ΣΧΟΛΗ ΚΟΙΝΩΝΙΚΩΝ, ΑΝΘΡΩΠΙΣΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ ΚΑΙ ΤΕΧΝΩΝ

ΤΜΗΜΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΚΑΙ ΚΟΙΝΩΝΙΚΗΣ ΠΟΛΙΤΙΚΗΣ

ΠΜΣ «ΝΕΥΡΟΕΠΙΣΤΗΜΗ ΤΗΣ ΕΚΠΑΙΔΕΥΣΗΣ»

Διπλωματική Εργασία

Η ΑΛΛΟΙΩΣΗ ΤΗΣ ΠΑΓΙΩΣΗΣ ΤΗΣ ΜΝΗΜΗΣ ΚΑΤΑ ΤΟΝ ΥΠΝΟ ΕΠΙΒΑΡΥΝΕΙ ΤΗΝ ΝΕΥΡΟΓΝΩΣΤΙΚΗ ΣΥΝΟΣΗΡΟΤΗΤΑ ΣΤΗΝ ΡΟΛΑΝΔΕΙΟ ΕΠΙΛΗΨΙΑ

ALTERED SLEEP-RELATED MEMORY CONSOLIDATION CONTRIBUTES TO NEUROCOGNITIVE COMORBIDITY IN BENIGN EPILEPSY WITH CENTROTEMPORAL SPIKES

της

ΒΙΚΤΩΡΙΑΣ ΓΕΩΡΓΟΠΟΥΛΟΥ

Επιβλέπουσα καθηγήτρια

Μαίρη Κοσμίδου

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Abstract

Our aim in this essay is to expand the concepts and the research designs used to explore neurocognitive comorbidity in benign epilepsy with centrotemporal spikes (BECTS). We review the latest data from the fields of neuroplasticity, sleep-related memory consolidation, epilepsy, and neurocognitive comorbidity in BECTS. We argue that the field needs to move beyond the assessment of daytime neurocognitive functioning and the over-reliance on seizure data. We suggest two additional foci: a) the interictal presentation of children with BECTS, and data on interictal epileptiform spikes (IES) in particular, and b) sleep-related memory consolidation (S-RMC).

IES interfere with S-RMC in two distinct ways. First, they alter the spatiotemporal coupling of the three cardinal oscillations involved. Second, IES undergo sleep-related consolidation processes utilizing mechanisms that were considered to be "reserved" for adaptive material of high relevance to the organism. Together, the two aforementioned processes adversely affect particular brain networks and eventually present as daytime neurocognitive comorbidity. Links have been made between functional differentiations in specific neuronal networks and BECTS neurocognitive deficits. For instance, alterations in frontal lobe connectivity affect attention and higher cognitive skills. Moreover, alterations in functional connectivity of the right inferior temporal cortex and the bilateral primary auditory cortex contribute to language processing difficulties. Finally, alterations in the perisylvian network are expected to adversely impact communication skills.

Reducing the frequency of IES, might potentially reduce the disturbance of the S-RMC, hence improving the child's neurocognitive presentation. This is a new prevention and treatment locum in BECTS. Another novel therapeutic target could be preventing the sleep-related consolidation of IES. Key findings of the impact of altered S-RMC on neurocognitive comorbidity in BECTS need to be channeled to front-line practitioners, along with efforts for better controlling excessive epileptiform activity during sleep. In this fast developing field, there is an urgent need to develop novel multidisciplinary methodologies so that each discipline can benefit from the progress made in any of the others.

Key words: neuroplasticity, pediatric epilepsy, NREM sleep, active system consolidation, oscillations.

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Dedicated to my parents

who have always encouraged and supported my studies

Contents

Introduction

Benign epilepsy with centrotemporal spikes (BECTS) belongs to a common group of idiopathic focal childhood epilepsies, often of genetic origin (Miano & Datta, 2019). It is conceptualized as an age-related neurodevelopmental dysfunction of a self-remitting nature (Miano & Datta, 2019). Traditionally, BECTS was thought to be free of structural abnormalities and this is still reflected in some of the diagnostic practices (Pavlou, Gkampeta, Evangeliou, & Athanasiadou-Piperopoulou, 2012). However, evidence of subtle functional and structural abnormalities in BECTS has been mounting (Dryżałowski, Jóźwiak, Franckiewicz, & Strzelecka, 2018; Pardoe, Berg, Archer, Fulbright, & Jackson, 2013). The onset of BECTS is between early childhood and middle adolescence. The incidence of the disorder is between 10-20: 100,000 in children between the ages of 3 and 15 (Parakh & Katewa, 2015; Smith, Bajomo, & Pal, 2016) and its prevalence is approximately 15% in children with epilepsy between the ages of 1 and 15 (Parakh & Katewa, 2015). In BECTS, the epileptogenic zone often includes the lower area of the precentral and postcentral gyri (see Figure 1) (Eom et al., 2017). This fact helps explain, at least partially, the presence of pathological autonomic responses that engage the aforementioned brain areas (Dryżałowski et al., 2018). Autonomic responses, when present, imply the involvement of Rei's insula, a brain structure critical for eliciting and mediating them.

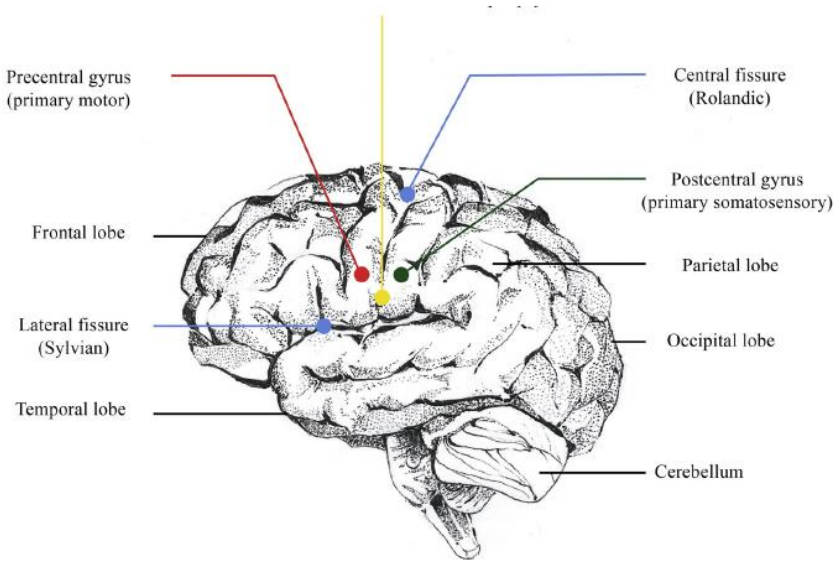

Figure 1. In BECTS the epileptogenic zone often includes the lower area of the precentral and postcentral gyri. Adapted from "Benign Epilepsy with Centrotemporal Spikes-Current Concepts of Diagnosis and Treatment," by P. Dryzalowski, S. Jozwiak, M. Franckiewicz, and J. Strzelecka, 2018, *Neurologia i Neurochirurgia Polska, 52,* p. 678. Copyright 2018 by the Polish Neurological Society.

Centrotemporal spikes are a key feature of BECTS and are documented through sleep-EEG during NREM sleep (Pavlou et al., 2012). Of note, such spikes are also present in a percentage of healthy children (Grant, Chau, Arya, & Schneider, 2016; Okubo et al., 1994), in children with attention deficit hyperactivity disorder (ADHD) (Kartal, Aksoy, & Deda, 2017; Lee, Choi, Yoon, & Bahn, 2016), and in children with autism spectrum disorder (ASD) (Capal et al., 2018; Nicotera et al., 2019). Although there appears to be a strong association between genetics and BECTS manifestation (Gkampeta & Pavlou, 2012), current data demonstrate genomic heterogeneity and phenotypic pleiotropism (Dryżałowski et al., 2018).

