that is critically dependent on

carbon dioxide (CO₂) in the blood. Indeed, in 1942, Gibbs et al. admonished brain researchers by suggesting that “*students of cerebral function have, in general, paid too little attention to carbon dioxide.*” (Gibbs et al., 1942) In that spirit, we begin by directing our attention to CO₂.

CO₂ is a waste product of *aerobic respiration*, the series of biochemical events utilized by cells to convert glucose metabolites into energy (Fig. 2). Once produced, CO₂ diffuses out of the tissue and into the blood plasma. Most plasma CO₂ enters red blood cells, where it associates with water to produce bicarbonate and a hydrogen ion, a reaction catalyzed by carbonic anhydrase. Plasma CO₂ that does not enter red blood cells is converted into carbonic acid (H₂CO₃), an uncatalyzed reaction. Carbonic acid, in turn, *dissociates* into bicarbonate and hydrogen ions. The concentration of the free hydrogen ions ([H⁺]), in turn, determines blood plasma pH. Naturally, this reaction can proceed in the reverse direction such that bicarbonate and a hydrogen ion *associate* to form carbonic acid. When this reverse reaction is favored, [H⁺] drops and the blood becomes more alkaline. The reverse reaction is favored when the partial pressure of CO₂ (pCO₂) drops.

Taking into account the aforementioned bicarbonate buffering system present in the blood plasma, we can begin to understand how hyperventilation alters blood pH (Fig. 2). Rapid breathing causes CO₂ levels in the plasma to drop; in short, the individual *blows off* CO₂. The drop in free CO₂ in the blood plasma is called *hypocapnia* and promotes the reverse reaction in which carbonic acid dissociates into CO₂ and water. The resultant drop in carbonic acid, in turn, promotes the association of bicarbonate and H⁺ ions to replenish depleted carbonic acid, a reaction that removes free H⁺ ions. *In toto*, as CO₂ drops, the [H⁺] in the blood also drops, causing the blood to become more alkaline. This process during which rapid breathing alkalizes the blood is called *respiratory alkalosis*.

An important consideration regarding respiratory alkalosis is that rapid breathing occurs when metabolic activity is low. Accordingly, the CO₂-producing, biochemical process of cellular aerobic respiration occurs at low rates. Under conditions of low CO₂ production and high respiratory CO₂ elimination, the pCO₂ of blood drops and the blood alkalizes, as described above (see Fig. 2, purple). In contrast, elevated breathing during exercise, a phenomenon known as *hyperpnea*, is associated with increased metabolic demands. Under such conditions, high CO₂ elimination is matched by high CO₂ production (Fig. 2, green). As the pCO₂ of blood is relatively stable during hyperpnea, the pH of blood does not change. The distinction between hyperventilation and hyperpnea is relevant, as the latter does not trigger seizures in absence patients (Esquivel et al., 1991), suggesting that absence seizures are specifically sensitive to blood pH.

Homeostatic mechanisms are in place to compensate for changes in blood pH. Namely, the vasculature responds when blood pH changes. Vessels normally dilate when blood acidifies, and constrict when blood alkalizes. The mechanisms by which vascular tone (i.e. dilation versus constriction) is modulated by blood pH are well-documented; as such, we direct the interested reader towards excellent reviews on the subject (Kontos et al., 1977; Cipolla, 2009; Boron and Boulpaep, 2009). Suffice to say, vascular tone is a highly regulated process that involves complex interactions between the endothelial cells that line the inner walls of

blood vessels and the smooth muscle cells that contract or relax to change vessel diameter. The canonical vasodilatory effect of nitric oxide (NO) underscores the intimate interaction between endothelial cells and muscle cells: sheer stress sensed by transient receptor potential (TRP) channels on endothelial cells triggers the production of endothelial nitric oxide synthase (eNOS) to catalyze the production of NO, a diffusible molecule that relaxes nearby muscle cells (Boron and Boulpaep, 2009). Vascular tone is also directly regulated by pH, a process that involves internal calcium stores, calcium-activated potassium (BK) channels (Koide et al., 2012) and, possibly, TRP channels (Sonkusare, 2012).

Regardless of the specific mechanism, it is clear that vascular tone responds to blood CO₂ and pH in healthy individuals. Interestingly, Nims et al (Gibbs et al., 1940) showed that inherent differences in this response likely exist between individuals with absence epilepsy and those without absence epilepsy. Specifically, the authors measured the CO₂ content and pH of the carotid artery and jugular vein blood supplies, thereby enabling them to compare the physiochemical properties of blood entering and exiting the brain, respectively. The authors observed a standard response to hyperventilation in both epileptic and non-epileptic cohorts insofar that arterial blood CO₂ dropped to comparable levels. However, following hyperventilation, the drop in CO₂ content and concurrent alkalization of the jugular blood in absence epileptic individuals was consistently larger and persisted longer than that of healthy individuals. Taken together, the data indicate that (1) the blood *supplying* the brain is normal in absence patients, (2) the blood *returning* from the brain is different in absence patients, and (3) hyperventilation unmasks this difference. Thus, not only does voluntary hyperventilation trigger seizures in absence patients, but the brain's response to hypocapnic episodes is also different. Although Nims et al. published their findings more than 75 years ago, it remains unclear if the two phenomena are related. The observation that CO₂ inhalation can temporarily abolish absence seizures (Cossette, 2002; Lennox, 1928; Yang, 2014) suggests interdependence.

At present, no consensus exists regarding whether the observed EEG changes in response to hyperventilation result from hypocapnia, the concomitant change in brain pH, or a combination of the two. An explanation will likely require a better understanding of pH-sensitivity among specific elements within the neural circuits that generate absence seizures. Below, we begin by describing results that highlight how crosstalk between structures in the cortex and in the thalamus, a subcortical structure, may precipitate seizures in response to hyperventilation. Then, we detail the neural circuits involved in absence epilepsy. Finally, we summarize evidence supporting the hypothesis that specific nodes within thalamic circuits are pH-sensitive.

6. Absence seizures: crosstalk between the thalamus and cortex

Decades of research highlight how reciprocal interactions between cortical and thalamic circuits act as critical architects of absence seizure generation (Avoli, 2012). As early as 1935 clinicians noted that highly synchronized seizure activity could be simultaneously recorded from EEG electrodes placed throughout the cortex, leading to the prescient postulation that subcortical structures with widespread cortical connectivity are likely

involved (Jasper and Kershman, 1941; Penfield and Erickson, 1941). The structure receiving early attention was the thalamus.

