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A brief history on the oscillating roles of thalamus and cortex in absence seizures

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Summary

This review summarizes the findings obtained over the past 70 years on the fundamental mechanisms underlying generalized spike-wave (SW) discharges associated with absence seizures. Thalamus and cerebral cortex are the brain areas that have attracted most of the attention from both clinical and experimental researchers. However, these studies have often favored either one or the other structure in playing a major role, thus leading to conflicting interpretations. Beginning with Jasper and Penfield's topistic view of absence seizures as the result of abnormal functions in the so-called *centrencephalon*, we witness the naissance of a broader concept that considered both thalamus and cortex as equal players in the process of SW discharge generation. Furthermore, we discuss how recent studies have identified fine changes in cortical and thalamic excitability that may account for the expression of absence seizures in naturally occurring genetic rodent models and knockout mice. The end of this fascinating tale is presumably far from being written. However, I can confidently conclude that in the unfolding of this "novel," we have discovered several molecular, cellular, and pharmacologic mechanisms that govern forebrain excitability, and thus consciousness, during the awake state and sleep.

Keywords

Absences; Cerebral cortex; Generalized spike and wave discharges; Thalamus

Prologue

Generalized, 3-Hz spike-wave (SW) discharges are the electroencephalographic concomitant of a fairly common form of generalized seizure, the absence attack of primary generalized epilepsy (which was also called petit mal epilepsy). These seizures are characterized by the most striking patterns in clinical electroencephalography (EEG), as no one looking at the record of such seizures, be they expert or novice, can fail to be impressed by the very sudden generalized onset of the discharge, its synchronization between the two hemispheres, and its

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sudden termination that occurs simultaneously in all brain regions (Fig. 1A). Furthermore, in contrast with what is observed after focal or generalized tonic–clonic seizures, there is no postictal depression of cerebral activity after the end of a generalized SW discharge.

Herein, I summarize more than seven decades of research aimed at establishing the fundamental mechanisms underlying generalized SW discharges in absence seizures. Since the beginning, thalamus and cerebral cortex have been the brain structures that have attracted most of the attention, but these studies have often led to conflicting interpretations (i.e., they set scenarios that were strongly favoring either one or the other of these brain structures in playing the major role). Indeed, this review is not aimed at covering the extensive literature that has appeared on the mechanisms that underlie absence seizures. Rather, its main goal is to discuss the long, fascinating tale that has evolved over the years around the concepts of abnormal thalamocortical function underlying SW discharges. Therefore, I apologize if some specific contributions, although of remarkable scientific relevance, were not included due to space limitation.

Absence Seizures at the Dawn of EEG and the Birth of the “Centrencephalic System”

Notions concerning generalized epilepsy with absence seizures go all the way back to the eighteenth century (Poupart, 1705 in Temkin, 1945; Tissot, 1783). However, the modern history of SW discharge electrophysiology started with the publication by Hans Berger (1933) of a single EEG record obtained from a patient during an absence attack. Although this sample showed a 3-Hz rhythm without “spikes” and it did not give any information on the generalized nature of the EEG pattern, the very rhythmic high voltage character of the discharge was evident. Of interest, Berger (1934) believed epileptic seizures to be caused by an abrupt withdrawal of tonic inhibitory influences exerted by the thalamus upon the cortex. His view, although not based upon factual data, prophetically focused on what later became a major topic of discussion: the role of the cortex and thalamus in the mechanism of generalized epilepsies. Two years later, Gibbs et al. (1935) gave for the first time a clear description of the EEG features of SW discharges associated with petit mal epilepsy.

Research on the mechanism of 3-Hz SW discharge was characterized since its inception by a conflict of views presumably reflecting a fundamental dichotomy in the conceptualization of cerebral function. Hughlings Jackson (Taylor, 1958) described these conflicting views as the attitude of the “universalizers” as opposed to that of the “localizers.” The basic proposition of the “universalizers” might be identified as holistic, since it considered any highly integrated activity of the central nervous system (e.g., consciousness, perception, or memory) as the expression of brain function as a whole (Goldstein, 1925; Lashley, 1929). The opposing view (i.e., that of the “localizers”) reflected a kind of Cartesian concept of cerebral organization, thus associating even highly complex brain functions with defined (“localized”) neuronal substrates (even though, at times, not too clearly defined anatomically). This dichotomy has dominated the discussion of the mechanisms underlying generalized 3-Hz SW discharges. As stated by Gloor (1978), Gibbs et al. (1937) expressed a

holistic view of generalized seizures and described these epileptic attacks as “paroxysmal cerebral dysrhythmia.”