BECTS was initially considered benign mainly due to its self-remitting nature, the sparsity of seizures and its quasi-optimal response to pharmacological treatment (Datta & Sinclair, 2007; Pavlou et al., 2012). Yet, in recent decades, the detrimental role of neurocognitive comorbidity in BECTS has been firmly acknowledged (Smith et al., 2016). In a considerable proportion of children and adolescents, EEG abnormalities and neurocognitive deficits persist, even when epilepsy is in remission, hence negatively impacting their quality of life, schooling, academic attainments, future employment and relationships (Parakh & Katewa, 2015). Currently, there is a growing interest in neurocognitive deficits in BECTS (Hermann et al., 2008; Jackson et al., 2013; Oostrom, Teeseling, Smeetis-Schouten, Peters, & Jennekens-Schinkel, 2005). Most of these studies include data on: (a) demographics, (b) type of epilepsy, (c) seizures, and (d) the daytime expression of neurocognitive difficulties, documented through direct neuropsychological testing or carers' reports. We argue that this type of research could better elucidate the etiology and nature of neurocognitive deficits in BECTS by incorporating data on: (a) sleep assessment (Moturi & Avis, 2010), (b) sleep-related neuroplasticity processes (Bower et al., 2017, 2015; Halász, Bódizs, Ujma, Fabó, & Szűcs, 2019; Halász, Ujma, Fabó, Bódizs, & Szűcs, 2019), and (c) interictal epileptiform discharges (IEDs) and the full electrophysiological presentation (Baglietto et al., 2001; Fujiwara et al., 2018; Tacke et al., 2018; Zhang et al., 2020). The focus of the present paper is on the latter two issues. However, we will briefly cover the relevance of sleep assessment data in this type of research. Sleep disorders are linked to similar neurocognitive deficits to those present in BECTS (Archbold, 2004; Blunden, Lushington, Lorenzen, Martin, & Kennedy, 2005; Bourke et al., 2011; Gregory, Caspi, Moffitt, & Poulton, 2009; Kohler et al., 2009; Mitchell & Kelly, 2006; Svingos, Greif, Bailey, & Heaton, 2018). Without assessing cohorts for sleep disorders, it is risky to attribute neurocognitive difficulties purely to BECTS. Indeed, the bidirectional relationship of sleep and childhood epilepsy has been proven in terms of clinical and behavioural manifestations (Stores, 2013).

We will now refer to the role of sleep-related neuroplasticity in clarifying neurocognitive comorbidity in BECTS. Sleep plays a key role in memory and learning. Specifically, sleep-related memory

consolidation (S-RMC) concerns many functional systems of the organism and is heavily involved in the shaping of children's neurocognitive functions (Rasch & Born, 2013). We therefore argue that S-RMC should be an integral part of studies of neurocognitive functions both in BECTS and in normally developing children.

Next, we will highlight the role of IEDs in elucidating neurocognitive comorbidity in studies of BECTS. Epilepsy, including BECTS, is a complex phenomenon with a multifaceted electrophysiological presentation that includes IEDs, meaning a combination of interictal epileptiform spikes (IES) and high frequency oscillations (HFOs) (Bourel-Ponchel, Mahmoudzadeh, Adebimpe, & Wallois, 2019). The evolution of the child's neurocognitive profile partially depends on the spike index and the localization of IEDs (Nicolai et al., 2007; Zhao, Chi, Chi, Shang, & Liu, 2007). Moreover, the frequency of IEDs is among the factors that determine whether BECTS will follow a typical or atypical trajectory (Kanemura, Sano, Aoyagi, Sugita, & Aihara, 2012). Finally, epileptic phenomena concern broader spatiotemporal areas of the brain than those initially considered (Eom et al., 2017; Luo et al., 2016). Thus, we believe that BECTS research will benefit from studies that include data on IEDs and, when possible, a combination of functional and structural data.

In summary, we argue that sleep-related neuroplasticity has the potential to clarify key aspects of both sleep neurophysiology and paediatric epilepsy. This topic is therefore within the remits of basic neuroscience research. Moreover, given its central role in learning, S-RMC can offer a powerful perspective through which to study neurocognitive comorbidity in BECTS. The present paper addresses the previously mentioned research gaps by reviewing and combining key findings concerning epilepsy, sleep neurophysiology, S-RMC, epilepsy-related neuroplasticity and neurocognitive deficits in BECTS.

Neuroplasticity

Remembering past experiences and learning from them is crucial to an organism's ability to adapt to internal and environmental demands and, hence, to survival. Neuroplasticity is the capacity of the central nervous system (CNS) to respond to normal or pathological stimuli by altering its structure and function in a temporary or permanent manner (Jarero-Basulto et al., 2018). The main types of stimuli that trigger plastic procedures in the CNS are: (a) environmental changes, (b) changes in the internal states of the organism, (c) injuries, and (d) disorders such as epilepsy (Jarero-Basulto et al., 2018).

The notion of neuroplasticity is closely linked to that of development. The interaction of the genome with the child's experiences and environment shapes development in general and CNS development in particular (Kolb, Mychasiuk, Muhammad, & Gibb, 2013). The external and internal environmental factors at play include: sensory stimuli, motor stimuli, stress, injury, gut microbiota, dietary issues, toxic or psychoactive substances and relationships. Epigenetic studies demonstrate that even prenatal factors influence brain development (Donald et al., 2015; Gawałek & Sliwowska, 2015; Kohlmeier, 2015; Labouesse, Langhans, & Meyer, 2015; Nalivaeva, Turner, & Zhuravin, 2018; Schepanski, Buss, Hanganu-Opatz, & Arck, 2018). Hence, neuroplasticity is part of the developmental process and, as such, it is a continuous process. Childhood is a period of intense expression of the phenomenon, nevertheless neuroplasticity plays a role throughout the lifespan (Glasper & Neigh, 2019; Power & Schlaggar, 2016; Shaffer, 2016).

Brain plasticity can be studied at different levels, such as: (a) the gene level, (b) the molecular level and the role of proteins, (c) the role of neurogenesis procedures, (d) the cell level, including dendritic and spine organization, (e) the functional level, including the development and alterations of neuronal networks, and (g) the behavioral level (Kolb et al., 2013). Neuroplasticity can also be categorized as: (a) experience-independent plasticity, (b) experience-expectant plasticity, and (c) experience-dependent plasticity (Kolb et al., 2013). Experience-independent neuroplasticity takes place mainly before birth. It aims at enhancing the connectivity of neuronal networks without environmental sensory input (Kolb, 2018). Experience-expectant neuroplasticity manifests during the postnatal period. It concerns species-specific characteristics and functions (Fandakova & Hartley, 2020; Greenough, Black, & Wallace, 1987)**.** Experience-dependent neuroplasticity, too, occurs during the child's development. Some of the already formed neuronal networks change according to the child's unique experiences. A wide range of inter-individual differences emerge as a result of the brain's experience-dependent plasticity (Greenough et al., 1987; Kolb, 2018).