Besides serving as a relay station for vision, proprioception and hearing (Jones, 2007), the thalamus houses critical neural circuitry responsible for electrical oscillations observed during sleep (Steriade and Llinás, 1988; McCormick and Bal, 1997) and seizures. Morison and Dempsey (Dempsey and Morison, 1942a,b; Morison and Dempsey, 1942), as well as Jasper and colleagues (Jasper and Kershman, 1941; Jasper and Droogleever-Fortuyn, 1947; Hunter and Jasper, 1949; Hanbery and Jasper, 1953), provided several key lines of evidence in support of the hypothesis that thalamic circuits play an important role in SWD generation. *First*, recordings from depth electrodes placed in the thalamus of cats reveal that thalamic circuits are highly oscillatory (Dempsey and Morison, 1942b; Morison and Dempsey, 1942). *Second*, electrical stimulation of the cat thalamus evokes generalized, cortical SWDs (Jasper and Droogleever-Fortuyn, 1947; Hunter and Jasper, 1949). *Third*, severing thalamus-cortex connections mitigates the capacity of thalamic stimulation to evoke SWDs (Hanbery and Jasper, 1953). Following these insightful studies, Fisher and Prince (Fisher, 1977), as well as Avoli and colleagues (Avoli and Gloor, 1982a,b; Avoli et al., 1983), used the feline generalized penicillin model of epilepsy (FGPE) to assess, on a more granular level, thalamic contribution to SWDs. The FGPE is an experimental epilepsy model in which a large, intramuscular injection of penicillin reliably evokes SWDs (Prince and Fischer, 1969). By closely examining temporal relationships of neuronal activity throughout the brain in the FGPE, it was possible to determine that excessive, hypersynchronous cortical activity likely initiates the SWD (Avoli and Gloor, 1982b; Avoli et al., 1983). A similar conclusion was later derived in an inbred rat model of absence epilepsy (van Heukelum et al., 2016; van Luijtelaar and Coenen, 1986). Thus, decades of work underscore the notion that a “close coupling” of activity produced by the thalamus and cortex contributes to the onset and maintenance of the SWD (Avoli and Gloor, 1982b).

7. The riddle in the middle: midline structures of the thalamus

The pioneering studies of Rose and Woolsey prompted an era dedicated to organizing the thalamic nuclei based upon structure and function (Jones, 2007). Using anatomical and electrophysiological methods, their work revealed that the cortex receives inputs from specific subdivisions of the dorsal thalamus (Jones, 2007). Rose and Woolsey divided the dorsal thalamus into two distinct divisions: *extrinsic* and *intrinsic*. The *extrinsic* nuclei included the anterior and ventral thalamic groups as well as the geniculate bodies. They proposed that these *extrinsic* structures projected to specific cortical areas, including motor, sensory and limbic areas. The *intrinsic* nuclei, consisting of the midline, intralaminar and posterior thalamic groups, were thought to receive only intrathalamic projections. However, the distinction between *extrinsic* and *intrinsic* was highly speculative and subsequent studies failed to demonstrate the existence of purely intrathalamic connectivity among thalamic nuclei.

Later, Morison and Dempsey proposed a second classification scheme to distinguish the dorsal thalamic nuclei. They used the term *specific* to describe dorsal thalamic nuclei with distinct, topographically-mapped connections to the cortex. In contrast, the term *non-*

specific (Dempsey and Morison, 1942a,b) was used to describe those nuclei, primarily the midline and intralaminar nuclei, with diffuse projections throughout the cortex. These non-specific nuclei are collectively called the *non-specific thalamic projecting system* (NSTPS) and include the mediodorsal nucleus, central medial (CM) nucleus, as well as other nuclei of the intralaminar complex (Jones, 2007). We illustrate the organization of the specific and non-specific thalamic nuclei in Fig. 3. Special attention will be given to the NSTPS, as this system appears to play a critical role in hyperventilation-induced changes in EEG patterns.

Morison and Dempsey first demonstrated that electrical stimulation of specific and non-specific thalamic nuclei in the anesthetized cat evoked divergent cortical responses. Stimulation of the specific nuclei evoked a localized, multiphasic response consisting of an early *primary response* and a later *augmenting response*. The latter response was so-called because it became larger after repetitive stimulation (Fig. 4A). In contrast, stimulation of the NSTPS evoked widespread responses in the cortex (Dempsey and Morison, 1942a,b; Morison and Dempsey, 1942), consistent with the diffuse nature of NSTPS projections. Interestingly, successive NSTPS stimuli delivered at 6–12 Hz often produced robust, high amplitude cortical responses that grew during the repetitive stimulus train (Fig. 4B). This latter feature led Morison and Dempsey to introduce the term *recruiting response*. There are several important characteristics that distinguish the recruiting response from the augmenting response (see Fig. 4: (1) the latency from stimulus to event onset is much longer for the recruiting response; (2) the recruiting response waxes and wanes with repetitive stimulation; (3) the recruiting response spreads throughout the cortex, while the augmenting response is highly localized; (4) the recruiting response is not preceded by the primary response. The phenomenon of the NSTPS-evoked recruiting response was subsequently confirmed in great detail by Jasper and colleagues (Jasper and Kershman, 1941; Jasper and Droogleever-Fortuyn, 1947; Hunter and Jasper, 1949; Hanbery and Jasper, 1953). Moreover, Jasper and colleagues demonstrated that even brief stimulation of the NSTPS in lightly anesthetized (Jasper and DroogleeverFortuyn, 1947) or unanesthetized (Hunter and Jasper, 1949) cats can evoke behavioral arrest and synchronized SWDs throughout the cortex that long outlasts the stimulus. The capacity for NSTPS stimulation to evoke either the recruiting response or prolonged SWDs accompanied with behavioral arrest likely depends on the state of anesthesia: recruiting responses are observed in anesthetized animals, while seizures are observed in unanesthetized animals. This observation firmly placed the NSTPS at the forefront of possible structures that drive absence seizures, even prompting Jasper to conclude that this collection of nuclei serves as the “diencephalic basis for [absence epilepsy], or a diencephalic pacemaker for its characteristic cortical discharge.” (Hunter and Jasper, 1949).