In contrast to the beliefs of Gibbs, Wilder Penfield and Herbert Jasper proposed a localizing view of generalized seizures by putting forward the concepts of the “centrencephalic system” and of “centrencephalic seizures” (Penfield & Jasper, 1947, 1954; Penfield, 1952). Presumably, much of the rationale for this approach rested on Jasper’s interest in defining at that time the anatomic and functional organization of the thalamocortical system as an integrating unit subserving physiologic functions (Jasper, 1949) (Fig. 1B). In this context, the paper of Jasper and Droogleever-Fortuyn (1946) on the functional anatomy of petit mal epilepsy deserves particular attention; these investigators searched in this study for “the anatomic substratum” capable of producing upon stimulation electrographic phenomena similar to those seen in absence attacks. Indeed, they could obtain a widespread cortical response—the so-called recruiting response of Morison and Dempsey (1942)—by stimulating at low frequencies the midline and intralaminar nuclei of the thalamus. Moreover, by delivering stimuli in these thalamic areas at a frequency of 3 Hz, they were able to evoke in some of their animals 3-Hz generalized SW discharges (Fig. 1C). Therefore, they concluded that “a local disturbance in a small area of the thalamus may produce” a pattern similar to that “recorded from widespread areas of both hemispheres during a petit mal seizure” (Jasper & Droogleever-Fortuyn, 1946).

This model of human petit mal epilepsy was, however, not universally accepted, mainly because of a lack of consistency in its experimental reproduction. Only a few years later, Pollen et al. (1963) succeeded in defining one of the most important factors favoring the appearance of generalized SW discharges in this model, namely, the level of the animal’s alertness; they found that intralaminar thalamic stimulation did not produce SW discharges in deep barbiturate anesthesia but that it succeeded when anesthesia was progressively lightened, and especially when animals became readily aroused by sensory stimuli. It appeared, therefore, likely that the state of excitability of the midbrain reticular formation played a role in the elaboration of SW responses, thus suggesting that this structure had to be fitted into the concept of the mechanisms of absence seizures. In line with this view, it was shown that 3-Hz trains of high-frequency stimuli applied to the midbrain reticular formation of cats could induce bilateral cortical SW discharges that were similar to those seen in humans (Weir, 1964). It should be emphasized that the influence of anesthesia levels on the expression of SW discharges has later been confirmed in several models of absence seizures. In the meantime, Penfield and Jasper introduced a more diffusely organized centrencephalic system (Penfield, 1957).

The Fabulous 1960s and the “Cortical Invasion”

At this time in history, some studies challenged the centrencephalic hypothesis on experimental grounds. Marcus and Watson (1966, 1968) were in fact able to induce generalized SW discharges in the EEG by bilaterally applying convulsant drugs to the frontal cortex of cats or monkeys; this EEG activity was associated in awake animals with an absence-like attack. Furthermore, they discovered that the bilateral synchrony of SW discharges in this model was disrupted by a section of the corpus callosum, and that two

large homologous cortical areas (one in each hemisphere), when isolated from subcortical structures, but mutually interconnected through the corpus callosum, could generate generalized SW discharges after bilateral application of convulsants to the cortex. Therefore, these experiments provided strong evidence for the role of the cortex in the genesis of generalized SW discharges while demonstrating that brainstem and thalamus (in this model at least) were not a necessary prerequisite for their appearance.

Arguments in favor of a cortical origin of primary generalized epilepsy also originated from studies performed in Robert Naquet's laboratory in the Senegalese baboon *Papio papio*; this primate presents a natural, genetically transmitted epileptic predisposition characterized by generalized SW discharges in response to photic stimulation. By employing cortical and depth EEG recordings, Fischer-Williams et al. (1968) found in these animals that bilaterally synchronous SW discharges (as well as the subsequent generalized tonic–clonic seizures) first appear in the frontorolandic cortex and only later spread to other cortical and subcortical structures. Furthermore, by studying the cortical responses evoked by light stimulation, Menini et al. (1970) reported that the frontorolandic cortex in these photosensitive primates was strikingly hyperexcitable. Subsequent studies demonstrated that, as in the experiments of Marcus and Watson (1966, 1968), corpus callosum section caused the epileptic activity to lose its bilateral and synchronous feature (Naquet et al., 1972). Hence, a growing body of evidence for a cortical role in generalized SW discharges built up in the 1960s.

Gloor's Corticoreticular Hypothesis and the Feline Generalized Epilepsy Model

More than 40 years ago, Pierre Gloor (1968, 1969) proposed the term "generalized corticoreticular epilepsies" to group under one heading the patients presenting with seizures who exhibited generalized SW discharges in the EEG. These clinical entities included "centrencephalic epilepsy," but also generalized epileptic conditions associated with atypical slow SW discharges in patients with diffuse cerebral damage (as in the case of the "Lennox-Gastaut syndrome"). The term "corticoreticular" was considered to be more in keeping with what appeared to be an unavoidable conclusion, namely that both subcortical "reticular" (i.e., "centrencephalic") and cortical mechanisms were involved in the pathogenesis of generalized SW discharges. Specifically, Gloor (1969) proposed that "the bilaterally synchronous paroxysmal discharges of centrencephalic epilepsy represent an abnormal oscillation within a corticoreticular net of neurons, which may result from the breakdown of some normal negative feedback control, regulating cortical and subcortical interaction and mediated by the diffuse projection systems of reticular origin, as well as by corticoreticular pathways." It became imperative, at that time, to search for an experimental model on which this new concept could be tested.