Early brain injury or neurological disorders, such as epilepsy, can also trigger neuroplastic processes and therefore influence functional outcomes. In this case, numerous factors need to be taken into consideration, such as: (a) the developmental stage at the time of the insult, (b) the type of function or behavior under study, (c) the child's age when the impact was assessed, (c) the localization of the insult in the child's brain, (d) whether the injury was unilateral or bilateral, and (e) the type of rehabilitation therapy offered (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Anderson, Spencer-Smith, & Wood, 2011; Kolb et al., 2013)

The organism's ability to form various types of memories, within the CNS and beyond, is crucial to its capacity to adjust to environmental and internal changes (Kolb et al., 2013). Memory is also essential in enriching the range of known behaviors in a given situation and in better selecting the most appropriate one according to the stimulus (Rasch & Born, 2013). Memory functions consist of sequential processes of encoding, consolidation and retrieval (Schreiner & Rasch, 2018), with each one of them corresponding to different states of the organism. Specifically, encoding and purposeful retrieval of memory traces are associated with wakefulness. Encoding has been studied extensively at the neuronal and the synaptic level. The type of plasticity that is linked to encoding is called "learning-induced synaptic plasticity" and it consists of: (a) long-term potentiation (LTP), and (b) long-term depression (LTD) (Collingridge, Peineau, Howland, & Wang, 2010; Hebb, 1949; Kandel, 2001). However, we will focus on memory consolidation, in which restful wakefulness and sleep play an essential role. Of note, memory consolidation is not a one-off process; memory traces go through various transformations and re-consolidation processes. For instance, there is a re-consolidation process every time memory traces are "replayed" during NREM sleep (Rasch & Born, 2013).

Two major types of neuroplasticity are associated with the memory consolidation process: (a) system consolidation, and (b) synaptic consolidation (Dudai, 2004). Systems consolidation involves the reactivation of newly encoded traces and their transfer from short-term to long-term storage, where they are integrated into wider memory networks (Frankland & Bontempi, 2005). Synaptic consolidation transforms the synaptic efficacy of neurons that form a memory trace. Specifically, the synapses involved become re-organised structurally, for instance, through changes in the quality and quantity of their spines (Kandel, 2001).

In the CNS, there are various memory systems; an important distinction is between non-declarative and declarative memory systems (Squire & Zola, 1996). A key characteristic of the latter is that they depend on medial temporal lobe networks (Squire, 2004). Within declarative memory systems, there is a further subdivision between episodic memories for events within concrete spatiotemporal contexts, and semantic memories for context-free facts (Tulving, 1983; Wheeler, Stuss, & Tulving,

1997). Non-declarative memories implicate diverse neuronal networks and consist of procedural memories, conditioning and implicit learning (Squire, 2004). Although neuropsychologists tend to think of memory as a higher cognitive function associated with the CNS, we invite the reader to think of it in a broad sense. In order to adjust to environmental and internal changes, every functional system in the organism needs plastic functions, which include memory formation and consolidation. The memory function of the immune system has been eloquently compared to that of the CNS; there are considerable procedural similarities in the subprocesses of encoding, consolidation and retrieval (Rasch & Born, 2013). Moreover, early night slow wave sleep (SWS) preferentially promotes adaptive immune responses and the consolidation of antigenic memory (Bierwolf, Struve, Marshall, Born, & Fehm, 1997; J Born & Fehm, 1998; Dimitrov, Lange, Nohroudi, & Born, 2007; Dimitrov, Lange, Tieken, Fehm, & Born, 2004; Lange & Born, 2011; Lange, Dimitrov, Fehm, Westermann, & Born, 2006). This is partially achieved through the sleep-related creation of appropriate endocrine and circadian mechanisms (Spaeth-Schwalbe, Hundenborn, Kern, Fehm, & Born, 1995; Spaeth-Schwalbe et al., 1993; Spiegel et al., 1995). Based on these and similar data, there is an emerging concept of sleep generally promoting memory consolidation across a number of functional systems (Besedovsky, Lange, & Born, 2012; Westermann, Lange, Textor, & Born, 2015). This in turn supports the role of sleep-related memory consolidation as an explanatory mechanism not only of epilepsy itself but also of some of its neurocognitive comorbidities.

Sleep-related memory consolidation

Sleep is a regularly occurring, homeostatically controlled state of limited responsiveness to environmental stimuli, during which the organism looses awareness of and purposeful interaction with the environment (Scammell, Arrigoni, & Lipton, 2017). Various and possibly interconnected functions have been suggested for sleep: (a) behavioural, in the sense of maintaining the organism in a state of immobility (Siegel, 2009), (b) physiological, including energy and temperature regulation (Schmidt, 2014), and (c) immunological (Opp, 2009). The theories that focus specifically on the role of sleep in CNS-related functions encompass two broad categories. The first type of theory highlights sleep's role in general maintenance and recovery (Benington & Heller, 1995; Scharf, Naidoo, Zimmerman, & Pack, 2008) as well as in detoxication functions (Xie et al., 2013). The second type of theory emphasizes the role of sleep in neuroplasticity; that is in strengthening specific neuronal networks or synaptic connections (Jan Born & Feld, 2012). However, consensus has not been reached, in terms of the exact neurophysiological mechanisms involved. One possible route could be through sleep-induced "synaptic downscaling", leaving the synapses "refreshed" for the next day's learning (De Vivo et al., 2017; Diering et al., 2017; Tononi & Cirelli, 2014). Another route could be through the reactivation of memory engrams, their selective qualitative transformation, and finally their uptake into extended long-term memory systems (Bergmann & Staresina, 2017).

The theory of memory consolidation, and the role of sleep in this process dates back over a century (Mueller & Pizecker, 1900). Specifically, the process of memory consolidation as a physiological process, which stabilizes and retains memory representations for the long-term, was first put forward in 1900 (Mueller & Pizecker, 1900). Numerous important conceptual changes have since taken place. First, our conceptualization of sleep's role in memory consolidation has changed from that of a passive to that of an active process. Initially, the accepted view was that sleep protects memory traces in a passive way, due to the lack of interfering stimuli (Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Ellenbogen, Payne, & Stickgold, 2006; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). However, current theories attribute an active role to the capacity of sleep to enhance memory traces (Klinzing, Niethard, & Born, 2019; Rasch & Born, 2013). Specifically, during sleep, memories undergo qualitative transformations and move from brain areas of temporary store to long-term neuronal networks (Rasch & Born, 2007, 2008). Second, the focus has moved from the role of REM sleep to that of NREM sleep and, in particular, that of slow oscillations and spindles (Ackermann & Rasch, 2014; Bergmann & Staresina, 2017). The majority of the electrophysiological phenomena to which we will refer in the present paper, are associated with NREM sleep. Third, current research has sought to clarify the role of REM and NREM sleep separately for each type of memory, such as declarative,

procedural and emotional. The following are the key approaches applied: (a) the dual process hypothesis (Fowler, Sullivan, & Ekstrand, 1973; Smith, 2001), (b) the sequential hypothesis (Ficca & Salzarulo, 2004), and (c) the active system consolidation hypothesis (Rasch & Born, 2007, 2008). We will refer to the first two briefly, whereas the third one will be covered subsequently in some detail. The dual process hypothesis argues that NREM enhances declarative memory, whereas REM facilitates the retention of non-declarative memory (Ackermann & Rasch, 2014; Smith, 2001). The sequential hypothesis states that, with their cyclic alterations, both sleep stages enhance the consolidation of memory traces but in a different way. Specifically, NREM sleep reduces the strength of non-adaptive memories, while simultaneously reinforcing adaptive memories. During the subsequent REM sleep stage, the aforementioned memory traces become integrated into extended long-term memory networks (Mednick, Nakayama, & Stickgold, 2003; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). In the context of the present paper, we will concentrate on NREM sleep's role in enhancing declarative memory, which is hippocampal-dependent. This line of research is also linked to the active system consolidation hypothesis (Rasch & Born, 2013).