Following these seminal findings, Dominick Purpura set out to determine how the NSTPS drives widespread cortical activity. He focused much of his efforts on intrinsic thalamic connectivity (Jones, 2007). By performing intracellular recordings of neurons in the specific and non-specific thalamic nuclei of anesthetized cats, Purpura and colleagues revealed complex, bidirectional interactions between the NSTPS and the specific thalamic nuclei (Desiraju and Purpura, 1970; Purpura and Cohen, 1962). Their findings also provided a glimpse into how these interactions may contribute to the aforementioned recruiting response. Many of their studies focused on the CM nucleus, a member of the NSTPS.

Purpura and colleagues showed that CM stimulation in the cat evokes post-synaptic potentials (PSPs) in neurons localized to several specific thalamic nuclei, including the ventral group of the dorsal thalamus and the reticular nucleus (Fig. 5). The evoked PSPs follow a complex pattern (Purpura and Cohen, 1962). CM stimulation evokes putative short-latency excitatory post-synaptic potentials (EPSPs) in neurons of the ventral group (i.e. ventromedial thalamus), followed by long-duration, inhibitory post-synaptic potentials (IPSPs) (Fig. 5). The short latency of the putative EPSPs led Purpura to posit that CM provided direct excitation to the ventral group.

The origin of CM-evoked IPSPs was more puzzling. When Purpura and Cohen recorded neurons of the reticular thalamus (RT), an inhibitory structure, the picture became clearer: CM stimulation activated RT neurons. As RT neurons inhibit many thalamic structures (Fuentelba and Steriade, 2005), a likely origin of the CM-evoked IPSPs observed in neurons of the ventral group was from the RT nucleus. Thus, it was proposed that CM provides direct excitation, as well as indirect, disynaptic inhibition, to neurons of the ventral group. The observed inhibition of ventral group neurons was quite robust and included a strong, long-lasting component indicative of activation of metabotropic, B-type, GABA (GABA_B) receptors. GABA_B receptor antagonists effectively inhibit experimentally-induced absence seizures (Vergnes et al., 1997).

Purpura and Cohen ultimately attempted to relate the progression of CM-evoked EPSPs-IPSPs observed in ventral group neurons to the CM-evoked recruiting response. They proposed that the initial, large component of the recruiting response associates with ventral group EPSPs, while the ensuing, secondary component of the response associates with ventral group IPSPs. Moreover, special attention was paid to the potential synchronizing effect neurons of the RT nucleus had on thalamic activity. In sum, these experiments provided an unprecedented, macroscopic understanding of the structures involved in generating absence seizures. Left unaddressed was whether the NSTPS was involved in hyperventilation-triggered absence seizures.

8. A basic modulation of the thalamus

Despite the long-established documentation of hyperventilation-induced (i.e. respiratory alkalosis-induced) absence seizures, few studies have attempted to experimentally recapitulate this phenomenon. Experiments performed by Ira Sherwin in the 1960s represent some of the few attempts to do so. Sherwin posed two key questions in his experiments: (1) what brain structures are recruited by hyperventilation to increase the occurrence of SWDs (Sherwin, 1965, 1967), and (2) do these structures possess a specific, element that is responsive to respiratory-induced changes in pH?

In the first study we discuss (Sherwin, 1965), Sherwin demonstrated that hyperventilating a cat elicits high amplitude, rhythmic slowing in the cortical EEG comparable to activity observed during HIHARS (Fig. 6). Stimulating the cortex during HIHARS further transformed the activity to include generalized cortical seizures similar to SWDs. To determine how the coupling of HIHARS and cortical stimulation evokes seizures, Sherwin used a common procedure at the time to assess cortical excitability: the direct cortical

response (DCR, see Fig. 6A). Briefly, local electrical field potentials are evoked and recorded in one area of the cortex by stimulating another area of the cortex. The activation of excitatory synapses formed between thalamocortical and cortical neurons is thought to contribute to the DCR. Using this assay of cortical excitability, Sherwin showed that the DCR was enhanced during hyperventilation. Severing connections between the cortex and subcortical structures (i.e. isolating the cortex) abolished this hyperventilation-induced DCR enhancement. These findings prompted Sherwin to conclude that some subcortical structure capable of enhancing cortical excitability was recruited during hyperventilation. A few years later, Sherwin performed experiments designed to identify this structure.

In 1967, Sherwin presented a study that demonstrated a critical role for the NSTPS in modulating cortical excitability (Sherwin, 1967). Sherwin specifically examined the contribution of the central lateral (CL) nucleus, a member of the NSTPS, to hyperventilation-induced changes in cortical excitability and HIHARS. Sherwin demonstrated that HIHARS was abolished after lesioning the CL (Fig. 6B), thereby presenting the strongest available data that provide an explanation for how hyperventilation alters cortical EEG patterns. At the time he could only postulate that the observed changes in cortical activity resulted from an element, likely in the thalamus, that is both chemoreceptive (Sherwin, 1967) and capable of enhancing cortical activity. The conclusions drawn by Sherwin were never pursued further in the context of absence epilepsy. Nonetheless, the few-yet-critical results documented by Sherwin uncovered the interesting possibility that the thalamus acts as a potential pH-sensor (or contains pH sensing pathways to the cortex). It remains uncertain how the NSTPS engages with other rhythmic microcircuits in the thalamus during hyperventilation-induced SWDs.

9. Rhythmic microcircuits in the thalamus

The decades leading up to the 1980s provided invaluable insights into the key brain structures associated with absence epilepsy. The decades that followed this era provided a much deeper, mesoscopic understanding of thalamocortical circuit dynamics that produce the SWD. A number of studies from the 1980 to 90s (McCormick and Bal, 1997; Jahnsen and Llinás, 1984a; Llinás and Jahnsen, 1982; Steriade et al., 1993; Contreras et al., 1996; Destexhe et al., 1998; Sherman and Guillery, 1996; Bal et al., 1995; Huguenard and McCormick, 1992; McCormick and Huguenard, 1992) support the hypothesis that thalamic circuits underlie the rhythmic nature of the SWD. Three neuronal populations are likely critical for orchestrating thalamocortical rhythms: glutamatergic thalamocortical relay (TC) neurons, glutamatergic corticothalamic (CT) neurons, and GABAergic neurons of the reticular thalamus (RT). The interactions among these three neuron subpopulations have been extensively described in several excellent review articles (Beenhakker and Huguenard, 2009; Huguenard and McCormick, 2007; McCormick and Contreras, 2001; Fogerson and Huguenard, 2016); therefore, we only briefly highlight salient aspects of the circuitry.