The model selected was feline generalized penicillin epilepsy (FGPE), which had just been discovered by Prince and Farrell (1969) (Fig. 2A). Generalized SW discharges in this model: (1) develop following intramuscular injection of a large dose of penicillin, (2) are associated with a clear decrease of behavioral responsiveness similar to human absence attacks, and (3)

when recorded from chronically prepared cats, are reduced in occurrence by those drugs (i.e., valproate and ethosuximide) that are effective on epileptic patients presenting with absence epilepsy (see for review: Gloor et al., 1990; Kostopoulos, 2000). The corticoreticular hypothesis tested in the FGPE model rested on the assumption and subsequent demonstration that similar thalamocortical circuits should operate during both sleep spindles and SW discharges of absence epilepsy in the awake state. Of interest, Gloor's view can be recognized 40 years later in a review by Beenhakker and Huguenard (2009) entitled "Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy?" These authors, however, failed to acknowledge any of the studies performed in the FGPE model.

Experiments carried out in the FGPE model (see for review: Gloor et al., 1990; Kostopoulos, 2000) demonstrated that: (1) transient functional depression of thalamic activity by local microinjection of KCl transitorily abolishes both spindles and SW discharges; (2) surgical removal of the neocortex hampers the occurrence of SW activity in thalamus; (3) reduction of cortical excitability by spreading depression makes SW discharges in the intact cat brain be replaced in both thalamus and neocortex by spindles; (4) intracortical and callosal connections are fundamental for the spread and generalization of SW activity. Moreover, when SW discharges developed gradually from sleep spindles following systemic injection of penicillin, their frequency "jumped" from that of spindles to slightly above half suggesting that SW activity could result from enhanced neocortical responsiveness to thalamic inputs with subsequent activation of intracortical feedback inhibition that annulled one every two spindle waves. In line with this view, single unit extracellular recordings revealed that the *spike* of the SW complex is associated with a marked increase in firing probability in both neocortex and thalamus, whereas during the *wave* the firing probability is reduced virtually to zero (Fig. 2B). Moreover, intracellular recordings from cortical neurons demonstrated that SW discharges of FGPE were reflected by depolarizations/action potential discharges in association with the *spikes* and by Cl^- mediated hyperpolarizations during the *waves* (Fisher & Prince, 1977; Giaretta et al., 1987). Overall, these findings indicated that the functional and anatomic integrity of both thalamus and cortex is required for generalized SW discharges to occur, and, even more specifically, that the activity of thalamic networks represents a sine qua non mechanism for SW discharge rhythmogenesis, whereas cortical hyperexcitability is the prerequisite for their generation.

Genetic Rodent Models and the Thalamus Resurgence in the 1980s and 1990s

Primary (idiopathic) generalized epilepsies are characterized by a major genetic component (Lennox & Lennox, 1960), although linkage studies have so far failed to reveal replicable susceptibility loci. Therefore, there was enormous interest in the scientific epilepsy community when genetic animal models of absence seizures were discovered in the mid-1980s. In particular, two rat models, although not yet defined in terms of their genetic background, have been used to understand the pathophysiology of absence attacks: the genetic absence epilepsy in rats from Strasbourg (GAERS) (Vergnes et al., 1982) and the Wistar Albino Glaxo/Rijswijk (WAG/Rij) (van Luijtelaar & Coenen, 1986). Both strains

present with generalized SW discharges that have pharmacologic profiles (e.g., responsiveness to ethosuximide) closely approximating absence seizures in humans. Early work carried out in these two models confirmed many of the data obtained from cats injected with penicillin, including the presence of rhythmic activity in synaptically connected regions of the thalamus and neocortex during SW discharges and the ability of cortical spreading depression to abolish SW discharges in both thalamus and neocortex. These studies—which have been reviewed by Danober et al. (1998) and by Peeters et al. (1990)—also showed that basal ganglia can modulate SW discharges in both genetic models. Findings obtained in subsequent studies are discussed below as the thalamus-cortex tale unveils.