We will now delineate the latter in some detail. During the day new stimuli are recorded simultaneously in two different "stores": (a) a hippocampal fast-learning temporary "store" and, (b) a neocortical slow-learning long-term "store" (Rasch & Born, 2013). According to the active system consolidation hypothesis, during SWS, newly formed memory traces are reactivated and "replayed". Through a process termed system consolidation, memory traces undergo significant qualitative transformations, as they move from hippocampal temporary neuronal networks into neocortical long term "storage" (Rasch & Born, 2008). Once they reach the neocortex, the newly reorganized memory representations need to be strengthened during subsequent REM sleep, through a synaptic consolidation process. This process results in new, strengthened cortico-cortical neuronal connections, which become integrated into pre-existing extended networks of memory representations (Navarro-Lobato & Genzel, 2019; Rasch & Born, 2007).

A key feature of the active system consolidation theory is its emphasis on selectivity. In relation to declarative memory traces, sleep preferentially strengthens the core concepts, the "gist" of the daytime-studied material. Sleep-related processes of abstraction and inference are the result of multiple cycles of reactivation and reorganization of memory engrams (Frankland & Bontempi, 2005; Rasch & Born, 2013). The more memory representations are "replayed" during sleep, the easier it becomes for common features and "schemata" to emerge (Lewis & Durrant, 2011). Hence, through this process declarative memory engrams become less dependent on their initial circumstances and acquire a context-free quality (Cairney, Durrant, Musgrove, & Lewis, 2011). The following factors help prioritize the consolidation of certain memory traces over others: (a) the extent to which

encoding was explicit and intentional (Fischer, Hallschmid, Elsner, & Born, 2002); (b) the emotional significance of the event for the person. Events that have high emotional meaning for the person are preferentially consolidated over emotionally neutral events (McGaugh, 2013); (c) the significance of the memory trace for the person's future intentions and projects (Wilhelm et al., 2011), and (d) the interaction between stress reactivity and sleep factors (Kim & Payne, 2020).

An advantage of the active system consolidation theory over the others, is that it describes the electrophysiological (Bergmann & Staresina, 2017; McDevit, Krishnan, Bazhenov, & Mednick, 2017) and neurochemical mechanisms (Oh et al., 2019), through which sleep enhances memory. We will delineate the electrophysiological mechanisms utilized by declarative memory consolidation processes. During NREM sleep, neuronal networks from different brain regions "dialogue" through the temporal coupling of their respective electrophysiological features (Buzsáki, 1996). Precisely, the temporal coupling involves the thalamic sleep spindles, the hippocampal ripples and the neocortical slow oscillations (Buzsáki, 1996). Sleep spindles are a characteristic feature of NREM sleep and play an important role in memory. They appear in both Stage 2 and SWS. Sleep spindles have a characteristic "waxing and waning" electrophysiological representation (Weiner & Dang-Vu, 2016). The temporal co-ordination of the key electrophysiological features (the thalamic sleep spindles, the hippocampal ripples and the neocortical slow oscillations) involves two temporal frames: (a) a top-down, and (b) a bottom-up (McDevit et al., 2017).

During the top-down frame, the neocortical slow oscillations act as a "metronome"; during certain phases they suppress spindles and ripples, while during other phases there is a rebound in the expression of the latter (McDevit et al., 2017). The bottom-up frame is an intricate process, during which hippocampal ripples nest within succeeding troughs of spindles and thus, convey replayed memory traces to spindles (Staresina et al., 2015). Next, spindles "pass on" this information to the neocortex. At an electrophysiological level, this happens through the temporal coupling of thalamic fast spindles with the upstates of neocortical slow oscillations (Latchoumane, Ngo, Born, & Shin, 2017) (see Figure 2)**.** Phase amplitude coupling is a terms that refers to the temporal precision with which one oscillation modulates its amplitude by the phase of another oscillation. There is now evidence that phase amplitude coupling is crucial in sleep-related consolidation of declarative memories; in old age and in certain pathological conditions, oscillations loose the ability to interact in a temporally precise way (Muehlroth et al., 2019). In summary, the aforementioned interactions clarify the electrophysiological mechanisms of memory reactivation and consolidation in NREM sleep.

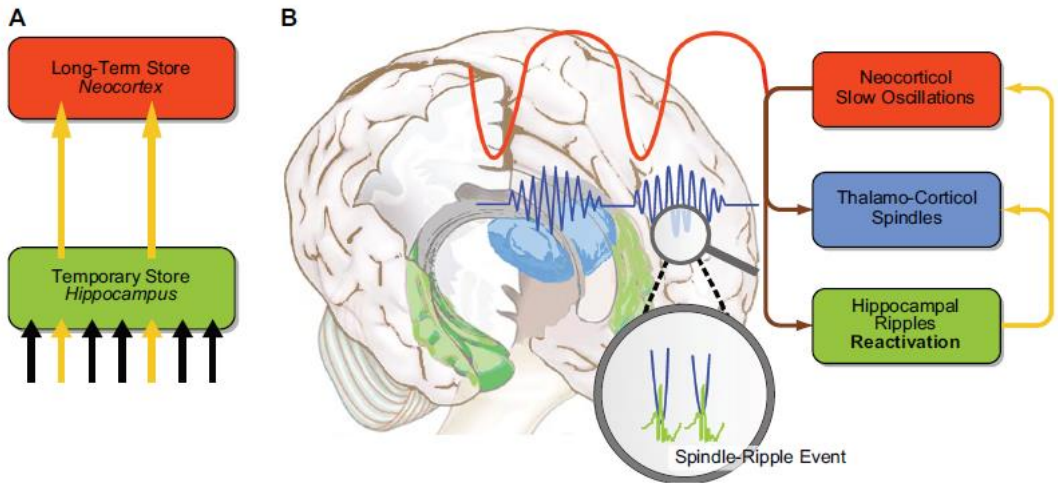

Figure 2. A model of active system consolidation during sleep. It depicts the "dialogue" of the three cardinal oscillations. Adapted from "About Sleep's Role in Memory," by B. Rasch, and J. Born, 2013, *Physiological Reviews, 93,* p. 691. Copyright 2013 by the American Physiological Association.

Next, we will present the developmental aspects of S-RMC. Childhood has unique characteristics; therefore, findings from adult studies should not be generalised to childhood. Adopting a developmental perspective is also of paramount importance in clarifying the mechanisms involved in sleep-related neuroplasticity, hence advancing basic neuroscience research (Rasch & Born, 2013). The following reasons further strengthen this point. Children sleep longer and deeper than adults (Wilhelm, Prehn-Kristensen, & Born, 2012). Childhood is a period of intense plasticity in many functional systems, including the CNS. It is a period of both formation and re-shaping of neuronal networks (Kolb, 2018), which take place within certain time frames. Critical periods in development are plastic themselves. They depend on the balance of excitatory and inhibitory systems and the maturation of the latter (Takesian & Hensch, 2013). Childhood is also characterized by an increased percentage of SWS (Wilhelm et al., 2012). SWS-related processes play a key role in the qualitative transformation of memory traces, such as: level of abstraction, gist, linking with existing neuronal networks (Frankland & Bontempi, 2005). Based on the two aforementioned facts, qualitative changes of memory traces are likely to be more pronounced in children than in adults. Specifically, the influence of children's sleep is stronger than that of adults' sleep on memory consolidation of declarative memories (Wilhelm et al., 2012). Moreover, children's sleep helps them infer explicit declarative knowledge from implicit training conditions better than adults on declarative memory tasks (Wilhelm et al., 2012). Finally, adolescents have the ability to increase the amount of SWS in order to compensate for factors such as reduced total sleep duration (Voderholzer et al., 2011).