As we illustrate in Fig. 7, CT neurons send excitatory projections to both RT neurons and TC neurons. RT neurons provide feedforward inhibition to TC neurons. TC neurons, in turn, provide recurrent excitation back to RT neurons. The populations of reciprocally connected RT and TC neurons constitute a critical circuit for generating rhythmic activity patterns in

the thalamus. As TC neurons project to the cortex, such rhythmicity is imposed on cortical neurons. Circuit rhythmicity is primarily observed during sleep and seizure states. In contrast, during wakefulness, most thalamic neurons fire action potentials in tonic mode, a firing property in which a neuron produces action potentials at a relatively low and arrhythmic rate. More detail on the firing properties of thalamic neurons and thalamocortical circuit connectivity can be found elsewhere (McCormick and Bal, 1997; Destexhe et al., 1998; McCormick and Huguenard, 1992; Fogerson and Huguenard, 2016; Guillery and Harting, 2003; Blumenfeld and McCormick, 2000; Llinás et al., 1998; Steriade and Contreras, 1995).

Several hypotheses attempt to account for the abrupt onset of highly rhythmic circuit activity observed during a SWD. Many of these hypotheses ultimately depend on the activation of robust burst firing in RT and TC neurons. In contrast to the aforementioned tonic firing mode, *burst* firing mode in thalamic neurons, first described by Jahnsen and Llinas (Jahnsen and Llinás, 1984a,b; Llinás and Jahnsen, 1982)**, is a firing property in which a neuron produces a brief, high-frequency burst of action potentials. Thalamic burst firing depends on low threshold, T-type calcium (Ca^{2+}) channels, and is proposed to play a critical role in sustaining thalamic circuit rhythmicity during SWDs (Chen et al., 2014; Cheong and Shin, 2014; Choi et al., 2015). Indeed, as described above, gain-of-function mutations in this channel are associated with absence epilepsy and ethosuximide, a T-type Ca^{2+} blocker, is used clinically to treat absence epilepsy.

As enhanced T-type Ca^{2+} channel activity represents a common thread in most hypotheses regarding SWD generation, many studies have focused on mechanisms that promote thalamic burst firing. We briefly highlight two. *First*, strengthened feedforward, RT neuron-mediated inhibition of TC neurons (see Fig. 7C) is known to promote robust burst firing in TC neurons. The T-type Ca^{2+} channel-mediated mechanism known as *post-inhibitory rebound* bursting drives this TC neuron behavior. Proposed mechanisms that account for augmented feedforward, RT-mediated inhibition include a breakdown of processes that normally dampen RT neuron activity (Huntsman et al., 1999; Destexhe et al., 1998; Castro-Alamancos, 1999) (see Fig. 7C). *Second*, diminished glutamatergic excitation of RT neurons is proposed to promote SWD generation (Menuz and Nicoll, 2008; Paz, 2011) and can lead to enhanced T-type Ca^{2+} channel-mediated bursting (Paz, 2011). Thus, perturbations in several nodes of the thalamocortical circuit likely contribute to SWD generation.

We have described only a small subset of the rich dataset, accumulated over many decades, that highlights the critical role that thalamocortical circuits play in the generation of absence seizures. But what of pH sensitivity in these circuits? For the remainder of this review, we attempt to describe more specifically how pH alters thalamocortical circuits to possibly trigger absence seizures.

10. pH sensitivity in the thalamus

Despite a considerable void in literature detailing pH sensitive mechanisms in the NSTPS, evidence demonstrates that certain neurons of the specific thalamic nuclei possess pH-sensitive ion channels that contribute to the resting membrane potential of thalamic neurons.

We focus on two such channels: the HCN channel responsible for the so-called h-current (I_h) (Soltesz, 1991), and TASK 1/3 channels responsible for a resting potassium current (I_{TASK}) (Meuth, 2006).

Meuth et al. revealed a complex, pH-sensitive interaction between I_h and I_{TASK} in thalamocortical (TC) neurons of the dorsal lateral geniculate nucleus, a “specific” thalamic nucleus that receives visual information from the retina (Meuth, 2006). The authors demonstrate that I_h and I_{TASK} exert opposing effects on TC neuron resting membrane potential. I_h is a mixed cationic (Na^+ and K^+) current that is activated at relatively hyperpolarized membrane potentials (Biel et al., 2009). The reversal potential of I_h is around -20 mV, meaning that when I_h is active, a neuron will typically depolarize towards -20 mV. Because the resting membrane potential of TC neurons is relatively hyperpolarized (~ -70 mV), partial activation of I_h is observed at rest and contributes to TC neuron resting membrane potential. Evidence for this last point comes from the more hyperpolarized resting membrane potential observed in TC neurons when I_h is pharmacologically or genetically removed: the resting membrane potential shifts towards -80 mV (Meuth, 2006). I_{TASK} , in contrast, is a K^+ current and, as such, has a reversal potential of around -90 mV, meaning that when I_{TASK} is active, a neuron will typically hyperpolarize towards -90 mV. I_{TASK} is often described as a background current because it is usually active at rest and contributes significantly to the resting membrane potential of neurons.

I_h and I_{TASK} are both pH-sensitive in TC neurons (Meuth, 2006). Extracellular acidification blocks both currents. Because these two currents have functionally opposing actions – I_h depolarizes cells while I_{TASK} hyperpolarizes cells – the net result of extracellular acidification is minimal; the resting membrane potential of TC neurons does not change much during extracellular acidification. The action potential firing properties of TC neurons are also unchanged during extracellular acidification. The results of Meuth et al. suggest that, functionally, TASK 1/3 and HCN expression levels are commensurate in TC neurons. If such expression levels were mismatched in a sub-population of TC neurons, then changes in pH would likely significantly impact TC neuron activity. Also, it remains formally possible that extracellular alkalization, as might occur during hyperventilation, might preferentially modulate one current (e.g. I_h) over another (e.g. I_{TASK}), thereby significantly changing TC neuron firing behavior. To date, this possibility remains purely speculative. It remains entirely unclear to what extent pH sensitivity in the so-called “specific” nuclei contributes to hyperventilation-induced absence seizures. After all, much of the aforementioned work suggests that the NSTPS plays a major role in absence seizures triggered by respiratory alkalosis.