At around the same time, the discovery in thalamic neurons of the low threshold (T-type) Ca^{2+} current (Deschenes et al., 1984; Jahnsen & Llinás, 1984a; Jahnsen & Llinas, 1984b) made basic research on absence seizures shift, once more, from the cortex to thalamus. This current, which is de-inactivated at a membrane potential more negative than rest, causes action potential bursts once the membrane potential goes to less polarized values, also thanks to the contribution of a hyperpolarization-activated cation current (I_h; McCormick & Pape, 1990) (Fig. 3A). As shown in Fig. 3B, thalamocorticothalamic circuits are organized in such a way that thalamic γ-aminobutyric acid (GABA)ergic neurons (mainly located in the reticular nucleus) are excited by inputs coming from the cortex and from thalamocortical relay cells. As a result, thalamocortical relay cells generate $GABA_A$- and $GABA_B$- mediated hyperpolarizing inhibitory postsynaptic potentials (IPSPs) that deinactivate the T-type Ca^{2+} current, thereby producing action potential bursts once the membrane is set to less-polarized values. These action potential bursts, in turn, will excite neurons in both cortex and reticular nucleus, thus starting another cycle of the oscillation (Fig. 3C) leading to rhythmic oscillatory activity as seen with sleep spindles (Steriade et al., 1993). Reticular thalamic cells are also endowed with the T-type Ca^{2+} current, whereas a noninactivating Na^+ current component in thalamocortical relay cells acts synergistically with the T-type Ca^{2+} current in burst generation (Parri & Crunelli, 1998). Hence, thalamic nuclei are endowed with mechanisms that can provide the rhythmogenesis peculiar of sleep spindles and, perhaps, of SW discharges in absence epilepsy; this aspect was analyzed in detail by Avanzini et al. (1993) in GAERS.

Studies published in the 1990s have indeed demonstrated that altered thalamic function is present in the genetic rodent models of absence seizures. Accordingly, enhanced T-type Ca^{2+} current was identified in isolated reticular nucleus neurons obtained from GAERS (Tsakiridou et al., 1995). In addition, microinjection of $GABA_B$-receptor antagonists into the thalamic relay nuclei of these rats could abolish SW discharges, presumably by removing the hyperpolarizing drive provided by the “type B” slow component of the IPSP that may be required for deinactivating the T-type Ca^{2+} current (Liu et al., 1992). Similar findings were also reported in lethargic mice; these animals represent another genetic model of primary generalized epilepsies (Hosford et al., 1992; Hosford et al., 1995). Around this time, experiments performed in brain slices of the ferret visual thalamus demonstrated that spindle waves—which in this preparation are generated by the interaction between perigeniculate (inhibitory) neurons and relay neurons—were changed by the $GABA_A$-receptor antagonist bicuculline into slow paroxysmal discharges with intense action potential bursting that were critically dependent upon $GABA_B$ receptors for their generation (Bal et al., 1995a,b) (Fig.

3D). This last point was further supported by experiments in which behavioral and EEG alterations similar to those seen during absence attacks were observed following injection of γ-hydroxybutyrate, a drug that activates $GABA_B$ receptors (Williams et al., 1995; Snead, 1996; Gervasi et al., 2003). In addition, Huntsman et al. (1999) reported that the oscillatory synchrony of thalamocortical relay cells is increased dramatically when the $GABA_A$ receptor β3 subunit is deleted; this subunit is restricted mainly to the thalamic reticular nucleus in rodents, and thus its deletion causes a selective reduction of inhibition in reticular nucleus, increasing its output activity and, in turn, producing in thalamocortical relay cell–enhanced hyperpolarizing IPSPs that deinactivate larger T-type Ca^{2+} current and cause robust action potential bursts.

The data summarized above did further highlight the intrinsic ability of the thalamus to produce oscillations along with the contrasting roles played by $GABA_A$ and $GABA_B$ receptor–mediated inhibition in determining the dominant frequency of these network oscillations. The importance of thalamus in absence seizure generation was further strengthened by the discovery in David Prince's laboratory that antiabsence drugs, such as ethosuximide, reduce T-type Ca^{2+} currents in both thalamocortical relay cells and GABAergic neurons of the reticular nucleus (Coulter et al., 1989, 1990). A few years later, Leresche et al. (1998) confirmed that ethosuximide reduces bursting in thalamocortical relay cells while increasing their tonic firing; however, the mechanism of action identified in this study appeared to rest mainly on the ability of ethosuximide to decrease a noninactivating Na^+ current.

The New Millennium and the Comeback of Cortical Networks in SW Discharges

While the case for a prominent role of the thalamus in the pathophysiogenesis of absence seizures was being built, the studies of Mircea Steriade and coworkers (see for review Timofeev & Steriade, 2004) drew, once more, the attention of epileptologists toward the cortex. By employing a feline model that approximates the EEG pattern seen in patients with Lennox-Gastaut syndrome, these experiments demonstrated that cortical SW complexes at approximately 3 Hz correspond in reticular nucleus neurons to bursts of action potentials that follow each cortical *spike* and, in turn, cause IPSPs in thalamocortical relay cells (Steriade & Contreras, 1995). Successive studies in bicuculline-treated cats confirmed that similar electrographic seizures reflected a local cortical phenomenon that was not influenced by removing the thalamus (see for review Timofeev & Steriade, 2004). It was, therefore, proposed that in this animal model of Lennox-Gastaut syndrome, the cortex represents the minimal substrate for seizure generation. Surprisingly, these experiments also indicated that the majority of thalamocortical relay cells generated steady hyperpolarization along with phasic IPSPs during seizure activity (Fig. 4A). Intracellular recordings obtained around the same time from thalamocortical cells in the GAERS model showed similar patterns of activity during generalized SW discharges, that is, tonic hyperpolarization occurring throughout the SW sequence along with rhythmic IPSPs (Pinault et al., 1998), whereas a subsequent study showed that interneurons in GAERS reticular nucleus participate actively to SW discharges (Slaght et al., 2002).