Next, we will cover the synaptic homeostasis hypothesis, which has been influential in memory consolidation issues (Tononi & Cirelli, 2006, 2014). The key propositions of this hypothesis will be

presented in parallel with their critique. First, slow wave activity (SWA) directly reflects the level of synaptic potentiation that takes place during the previous waking period. When certain daytime tasks result in high synaptic potentiation in cortical neuronal networks, there is then increased SWA in subsequent NREM sleep (Tononi & Cirelli, 2003). Second, SWA, and slow oscillations in particular, globally depotentiate the synapses that were potentiated, through the encoding of information during wakefulness (Tononi & Cirelli, 2006). However, the concept of global downscaling cannot fully account for the phenomena involved. In the same way that encoding during waking hours is regulated by both long-term potentiation (LTP) and long-term depression (LTD), it is equally likely that sleep-related memory consolidation is regulated by both LTP and LTD (Frank, 2012). Third, memory representations are enhanced by SWA as a by-product of the synaptic downscaling process. Synapses that were weakly potentiated during wakefulness are nullified, once their strength is further weakened below a certain threshold. Synapses that were strongly potentiated during waking hours, retain some of their impact, because, even when their strength is reduced, it remains over the required threshold. This process improves the signal-to-noise ratio, in favor of the strongly encoded memory trace (Tononi & Cirelli, 2014). However, under certain conditions, weaker representations are preferentially strengthened over stronger memory representations (Fischer et al., 2002; Wilhelm et al., 2011). An example of the latter is when the emotional significance of the representation is strong for the organism (McGaugh, 2013).

Overall, current findings support selective consolidation mechanisms, through which some memory traces are strengthened, while others are weakened (Fischer et al., 2002). Therefore, the synaptic homeostasis hypothesis cannot account for the aforementioned phenomenon. Neither can it account for findings evidencing reactivation and qualitative transformation of memory traces (Rasch & Born, 2008). Implicit in the latter is the fact that some aspects of a memory trace are up-scaled, whereas others are down-scaled. Further compelling evidence against exclusive global downscaling mechanisms emerges from the fact that SWA is also regulated locally in addition to its global regulation by certain brain structures. Daytime encoding that activates certain neuronal networks increases SWA in the same networks during subsequent sleep (Krueger et al., 2008; Nir et al., 2011; Rasch & Born, 2007). In this section we have reviewed some key sleep-related mechanisms.

Epilepsy

In the present paper, the impact of seizures on neurocognitive deficits is not a priority, for a number of reasons. First, the role of seizures has been studied extensively elsewhere (Hermann, Jones, Jackson, & Seidenberg, 2012; Jackson et al., 2013; Oostrom et al., 2005). Second, seizures alone cannot fully explain the impact epilepsy has on children's neurocognitive development. For instance, neurocognitive deficits appear already at the very early phase of the disease, when a small number of seizures occur, and they persist, even when seizures are in remission or well-controlled pharmacologically (Bailet & Turk, 2000; Germanò et al., 2005). We will therefore consider a wide range of interictal EEG features in BECTS.

We will start by defining some key interictal phenomena. IEDs are very brief epileptic phenomena (<200ms), which take place during the interictal period without clinical manifestations (Frauscher & Gotman, 2019a). They include interictal epileptiform spikes (IES) and high frequency oscillations (HFOs). IES follow a circadian rhythm; during SWS, possibly due to increased synchronization in this sleep stage, they have an extended electrical field and become prominent (von Ellenrieder, Dubeau, Gotman, & Frauscher, 2017). IES also follow multidien rhythms of approximately 20-30 days (Frauscher & Gotman, 2019a). HFOs, which are also known as ripples, consist of at least four oscillations, which contrast to their EEG background. There is a distinction between slow and fast ripples, with fast ripples usually being pathological (Frauscher et al., 2017; von Ellenrieder et al., 2017). It is not always easy to discern pathological from physiological ripples (von Ellenrieder, Frauscher, Dubeau, & Gotman, 2016). A recent development is the use of HFOs as markers of the epileptogenic brain area and the seizure onset area (Frauscher et al., 2018). Other clinical applications of HFOs include the evaluation of epilepsy severity (van Klink et al., 2016) and the monitoring of pharmacological therapy (Frauscher et al., 2017). In focal epilepsies, the temporal and spatial coupling of IES and HFOs with specific NREM phasic features partially illuminates the complex interplay between sleep and epilepsy. Of note, in BECTS, IES couple with spindles rather than with slow waves, which is the pattern in all other types of epilepsy (Nobili et al., 2000). The reason remains a riddle.

Contrary to traditional diagnostic criteria, BECTS is not characterized by the occasional occurrence of seizures in otherwise physiologically functioning neuronal networks. In BECTS, the epileptic brain presents with considerable irregularities, expressed through specific events, such as IES and HFOs, and widespread neuronal deregulation (Bourel-Ponchel et al., 2019). The following functional and diffuse structural disorganization issues have been documented in BECTS:

- Significant functional alterations are present simultaneously in the epileptogenic zone and other brain areas, even during IES-free periods (Adebimpe, Aarabi, Bourel-Ponchel, Mahmoudzadeh, & Wallois, 2016; Ji et al., 2017; Zeng et al., 2015);
- Considerable alterations in functional and effective connectivity indicate aberrant integration of the task positive network (TPN) and the default mode network (DMN) (Luo et al., 2016). Functional connectivity studies have shown that, during the interictal state, BECTS disrupts small-world functional properties (Adebimpe et al., 2016; Zeng et al., 2015). Moreover, effective connectivity studies have demonstrated that the epileptogenic zone produces alterations to distant subcortical and cortical areas, such as the frontal, the temporo-parietal junction and the temporal pole (Adebimpe, Bourel-Ponchel, & Wallois, 2018; Wu et al., 2015);
- Time-frequency analysis studies indicate that functional alterations start 400 ms prior to IES and have the same duration in the epileptogenic zone and distant brain areas (Bourel-Ponchel, Mahmoudzadeh, Berquin, & Wallois, 2017);
- Taken together, the previously mentioned findings indicate a widespread functional disorganisation in the epileptogenic and distant brain areas in the absence of IES as well as in close temporal proximity to their appearance. In other words, IES appear within already aberrant functional networks and they further accentuate functional disorganization issues. Specifically, IES increase various types of power spectra in the centrotemporal brain areas and the synchronisation phase (Adebimpe, Aarabi, Bourel-Ponchel, Mahmoudzadeh, & Wallois, 2015).

Another key issue is whether there is structural disorganization in BECTS. By definition, MRI abnormalities are incompatible with BECTS diagnosis (Pavlou et al., 2012). However, grey matter differentiations have been recorded in the epileptogenic area as well as in remote brain regions (Garcia-Ramos et al., 2019; Jiang et al., 2018; Kim et al., 2015; Luo et al., 2015; Pardoe et al., 2013). A common finding concerns aberrant differentiations in the degree of cortical thickness. Moreover, significant white matter abnormalities in the epileptogenic and remote brain areas, have also been demonstrated in BECTS (Ciumas et al., 2014; Kim et al., 2015; Xiao et al., 2014). The aforementioned findings suggest that epileptogenic processes adversely affect normal brain development and are hence expected to interfere with physiological neuroplastic functions during sleep.