11. Conclusion

Herein, we highlight the potential link among thalamocortical networks, hyperventilation, and absence epilepsy. Specifically, we focus on studies indicating that the NSTPS of the thalamus may be capable of evoking hyperventilation-induced absence seizures. This conclusion is derived from demonstrations that the NSTPS appears critically involved in both SWDs and hyperventilation-triggered cortical activity patterns. Moreover, some thalamocortical circuit elements appear to be endowed with pH-sensitive proteins. What

remains unclear is whether these observations point to a common mechanism accounting for hyperventilation-triggered absence seizures, a striking phenomenon shared by over 90% of absence patients. Perhaps the next few decades of thalamic research will shed light on this possibility.

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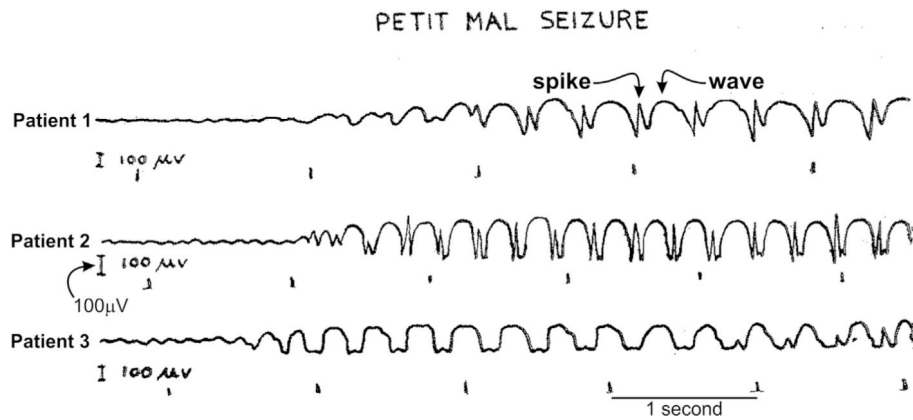


Fig. 1.

Early electroencephalogram (EEG) recordings of absence seizures. A single electrode was placed on the vertex of the skull. A second, reference electrode was placed into the lobe of the ear. Hypodermic needles were used as electrodes. Absence seizure recordings from three different patients are shown. The seizure is associated with periodic, three-per-second events that are composed of a relatively slow, rounded component (i.e. the wave) that is punctuated by a sharp, rapidly evolving upward component (i.e. the spike). Note the abrupt onset of the seizure. Modified from Gibbs et al. (1935).

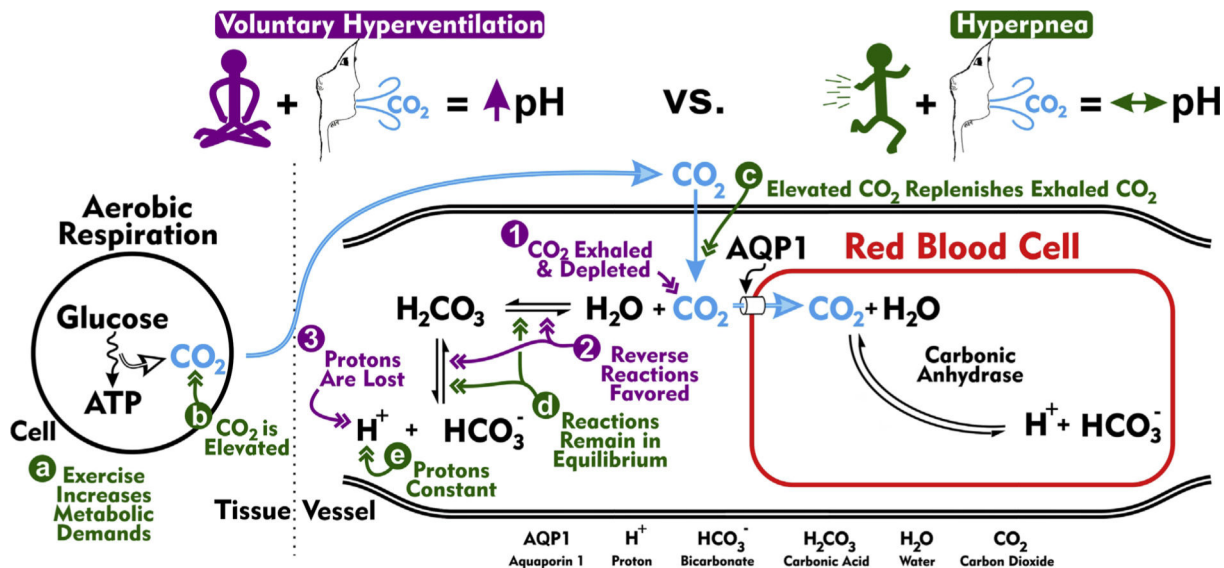


Fig. 2. Acid-base blood physiology during rapid breathing. The schematic depicts biochemical reactions largely responsible for establishing blood pH. On the left is shown a cell situated in the tissue undergoing aerobic respiration, the process of converting glucose into ATP. Carbon dioxide (CO₂) is produced during this conversion process. CO₂ then diffuses into capillary plasma, after which the bulk is primarily transported into erythrocytes (red blood cells) via aquaporin 1 (AQP1) channels (Endeward, 2006). Within the red blood cell, CO₂ associates with H₂O (water) to produce H⁺ (proton) and HCO₃⁻ (bicarbonate), a reaction catalyzed by carbonic anhydrase. Carbonic anhydrase is found in abundance in red blood cells, but not in the plasma. The dissociated proton acidifies the red blood cell and, in doing so, promotes the dissociation of hemoglobin and oxygen. A small portion of CO₂ entering the capillary remains in the plasma. As in the red blood cell, plasma CO₂ is also converted into H⁺ and HCO₃⁻, but this reaction is primarily *not* catalyzed by carbonic anhydrase [i.e. an *uncatalyzed* reaction (however, some carbonic anhydrase isoforms are localized to the extracellular surface of many cells (Boron, 2010; Svichar and Chesler, 2003), including red blood cells, and contribute to the catalyzed production of H⁺ and HCO₃⁻ from CO₂ and H₂O (Svichar and Chesler, 2003)]. The uncatalyzed reaction reversibly proceeds through H₂CO₃ (carbonic acid) and occurs at low basal rates. *Purple (1–3).* Acid-base physiology during voluntary hyperventilation. Voluntary hyperventilation is defined by excessive breathing (high rate and quantity) leading to the pronounced ventilation of CO₂ and ensuing respiratory alkalosis, a phenomenon in which blood plasma becomes alkaline. (1) Excessive ventilation reduces plasma concentrations of CO₂. (2) CO₂ depletion promotes the association of plasma H⁺ and HCO₃⁻ to replenish, via H₂CO₃, CO₂. (3) Favoring the reverse reactions reduces the concentration of plasma H⁺, thereby making the blood more alkaline. *Green (a–e).* Acid-base physiology during exercise-related hyperventilation (i.e. hyperpnea). (a) Unlike during voluntary hyperventilation, hyperpnea occurs during times of heightened metabolic demand. (b) Aerobic respiration associated with high metabolic demands produces high levels of CO₂. (c) Increased CO₂ production and subsequent diffusion into