At the beginning of the new millennium, two studies also established that an increase in cortical excitability can influence both the frequency and the amount of synchronization of thalamic network oscillations (Bal et al., 2000; Blumenfeld & McCormick, 2000). In these experiments—which were performed in the ferret visual thalamus in an in vitro brain slice preparation—cortical inputs were mimicked by electrically stimulating corticothalamic fibers each time thalamic relay cells became active. Both groups of investigators found that weak corticothalamic stimuli phaselocked the spontaneous spindle oscillations, whereas strong stimuli caused more synchronized, slower oscillations that depended on $GABA_B$ receptor–mediated signaling. Hence, corticothalamic input strength can influence rhythmogenesis in the thalamus and transform a spindle-like rhythm into that of an SW discharge.

However, the most compelling evidence for the primary role played by cortical networks in absence seizures came from experiments in which nonlinear association analysis was applied to EEG signals that were recorded simultaneously from multiple cortical and thalamic structures during SW discharges generated by freely moving WAG/Rij rats (Meeren et al., 2002). This analytic approach revealed a consistent cortical site of initiation within the perioral region of the somatosensory cortex, whereas SW discharges recorded at other cortical sites lagged with time delays that increased as a function of the electrode distance. In addition, these experiments demonstrated that cortical and thalamic sites interacted bidirectionally, but during the first 500 msec of SW discharge the cortical initiation site consistently led the thalamus (Fig. 4B). Shortly thereafter, Manning et al. (2004) draw similar conclusions by testing the ability of local application of the antiabsence drug ethosuximide to different somatosensory and motor cortical areas of freely moving GAERS. In addition, in this genetic model of generalized SW discharges, the perioral area was the site of application most effective in abolishing absence seizures. More recently, in vivo intracellular recordings have shown that SW discharges in GAERS are initiated in layer 5/6 neurons of the facial somatosensory cortex (Polack et al., 2007). Therefore, absence seizures in these two genetic rodent models have a clear cortical, and indeed localized, origin. Historically, a “focal” cortical theory in the genesis of absence seizures in humans dates back to the stereotaxic recordings performed by Bancaud in patients with epilepsy (Bancaud et al., 1974). These studies demonstrated that absence seizures associated with bilaterally synchronous generalized SW discharges can be produced by mesial frontal stimulation. This was indeed not really a new observation, since Penfield and Jasper (1954) had already shown that mesial frontal foci could mimic some electrographic and clinical features of generalized epilepsy.

Back to the Future

Because history (along with scientific research) often goes in circles, we are presumably living now a new “thalamic cycle” in the tale of absence epilepsy pathophysiology. Accordingly, Bessaïh et al. (2006) reported that miniature $GABA_A$ receptor–mediated IPSCs in GAERS reticular nucleus neurons have larger amplitude and faster decay, and are less sensitive to the $GABA_B$-receptor agonist baclofen when compared to age-matched nonepileptic controls. These differences were not present in cortical and thalamocortical relay cells, indicating that subtle, nucleus-specific, abnormalities in $GABA_A$-receptor

function occur in this genetic model of absence seizures. Changes in reticular nucleus excitability may also result from dysfunction of glutamatergic transmission, in particular of the ionotropic (2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid) (AMPA) receptor. Beyer et al. (2008) have found that inbred mice prone to absence seizures present with a mutation in the gene encoding Gria4, a subunit that is highly expressed by reticular nucleus cells and that confers rapid decay kinetics to AMPA receptor–activated currents. In addition, when the Gria4 gene is knocked out, mutant mice have frequent SW discharges along with more prolonged EPSCs in reticular nucleus cells, suggesting that enhanced excitation in these GABAergic neurons may play a role in SW-discharge generation.

These data, however, contrast with those obtained by Menuz and Nicoll (2008) in another genetic model of absence epilepsy, namely the stargazer mouse (Noebels et al., 1990). AMPA receptor–mediated EPSCs generated by stargazer reticular nucleus neurons are, in fact, smaller and less frequent than in wild type mice. According to these authors, a decrease in nucleus reticularis excitability should cause thalamocortical network disinhibition and thus promote SW discharge (Menuz & Nicoll, 2008). The role of changes in thalamic excitability has also been highlighted in a more recent study in which $GABA_A$ receptor–dependent tonic inhibition (i.e., an “always on” current due to activation of extrasynaptic $GABA_A$ receptors by ambient GABA Cope et al., 2005) was analyzed in several genetic (i.e., GAERS as well as stargazer, lethargic, and tottering mice) and pharmacological (i.e., γ-hydroxybutyrate or THIP) models of absence seizures (Cope et al., 2009). These experiments have shown that tonic inhibition is augmented in thalamocortical relay cells in many of these genetic models and that this increase results from compromised GABA uptake by the GABA transporter GAT-1. In addition, SW discharges (and their behavioral correlates) in normal animals treated with either γ-hydroxybutyrate or THIP are characterized by selective activation of extrasynaptic $GABA_A$ receptors. Therefore, these data suggest that tonic inhibition upregulation in thalamus represents a common feature of absence seizures, a finding that may be relevant for developing novel therapeutic approaches.