Epilepsy and neuroplasticity

The idea that epilepsy, apart from being a neurological disease, elegantly exemplifies many types of neuroplasticity is not new. As mentioned earlier in the present paper, neuroplasticity refers to the ability of the nervous system to alter its structure or function either permanently or transiently as a response to a range of stimuli including epilepsy (Jarero-Basulto et al., 2018). In some texts, plasticity in response to insult bears a positive connotation, meaning that the actual change serves an adaptive purpose for the organism. However, this is not always the case. The organism responds to insult, including epilepsy, in the best way it can under the circumstances. Even when the organism elicits a compensatory mechanism in response to epilepsy, that very same mechanism might actually have an epileptogenic nature (Scharfman, 2002). To further confound the picture, there might be both adaptive and maladaptive aspects within a unique plastic change, such as protein expression.

It is no coincidence that research teams that study the hippocampus, were among the first ones to claim that epilepsy can serve as a model of neuroplasticity. This brain structure is highly susceptible to ictal phenomena, to which it tends to respond with functional and structural changes (Sierra, Gröhn, & Pitkänen, 2015). Moreover, the laminar structure of the hippocampus allows scientists to easily notice cells that are out of their usual layer and other plastic changes in response to seizures (Scharfman, 2002). The hippocampus presents numerous alterations in response to seizures (Jarero-Basulto et al., 2018) including: (a) selective neuronal loss, (b) axonal sprouting in the granule cells, (c) transciptional alterations, (d) aberrant neurotransmission, (e) differentiations in glial responses, and (f) increased neurogenesis (Sierra et al., 2015). Following seizure-induced neurogenesis, some of the resulting cells develop altered migration paths. In their unexpected positions they maintain the characteristic membrane properties of their cell type but develop aberrant connectivity. Specifically, many of these cells develop epileptiform discharges, which have an impact not only on their own qualities but on the expression of the wider neuronal networks they gradually develop (Scharfman, 2002).

Given our focus, we will concentrate on one type of neuroplasticity, sleep-related memory consolidation. Many terms have been used to describe the way epilepsy interacts with physiological neuroplasticity. The term "hijacking of certain brain systems" refers to the possibility that early-onset epilepsy, through repetitive overexcitation of particular neuronal networks, eventually controls their regulation (Beenhakker & Huguenard, 2009). The term "derailment of normal plasticity" refers to the possibility that the NREM-related physiological processes of memory consolidation become deregulated due to the detrimental involvement of IES and HFOs (Halász, Bódizs, et al., 2019). Sleep-related memory consolidation is indeed based on the precise spatiotemporal coupling of the three

cardinal oscillations: (a) cortical slow oscillations, (b) thalamic spindles, and (c) hippocampal ripples (Bergmann & Staresina, 2017). IES and HFOs interfere with this process. Specifically, they temporally couple at the point where slow oscillations transition from their "up states" to their "down states". This is significantly different from the temporal coupling of physiological oscillations, which tend to present during the "up states" of the slow waves (see Figure 3) (Frauscher & Gotman, 2019a). Figure 3 depicts the physiological processes involved in the temporal coupling of oscillations.

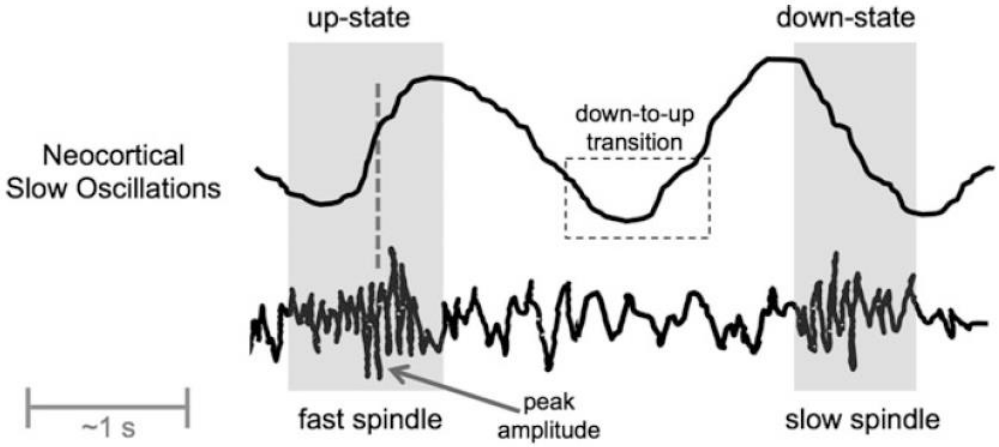

Figure 3. The temporal coupling of sleep spindles in physiological sleep-related memory consolidation. Adapted from "The Role of Sleep Spindles in Sleep-Dependent Memory Consolidation," by E. A. McDevitt, G. P. Krishnan, M. Bazhenov, and S. C. Mednick, 2017, In N. Axmacher and B. Rasch (eds), *Cognitive Neuroscience of Memory Consolidation,* Studies in Neuroscience, Psychology and Behavioural Economics, p. 211. Copyright 2017 by Springer International.

According to recent findings, seizures and IES undergo sleep-related reactivation and consolidation processes utilizing physiological mechanisms that were considered to be reserved for meaningful stimuli (Bower et al., 2017, 2015). Given the invasive nature of the intracranial macroelectrode recordings, data can be derived only from patients with refractory epilepsy. First, we will outline the seizure-related data, despite the fact that seizures are not the focus of this essay. Neuronal networks that were found to be activated by seizures during daytime, were preferentially consolidated during post-seizure SWS. Hence, seizure-related networks were strengthened through physiological memory consolidation mechanisms (Bower et al., 2015). They were processed as if they were adaptive stimuli that could improve the organism's response to future challenges. Yet, this was definitely not the case. Seizure-related neuronal networks and their replay during SWS represent pathological mechanisms (Bower et al., 2015). A pertinent question is whether this is actually an

epileptogenic mechanism; that is could the night-time strengthening of seizure-related neuronal assemblies essentially be increasing the stakes for future seizures (Bower et al., 2015).

It is not only seizures that act as memory engrams, however; pre-seizure IES act in similar ways as well. In the same series of studies, the pattern of changes that was documented in IES before seizure activity, was subsequently observed during SWS after seizure. The pathological patterns of the IES were preferentially reactivated during SWS (Bower et al., 2017). Again, this is a process that was believed to be "reserved" for adaptive material of high relevance to the organism. The aforementioned data offer a groundbreaking perspective on how epilepsy interacts with sleep-related neuroplasticity mechanisms. These studies also highlight the importance of collecting IES data.

Seizure-related consolidation (SRC) is the theory based on the data mentioned previously; the processes involved bear significant resemblance to learning-related consolidation processes (Bower et al., 2017). In essence, SRC theory and the data it is based on, postulate the post-seizure consolidation of epileptiform activity as memory engrams (Bower et al., 2017). Of note, earlier researchers made similar claims; they viewed epilepsy within the range of activity-dependent change. This was a very advanced claim, considering that it was based on intricate function-structure inferences in epileptic rodent models without access to human clinical samples (Scharfman, 2002). The theoretical extension of the SRC idea, for which there is no empirical data at present, is that SRC underlies epileptogenesis (Bower 2020, personal communication). The justification for this generalization is parsimony; the development of epilepsy only requires the occurrence of epileptiform activity, whereas neural plasticity mechanisms create the rest of the epileptogenetic phenomenon. Based on current data, there is no requirement for a special epileptogenic process specific to epilepsy. This fact partially explains why extensive investigations for such a process have not been successful (Bower 2020, personal communication).