capillaries balances the increased CO₂ exhalation. (d) The equilibria underlying CO₂-H₂O biochemical reactions remain unperturbed. (e) As these biochemical reactions remain in equilibrium, plasma protons are not lost and plasma pH is stable. Importantly, absence seizures are triggered by voluntary hyperventilation, but not hyperpnea.

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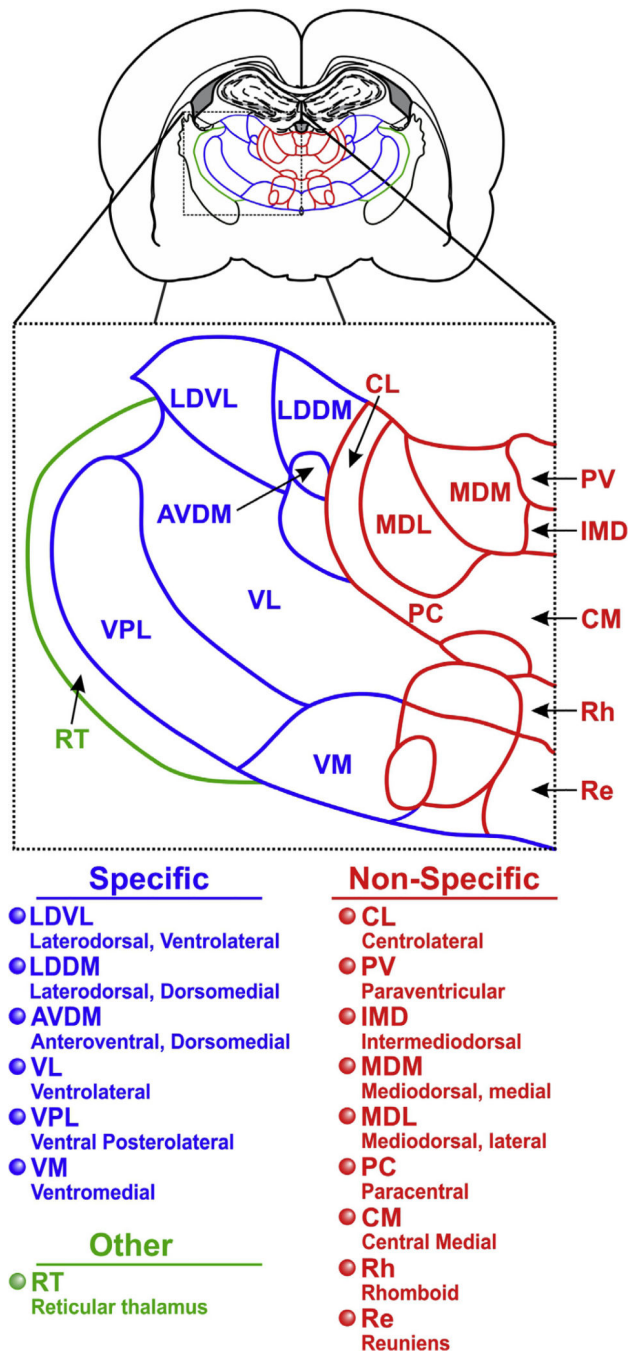


Fig. 3. Specific and non-specific nuclei of the thalamus. On top is shown a coronal section of a rat brain (Paxinos and Watson, 2007). An expanded view of nuclei from the thalamus on one side is shown directly below the full coronal section. Nuclei abbreviations are found below the expanded view. Structures outlined in blue represent the specific thalamic nuclei, whereas the structures outlined in red represent the non-specific nuclei. Collectively, specific and non-specific nuclei comprise the dorsal thalamus. The reticular nucleus (green), a member of the ventral thalamus, forms a thin, shell-like structure that surrounds the dorsal

thalamus. Nuclei along the midline are considered members of the Non-Specific Thalamic Projection System (NSTPS). The following structures are not labeled: submedial thalamic nucleus (dorsal and ventral), anteromedial thalamic nucleus, ventral reuniens, mammillothalamic tract.

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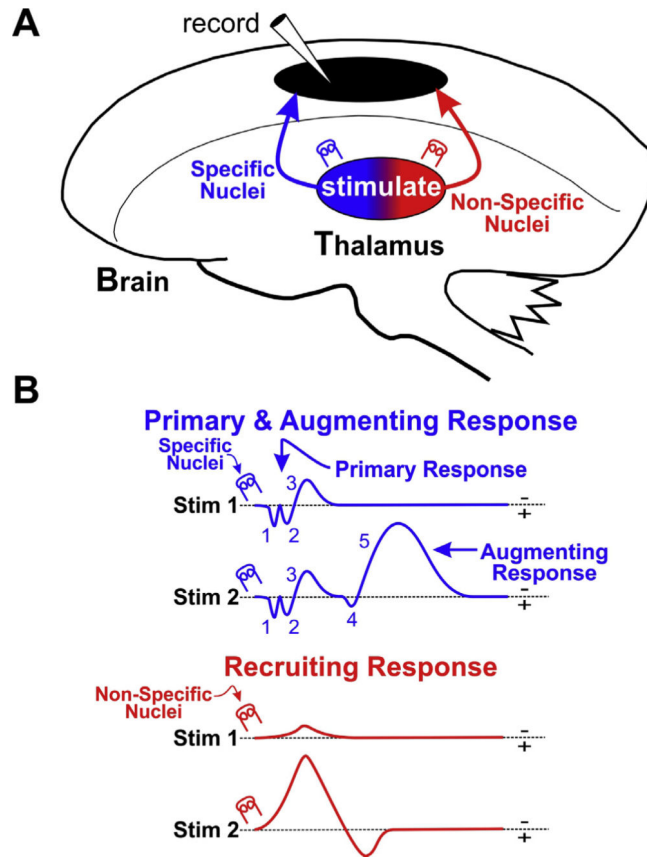