Conclusive Remarks

Going through the fascinating tale of the scientific work done on the pathophysiology of absence seizures unveils mechanisms of neuronal function that go beyond the title of this review (i.e., the roles of thalamus and cortex in the generation of SW discharges). Indeed, although the core of the debate has rested traditionally on the contribution of these two forebrain structures, most of the recent findings indicate that even when focusing on a specific network (e.g., the thalamus), different cellular (as well as pharmacologic or molecular) dysfunctions can lead to similar abnormal brain rhythms and concomitant behavioral deficits. Therefore, in this context, generalized SW discharges should be considered as a pathologic phenomenon arising from the malfunction of any of several specific voltage- or ligand-gated mechanism in the thalamocorticothalamic network. It should also be remarked that the thalamic activity recorded from depth electrodes in patients with absence epilepsy is oscillatory and phase-locked with the SW activity seen in the scalp EEG (Williams, 1953). This study, besides the inherent value of being undertaken in humans, anticipated much of the evidence obtained in the cat penicillin model and in rat

genetic models 30 years later, and suggested that both thalamic and cortical networks are involved in the expression of absence seizures. A similar conclusion has recently been reached by analyzing SW discharges in patients who present with idiopathic generalized epilepsies by employing combined EEG-functional magnetic resonance imaging (fMRI) tools (Tyvaert et al., 2009; Moeller et al., 2010). However, at the end of this historical paper, one may wonder whether thalamus and cortex have not attracted too much attention as players in SW-discharge generation. Remarkably, recent experiments performed in patients with primary generalized epilepsy by employing fMRI-EEG recordings indicate that brain areas such as the insula or cerebellum are implicated as well in generalized SW discharges. In addition, these studies have revealed that the *default mode network* involved in monitoring the external world may be deactivated and therefore responsible for the impaired consciousness seen in these patients during SW discharges (Gotman et al., 2005; Hamandi et al., 2006).

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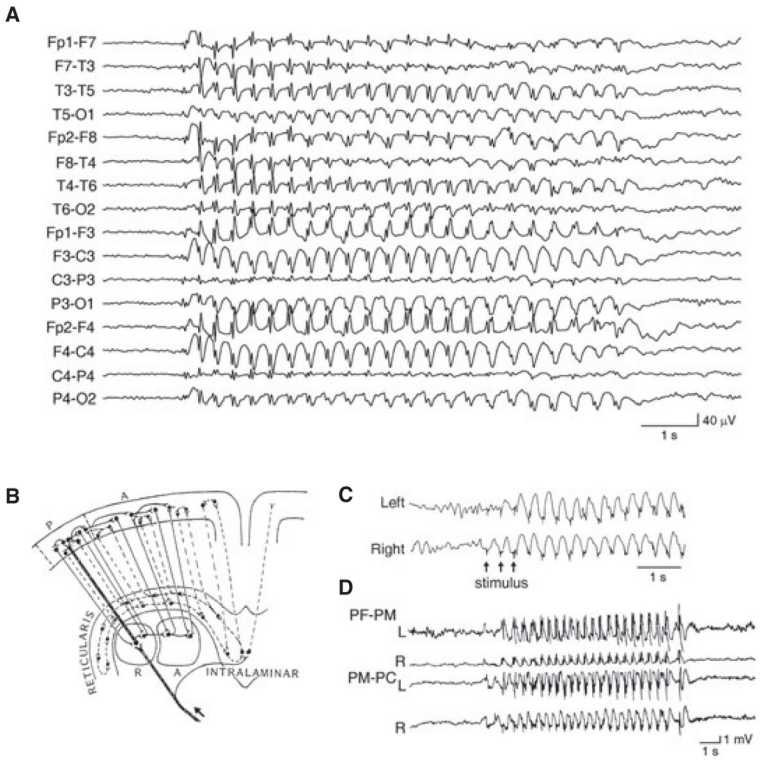

Figure 1.

(**A**) Generalized 3-Hz SW discharges recorded from a 10-year-old boy with childhood absence epilepsy. Note the generalized onset of the discharge, its synchronization between the two hemispheres, and its sudden termination that occurs simultaneously in all brain regions. EEG recording kindly provided by Drs. Francesca Pittau, Jean Gotman, and Francois Dubeau at the Montreal Neurological Institute & Hospital. (**B**) Drawing of the hypothetical organization of the thalamocortical systems showing the direct specific relay system (R), the specific association system (A), as well as the superimposed polineuronal thalamic reticular system. Modified from Jasper (1949). (**C**) Bilaterally synchronous SW pattern produced in the cat cortex by 3-Hz stimulation of the thalamic massa intermedia. Modified from EEG recordings as in Jasper and Droogleever-Fortuyn (1946). (**D**) Generalized SW discharges induced by bilateral application of cobalt to the frontal areas of a rhesus monkey; these seizures were associated with absences and, at times, with single myoclonic jerks. Bipolar EEG recordings were obtained from the prefrontal (PF), premotor (PM), and precentral regions. Modified from EEG recordings as in Marcus and Watson (1968).