Neurocognitive deficits in BECTS

This part of the article links epilepsy manifestations and sleep physiology to neurocognitive deficits in BECTS. First, IES in BECTS interfere with and alter the precision of the spatiotemporal co-ordination of the three main types of oscillations during SWS. For instance, IES couple with slow wave oscillations at different transitional points (up to down states) to what physiological oscillations do (down to up states) (Frauscher & Gotman, 2019b). As a result of this process, sleep neuroplasticity develops an epilepsy-related derailment and is not in a position to "deliver memory consolidation services" as efficiently as it should (Halász, Bódizs, et al., 2019). This has in turn an impact on daytime neurocognitive functioning. Moreover, the location of IES in BECTS is of paramount importance, given that they affect the perisylvian area, which plays a key role in communication and numerous cognitive functions (Halász, Bódizs, et al., 2019). Additionally, IES-related neuronal deregulation, negatively affects both local and remote networks (Bourel-Ponchel et al., 2019). Taken together the previously mentioned facts further clarify the link between IES and neurocognitive functions.

Second, seizures and IES undergo sleep-related consolidation processes through physiological mechanisms that were assumed to be reserved for meaningful stimuli (Bower et al., 2017, 2015). There are twofold consequences in relation to neurocognitive comorbidity. The first consequence is that this is actually an epileptogenic mechanisms, hence creating further perturbation of the perisylvian network and possibly a further deterioration of the related cognitive functions. The second one is that while certain brain networks reactivate and consolidate IES and seizures, they become "deserviceable" to meaningful memory engrams, thereby negatively affecting learning and cognitive functions (Bower et al., 2017, 2015). Third, SWS sleep in BECTS is also characterized by the detrimental impact of HFOs and a wide range of functional disorganization. The latter presents in the epileptogenic as well as in distant networks and has been linked to various forms of neurocognitive comorbidity (Bourel-Ponchel et al., 2019).

Research teams that view epilepsy as a system disorder make links between certain neurocognitive deficits, known to be present in BECTS, and functional differentiations in specific neuronal networks. Some examples follow. In BECTS there is an aberrant flow from the central to frontal areas. Connectivity studies have shown frontal deactivation and connectivity alterations (Zeng et al., 2015). Frontal lobes play a key role in attention and higher cognitive skills. Alterations in activation and connectivity of the former could therefore partially explain these types of difficulties in BECTS (Xiao et al., 2015). Additionally, alterations in functional connectivity that concern the right inferior temporal cortex and the bilateral primary auditory cortex could partially explain the language processing difficulties in BECTS (Adebimpe et al., 2016). Various forms of communication difficulties

in BECTS can be explained by the fact that the perisylvian network that plays a key role in communication becomes affected by epileptic phenomena including IES (Halasz 2020, personal communication).

So far, we have implied that sleep-related neuroplasticity phenomena are sufficient to independently trigger neurocognitive deficits in BECTS. This might be so. However, it is equally important to keep in mind the "big picture"; maturational processes involve many interacting levels. A genetic mutation can cascade through to the behavioural/phenotypic level, in constant interaction with environmental, social and internal factors. Specifically, a genetic mutation can lead to aberrant neuronal migration and differentiated neuronal connectivity in the infant's brain. The latter can trigger alterations in the expression of neurotransmitters resulting in aberrant cortical organization and connectivity. The end point of such a process, the behavioural/phenotypic expression of the phenomenon, is likely to include deficits in particular neurocognitive functions (Lo-Castro, D'Agati, & Curatolo, 2011).

With the advent of epigenetics, it is now widely accepted that the organism's lived experience and key environmental stimuli can lead to altered gene expression. When studying highly complex phenomena, such as BECTS and sleep-related neuroplasticity, it is difficult to identify the initial trigger that diverted the organism from its normal developmental trajectory. Within the field of sleep-related epilepsies, an approach that helps clarify these issues is a thorough study of genotypes, endophenotypes and phenotypes (see Figure 4) (Halász, Bódizs, et al., 2019). Of note, centrotemporal spikes constitute an endophenotype shared by CECTS, ASD and ADHD (Halász, Bódizs, et al., 2019).

Another "big picture" issue concerns the close interaction between the CNS, the immune system and the endocrine system. Neurotransmitter alterations and endocrine and immunologic disturbances are highlighted as pathogenic mechanisms within: (a) sleep disorders research, (b) sleep-related memory consolidation research, and (c) epilepsy research (Kanner et al., 2017; Rasch & Born, 2013). Again, it is difficult to perceive the initial pathogenesis within the aforementioned closely collaborating systems of the organism. A phenomenon, that presents as epilepsy-related (CNS) could actually have its basis in an immunological or endocrinal disturbance and vice-versa.

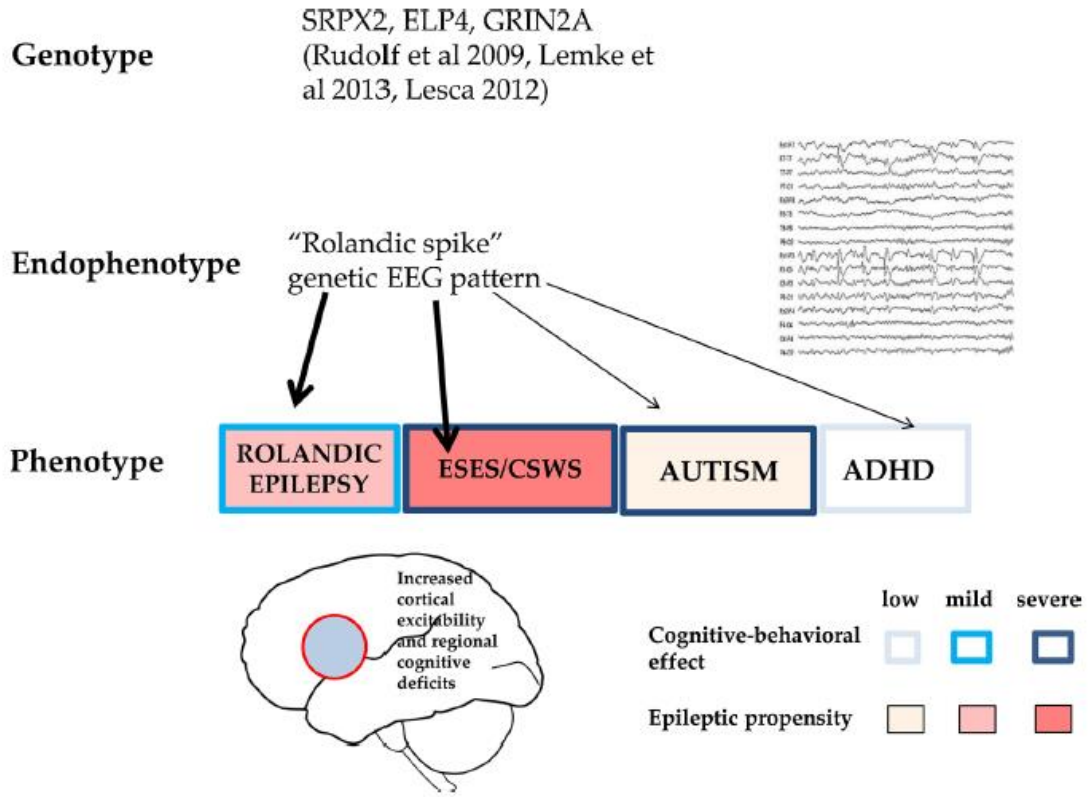

Figure 4. The study of genotypes, endophenotypes and phenotypes in sleep-related epilepsies. Adapted from "Strong Relationship between NREM Sleep, Epilepsy and Plastic Functions- A Conceptual Review on the Neurophysiology Backgound," by P. Halasz, R. Bodizs, P. P. Ujma, D. Fabo, and A. Szucs, 2019, *Epilepsy Research, 150,* p. 102. Copyright 2018 by Elsevier.