Fig. 4. Electrophysiological cortical response to electrical stimulation of specific versus non-specific thalamic nuclei. (A) Schematic representing experiment. Field responses are recorded in the cortex (e.g. anterior sigmoid gyrus, visual cortex). Electrical stimuli are delivered to either the lateral thalamic nuclei (blue), or the midline thalamic nuclei (red). (B) A single electrical stimulation of the lateral thalamic nuclei evokes events known as the primary and augmenting responses (top, blue). The primary response is collectively composed of two positive deflections (1 & 2), followed by a larger negative component. Repetitive lateral nuclei stimulation produces a secondary component known as the *augmenting* response. In contrast to lateral nuclei stimulation, a single electrical stimulation of the midline thalamic nuclei evokes a single, small, negative component (bottom, red). Successive midline stimuli yield a progressively larger event known as the *recruiting* response. Schematized responses are based on those described in *The Thalamus* (Jones, 2007).

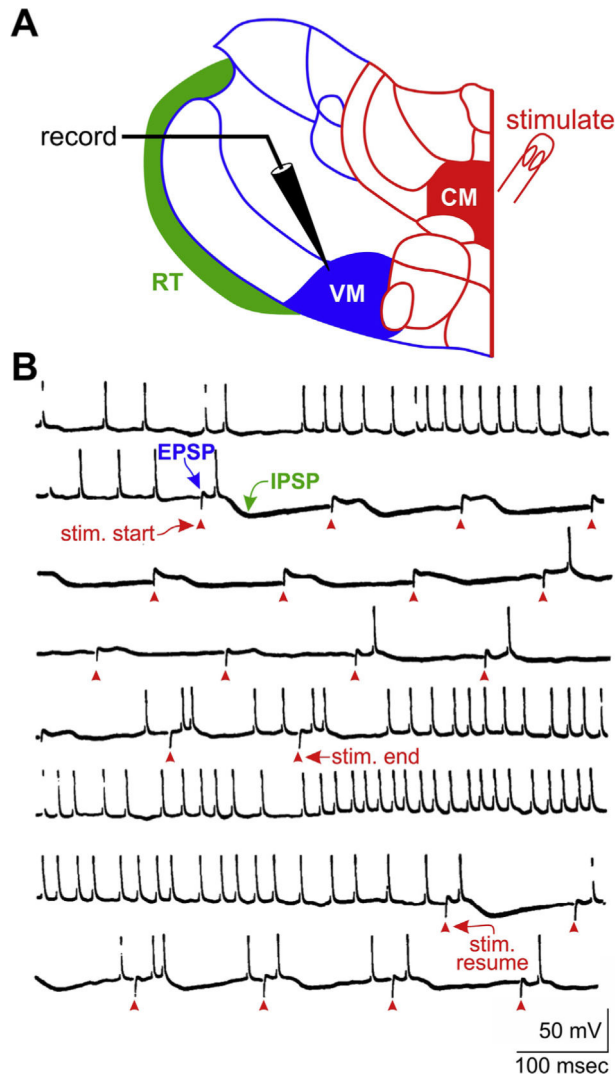


Fig. 5.

The central medial (i.e. non-specific) nucleus of the thalamus is functionally connected to specific and reticular thalamic nuclei. Shown are experimental results from Purpura and Cohen (Purpura and Cohen, 1962). (A) Experimental preparation. *In vivo* experiments were performed in the cat. The central medial (CM) nucleus was stimulated with an extracellular stimulating electrode. Responses to such stimulation were recorded in neurons of the ventromedial (VM) using intracellular recording pipettes. Thalamic structures that are likely involved in the VM neuron responses are filled in with red, blue or green. (B) An example, intracellular recording of a VM neuron. Each red arrowhead represents a single electrical stimulus delivered to CM. Prior to CM stimulation, action potentials are spontaneously generated by the VM neuron. The first electrical stimulus elicits a putative excitatory postsynaptic potential (EPSP, blue) with a short latency in the recorded neuron. The putative EPSP is followed by a longer latency inhibitory postsynaptic potential (IPSP, green). Purpura and Cohen speculated that rapid EPSP occurred as a result of direct, monosynaptic connectivity between CM and VM nuclei. The IPSP, in contrast, likely resulted from an indirect, disynaptic connection that initially involved excitation of GABAergic neurons of

the reticular thalamic (RT) nucleus, followed by RT-mediated inhibition of VM neurons. This EPSP-IPSP combination is observed to differing extents with subsequent CM stimulation. Following CM stimulation (i.e. stim. end) results in a phase of slow VM neuron depolarization. Resumption of CM stimulation again evokes the EPSP-IPSP combination.