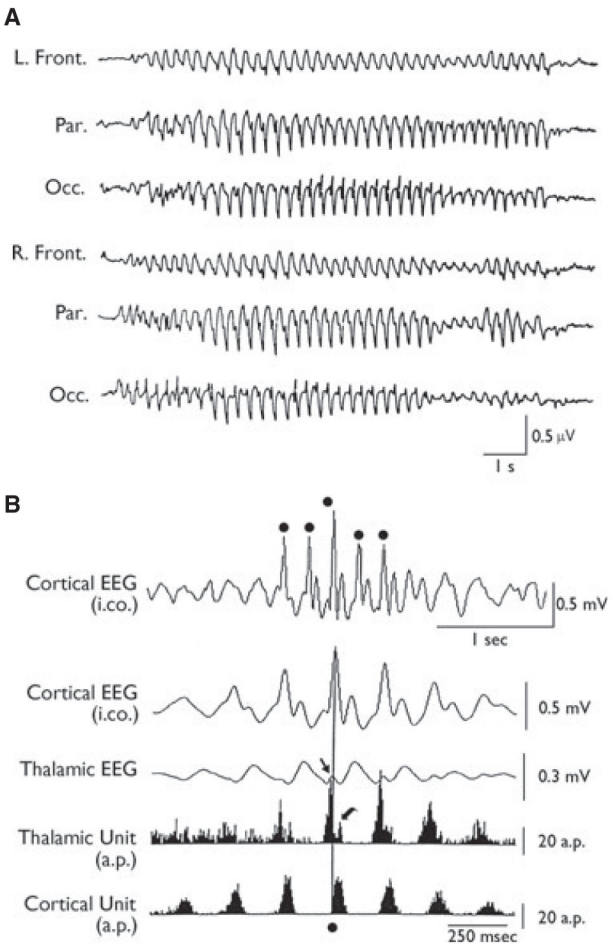

Figure 2.

(**A**) Generalized SW discharges recorded in a cat following intramuscular injection of a large dose of penicillin. Note the EEG similarities (but for the higher frequency) between cat and human recordings as shown in Fig. 1A. (**B**) EEG averages and single-unit perievent histograms triggered by the negative peaks of the *spikes* of SW discharges induced by penicillin injection and recorded intracortically (dots in the upper trace). The cortical unit was recorded in the middle suprasylvian gyrus, whereas the thalamic unit was recorded simultaneously from the nucleus lateralis posterior/pulvinar complex. Note the late involvement of the thalamic unit in SW firing as well as the two peaks of firing probability, one (straight arrow) preceding, and the other (curved arrow) coinciding, with the cortical peak of firing probability. The thalamic unit recorded in this experiment was orthodromically activated by electrical stimuli delivered in the cortex middle suprasylvian gyrus (not illustrated).

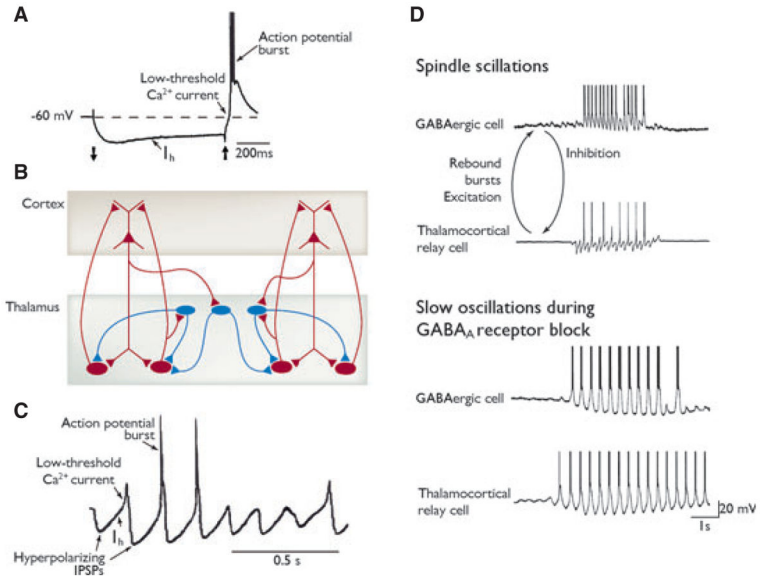

Figure 3.