Implications for basic neuroscience research

Focusing concurrently on sleep, epilepsy and sleep-related neuroplasticity, can help deepen our understanding of these terms and phenomena. For instance, through this type of work, BECTS can be conceptualized within the sleep-related epilepies, as a neuronal network disorder or system epilepsy. These are closely related terms. The term network disorder refers to the purposeful link between epileptic phenomena and existing neuronal networks. System epilepsy refers to the fact that the epileptic network becomes interwoven with a particular brain system and modifies its development and functioning (Halász & Szűcs, 2018b). Due to the interwoven nature of the epileptic mechanisms with those of the specific brain system, there are bidirectional influences: (a) epileptiform discharges might be triggered by the activation of the specific brain system, and (b) epilepsy-related mechanisms might distort the functioning and maturation of the specific brain system (Halász & Szűcs, 2018a). One important point emerging from the system epilepsy concept, is that the brain system's activation could be in itself an epileptogenic trigger; there is no need for external triggers (Halász & Szűcs, 2018a). Evidence for the system epilepsy concept emerges from the nature of epileptic deregulation. Epileptic discharges do not remain circumscribed within certain brain structures; they tend to affect extended functional brain systems. Some parts of the brain system involved are distant to the initial epileptogenic focus (Halász & Szűcs, 2018a).

Based on the data reviewed in the present study, sleep appears to play a crucial role in memory consolidation across a range of CNS functions and even non-CNS functions, including the immune system. In that respect, sleep and memory consolidation are closely linked to the development of a wide range of functions. This fact is likely to shift the conceptualization of neurocognitive functions both in the general population and in BECTS. Specifically, memory and sleep-related memory consolidation can be conceptualized as forming part of every function, rather than being separate functions in themselves. Subsequently, pathological alterations in sleep-related memory consolidation, are likely to cause a wide range of neurocognitive comorbidities in children with epilepsy, rather than a few well circumscribed areas of impairment. Some of the mechanisms, through which those pathological alterations emerge, are now known. IES and other EEG features of paediatric epilepsy, such as HFOs, subtle changes in neuronal connectivity and mild structural abnormalities significantly disrupt NREM-related memory consolidation, during key stages of development. In many cases, IES persist, even when seizures are controlled or in natural remission, and appear to contribute to the ongoing deficits (Parakh & Katewa, 2015). Consequently, future research in neurocognitive comorbidity in BECTS needs to include data on:

- daytime functioning and learning processes;

- IES and the wider electrophysiological abnormalities in addition to seizure data;
- sleep-related memory consolidation processes for each function studied (these functions are generally grouped under declarative, procedural and emotional memory tasks);
- subtle functional and structural disorganization issues.

A further interesting line of basic neuroscience research concerns whether children with BECTS, actually manifest the expected sleep-related benefit in memory consolidation, when compared to healthy controls. Initial findings indicate that children with epilepsy do not actually benefit from sleep in the same way that healthy children do (Chan, Pressler, Boyd, Baldeweg, & Cross, 2017; Urbain, Di Vincenzo, Peigneux, & Van Bogaert, 2011). Considering the small sample sizes of the aforementioned studies and possible publication bias issues, these early findings need to be viewed with caution. In this type of research, increasing the number of sleep intervals is likely to increase ecological validity; children acquire and consolidate new skills within larger time periods (Rasch & Born, 2013).

So far, we have outlined how sleep-related alterations in memory consolidation could be a key mechanism causing neurocognitive deficits in BECTS. This could partially explain why sleep problems are among the first symptomatic manifestations of various disorders, both neurological and psychiatric (Bassetti et al., 2015). It might be reasonable to expect that disorders that co-present with impaired sleep-related memory consolidation, are likely to be accompanied by a range of neurocognitive deficits (Bassetti et al., 2015). Sleep-related neuroplasticity in epilepsy offers insight into yet another possible common underlying mechanism between neurological and psychiatric disorders. Recent research findings demonstrate that seizures and IES are in essence treated by the organism as adaptive memory engrams and utilise the physiological memory consolidation mechanisms (Bower et al., 2017, 2015). This is groundbreaking information. Prior to that, it was considered that the organism preferentially consolidates engrams that increase its capacity to respond to future demands (Wilhelm et al., 2011). Further research is needed to clarify whether key psychiatric symptoms, such as auditory and visual hallucinations, go through sleep-related memory consolidation processes too. This could be a psychopathogenic mechanism, in the sense that it makes subsequent psychiatric symptoms more likely to occur.

Finally, some important questions remain to be answered. For instance, further research is needed into the mechanisms through which learning-related (physiological) memory engrams compete for sleep-related memory consolidation prioritization with epilepsy-related pathological memory engrams.

Implications for clinical research

Exploring the role of IES, HFOs and wider functional neuronal disorganization issues in BECTS is promising in associating neurophysiological features of epilepsy with neurocognitive outcomes (Bourel-Ponchel et al., 2017). This could in turn lead to the identification of new prevention and treatment loci for BECTS. For instance, stabilizing sleep structures and reducing IEDs seem important in preventing neurocognitive deficits (Miano & Datta, 2019). Specifically, acknowledging the role of IEDs in the neuropathology of epilepsy offers clinical research two new therapeutic targets. The first target could be to reduce the frequency or to stop the occurrence of the IES and pathological HFOs (Bourel-Ponchel et al., 2019). The expected benefit is reduced disturbance of the physiological sleep-related memory consolidation systems caused by IEDs and hence reduced neurocognitive deficits (Bourel-Ponchel et al., 2019). The second therapeutic target could be to prevent sleep-related consolidation of seizures and IES, which is in essence an antiepileptogenic therapeutic goal (Bower et al., 2017, 2015). If these therapeutic goals are met, we can reasonably expect a considerable improvement in neurocognitive outcomes in children with epilepsy.

Moving beyond epilepsy-related therapeutic goals, SWS-related memory consolidation could have therapeutic implications for psychiatric disorders too. Should it be confirmed that psychiatric symptoms, such as hallucinations, utilise sleep-related memory consolidation processes too, we could then target a well-defined psychopathogenic mechanism (Szucs et al., 2018). This could apply to a range of mental health conditions. For instance, in post-traumatic stress disorder, one therapeutic target could be to reduce or stop the sleep-related memory consolidation of the trauma-related engram, eventually allowing the organism to forget and recover (Szucs et al., 2018).

Implications for practice

Research teams across the globe work incessantly to further understand sleep-related memory consolidation in paediatric epilepsy, and in BECTS in particular. In the meantime, it is important to strengthen the research-practice interaction by disseminating key information to front-line practitioners. Key findings on the interface of epilepsy, sleep, sleep-related memory consolidation and neurocognitive deficits in children with epilepsy could be channeled through: (a) undergraduate and postgraduate training, (b) continuing professional development events, (c) congresses, (d) publishing in journals read by front-line staff.

Multidisciplinary collaboration is of paramount importance given the multifaceted nature of the phenomena described in this article (sleep, epilepsy, sleep-related memory consolidation assessment) (Goldstein et al., 2004; Sevecke & Meadows, 2018). Within the wider neuroscience network, disciplines, such as neurophysiology, neuroimaging, neurology, neurobiology and neuropsychology need to work closely together; none can cover all aspects of the phenomena on their own. Joint work could be enhanced through the creation of sleep-epilepsy centers, either actual or virtual, through protocols of collaboration among existing centers. There is also a need to develop new practices to transfer viewpoints, methodologies and datasets from one discipline to the others. Multidisciplinary consortia and conferences might further advance cross-discipline dialogue. The "Fourth International Halifax Conference and Retreat in 2016" and the "Workshop on the Neurobiology of Epilepsy" constitute pioneering examples towards this direction (Kanner et al., 2017; Mahoney et al., 2019; Scharfman et al., 2018).

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