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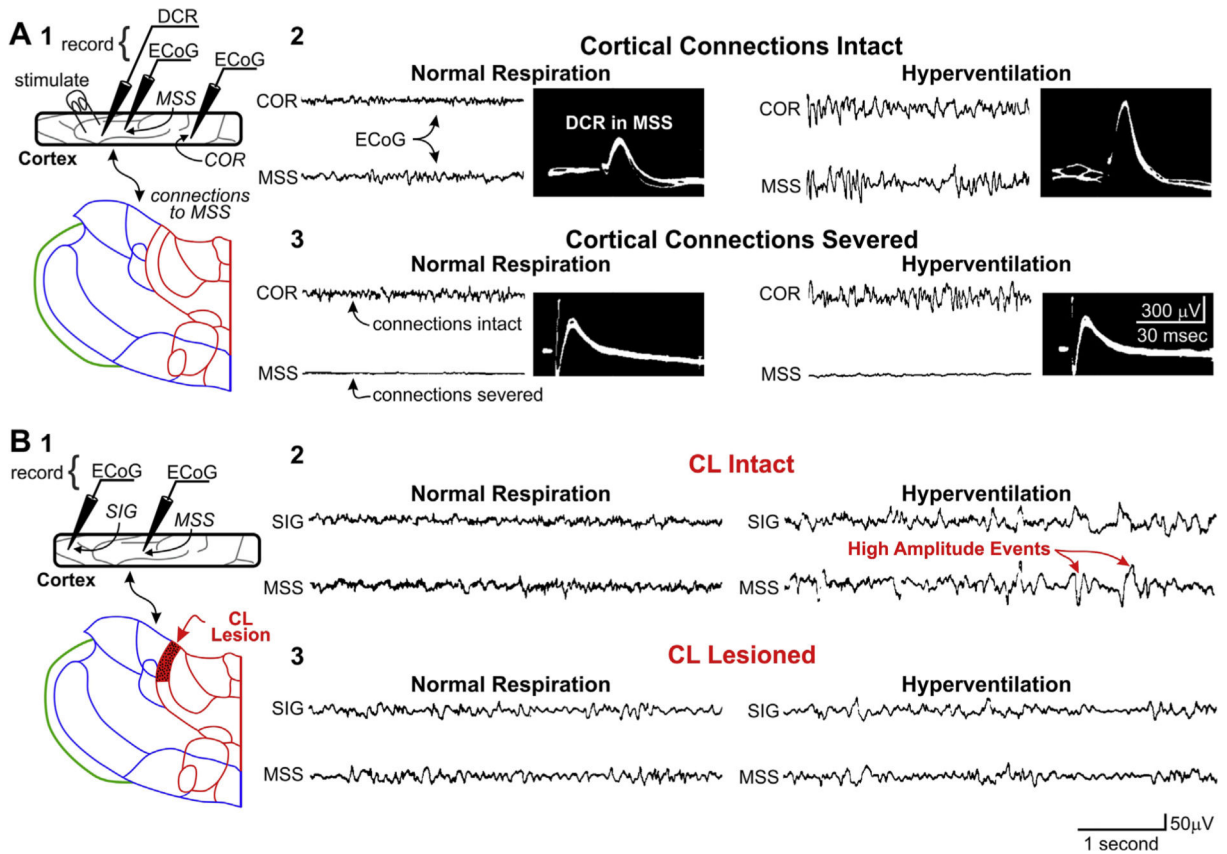


Fig. 6. Hyperventilation-induced, high-amplitude slowing of cortical activity depends on non-specific thalamic nuclei. Panels A and B represent experimental observations from two *in vivo* cat studies performed by Sherwin (1965, 1967). (A) In the first study, electrophysiological recordings were obtained from the cortex (1). Electrocorticogram (ECoG) recordings, similar to EEG recordings, were used to measure large-scale cortical activity in the mid-suprasylvian gyrus (MSS) and the coronal gyrus (COR). Local field recordings recorded in the MSS reveal the direct cortical response (DCR) evoked by a nearby electrical stimulating electrode. Importantly, the DCR is hypothesized to arise from direct activation of afferents that originate from the thalamus (Adrian, 1939; Chang, 1951; Burns, 1950). The experiment compared ECoG and DCR responses during hyperventilation before and after subcortical connections to the MSS were selectively severed. Cortical responses recorded before (2) and after (3) severing connections between the cortex and thalamus. With intact thalamus-cortex connectivity, normal respiration was associated with low-amplitude ECoG activity, as well as an evoked DCR of moderate amplitude. Hyperventilation produced high-amplitude, slow ECoG activity in both the MSS and COR. Also, the evoked DCR was larger. After severing thalamus-MSS connections, hyperventilation did not alter ECoG activity recorded in the MSS. Importantly, after severing connections, hyperventilation also did not augment the DCR. (B) In the second study, the effects of CL lesion on hyperventilation-induced, high amplitude ECoG signals were assessed (1). As in panel A, hyperventilation elicits ECoG signals that consist of high

amplitude events in the intact sigmoid gyrus (SIG) and MSS. (2). After CL lesion, these hyperventilation-induced events are not observed (3).

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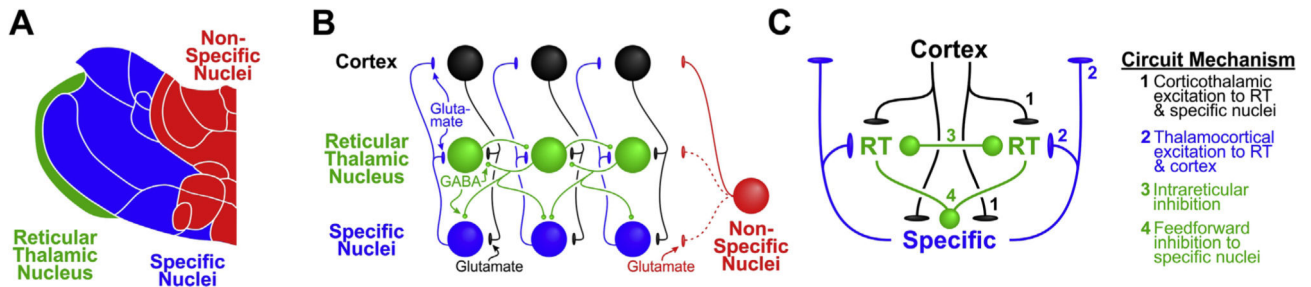


Fig. 7.

Rhythm generating circuits of the thalamus. (A) Schematic representation of thalamic nuclei likely involved in electrical oscillations produced by the thalamus. Several hypotheses propose that circuit rhythmicity can be achieved through interactions between the reticular thalamic (RT, green) nucleus and specific thalamic nuclei (blue). (B) Circuit diagram representing connections among cortical and RT neurons, as well as neurons of the lateral specific nuclei. Cortical neurons (black) provide direct, glutamatergic excitation to both RT neurons (green) and specific thalamic neurons (blue). Specific thalamic neurons provide direct, glutamatergic excitation to both RT and cortical neurons. RT neurons provide GABAergic inhibition to other RT neurons and neurons of the specific nuclei. Based on the conclusions of Purpura and Cohen (1962), neurons of the non-specific nuclei (red) putatively excite neurons of the specific nuclei and the cortex. As there is little anatomical evidence for this conclusion, we represent such connectivity with a red dashed line. There is limited evidence demonstrating that the non-specific nuclei project to the RT (red dash line). (C) Simplified representation of circuit dynamics shown in (B) to highlight nodes proposed to regulate SWD generation. Studies that have discovered these nodes have primarily focused on the specific nuclei. Therefore, the non-specific connections were omitted for simplicity. Elements highlighted in 1 & 2 represent excitatory, glutamatergic nodes. Intrareticular inhibition node (node 3) represents inhibition among RT neurons proposed to desynchronize thalamic circuit activity and limit seizure activity (Sohal et al., 2000). RT-mediated, feedforward inhibition (node 4) is proposed to promote burst firing and seizure-related activity patterns (Kim et al., 1997; Sanchez-Vives and McCormick, 1997).