(**A**) Drawing of an intracellular signal recorded from a thalamocortical relay neuron that was hyperpolarized with injection of a square pulse of negative current (arrows point at the onset and termination of the hyperpolarizing command). Note the “sag” of the membrane that leads over time to less polarized values as well as the burst of action potentials generated upon termination of the pulse. These two phenomena are known to be caused by I_h and by T-type Ca^{2+} current, respectively. (**B**) Schematic diagram of the thalamocortical loop. Glutamatergic cortical and thalamocortical relay cells are shown in red, whereas reticular nucleus GABAergic interneurons are colored in blue. (**C**) Drawing of the intracellular activity generated by a thalamocortical relay neuron during a “sleep” spindle. Each cycle of the spindle begins with a hyperpolarizing IPSP that deinactivates the T-type Ca^{2+} current and causes a progressive activation of I_h. As the membrane becomes less polarized a low threshold Ca^{2+} spike, which can cause action potential bursting, is generated; these action potentials will excite reticular nucleus GABAergic cells which, in turn, will cause a hyperpolarizing IPSP in thalamocortical relay cells thus starting another spindle cycle. (**D**) Intracellular, spindle oscillations recorded in vitro from a perigeniculate (GABAergic) and geniculate (relay) neuron under control conditions and during blockade of $GABA_A$ receptors (bicuculline) (Modified from Bal et al., 1995a).

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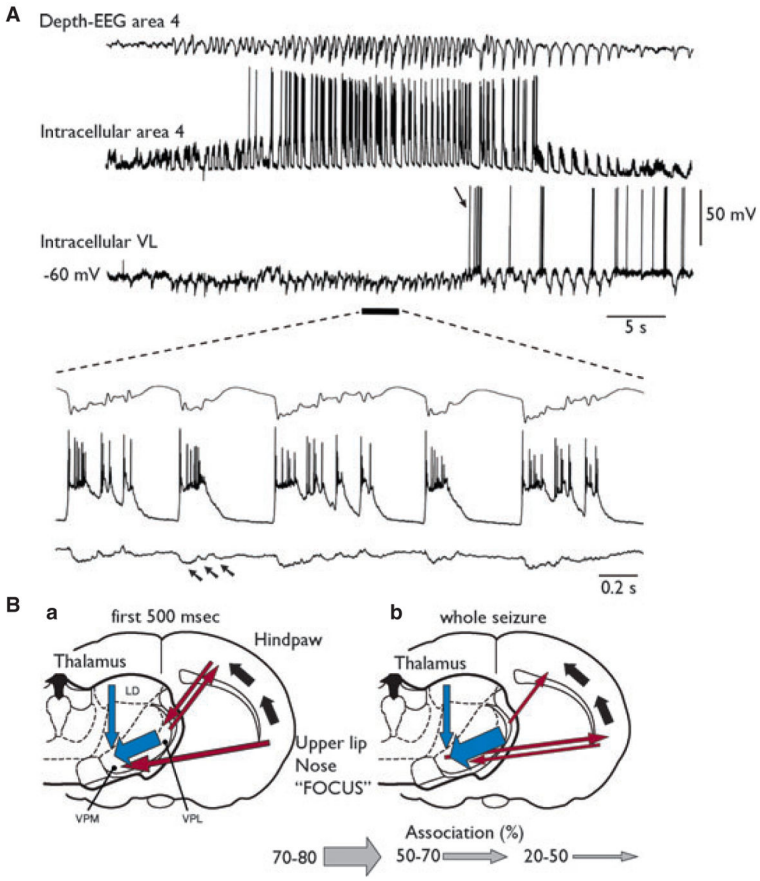

Figure 4.

(**A**) SW discharge recorded intracortically (depth-EEG area 4) and simultaneously with dual intracellular recordings from a cortical (Intracellular area 4) and a thalamocortical (intracellular VL) neuron in a cat under ketamine–xylazine anesthesia. The portion indicated by the thick line is expanded below. Note the progressive steady depolarization and concomitant action potential bursting in the cortical neuron while phasic IPSPs (arrows) occur in the thalamocortical cell in phase with the cortical excitatory events. Note, also, that the brief period of quiescence in cortical discharge coincides with action potential firing in the thalamocortical cell (arrow) (modified from unpublished data by M. Steriade and D. Contreras). (**B**) Simplified diagrammatic summary of the results obtained by Meeren et al. (2002) by employing nonlinear association analysis of the EEG signals recorded simultaneously from multiple cortical and thalamic structures during spontaneous SW discharges in WAG/Rij rats. Corticocortical (black arrows), intrathalamic (blue arrows), and thalamocorticothalamic (red arrows) interdependencies are shown during the first 500 msec of the SW discharge (**a**) and for the entire duration of the SW discharge (**b**). The thickness of the arrow represents the average strength of the association, and the direction of the arrowhead points to the direction of the lagging site. Note that SW discharge initiates in the upper lip/nose area of the somatosensory cortex and then propagates to other cortical regions and to thalamus, mainly to its laterodorsal nucleus. When the entire seizure is analyzed as one epoch, the same cortical initiation site (“focus”) as during the first 500 msec is found

consistently but, compared with the first 500 msec, the strength of association between ventroposterior lateral (VPL) and ventroposterior medial (VPM) nuclei has increased, and the direction of the thalamocorticothalamic couplings has changed.