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D/EE-SWAS: NEUROPSYCHOLOGICAL PROFILES WITH IC-CODE AND ANALYSIS OF THE FUNCTIONAL CONNECTIVITY IN A TWO-CENTRE COHORT

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OVERVIEW

Developmental and Epileptic or Epileptic Encephalopathy with Spike-Wave Activation during Slow Sleep (D/EE-SWAS) is a rare and complex neurological disorder characterized by marked activation of spike-and-wave discharges during sleep in association with significant cognitive and/or behavioural impairments resulting in a high burden of long-term sequelae.

In the introduction we provide a thorough overview of the historical evolution and a review of current knowledge surrounding this pathology, laying a robust foundation for the study. We observed that current conceptual models often focus on individual features (such as aetiology, EEG patterns, and neuropsychological symptoms) and subsequently attempt to establish intercorrelations through direct causal mechanisms. Achieving a more comprehensive understanding requires the adoption of complex frameworks wherein individual features are integrated through a neurodevelopmental network-based perspective.

Based on these considerations, we designed a retrospective observational study aiming to the development of novel approaches for the neuropsychological and neurophysiological characterization of D/EE-SWAS, with the goal of contributing to a more nuanced understanding of this complex condition from a network-based perspective. The efficacy of these approaches was evaluated through their application to a cohort of 28 patients diagnosed with idiopathic D/EE-SWAS, who were selected from those followed in the last 11 years at two distinct neuropediatric centres.

The study is structured in two parts, beginning with a comprehensive description of the patients' clinical, neurophysiological, neuroradiological, and genetic characteristics.
In line with new approaches recently proposed in the field of epilepsy, neuropsychological data collected at the time of clinical nadir were analysed through a multidomain model inspired by the IC-CoDE framework, enabling:

- identification of the predominant involvement of linguistic and attentional domains, and their role in determining clinical outcomes.

- delineation of three clusters based on neuropsychological profiles and observation of their prognostic potential, providing an innovative tool for the phenotypic characterization of D/EE-SWAS patients.

The second part of the study focused on the application of advanced neurophysiological techniques to a subcohort of 13 patients. Powers Spectral Analysis and Partial Directed Coherence was applied to IEDs-free epochs of EEG recorded during phase II sleep, and the results were then compared to a sex- and age-matched control group.
This analysis allowed the identification of:

- regions of increased delta-band activity, suggesting a potential contributory role in pathogenesis.

- alterations in connectivity within the perisylvian and frontal regions, constituting a common pattern irrespective of the localization of epileptic foci during wakefulness.

These findings support the application of novel methodologies to larger cohorts of patients with D/EE-SWAS in order to enhance our understanding of this multifaceted disorder. Furthermore, they advocate for the adoption of a network-based approach to effectively address the inherent complexities of this condition and its neurodevelopmental underpinnings.

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INTRODUCTION

D/EE-SWAS: from the 'functional ablation' model to a neurodevelopmental network perspective

The interplay between epilepsy and cognition is intricate and multifaceted, particularly in the context of childhood-onset epileptic disorders where epileptic activity can significantly interfere with and disrupt the delicate, highly plastic and environment-related trajectories of neurodevelopment. Developmental and Epileptic or Epileptic Encephalopathy with Spike-Wave Activation during Slow Sleep (D/EE-SWAS) is a poignant model and offers a unique framework for exploring these complex relationships.

D/EE-SWAS has been lately introduced by ILAE to identify a spectrum of childhood-onset epilepsies featuring marked activation of spike-waves during sleep in association with cognitive and/or behavioural impairment, even in the absence of clinical seizures[1]. In D/EE-SWAS cognitive and/or behavioural impairment is frequently the very first signal of disease onset, characterises its active phase and ultimately conditions its long-term outcome.

HISTORICAL BACKGROUND AND CURRENT DEFINITION

The potential link between abnormal electrical activity and cognitive alterations was seminally identified in 1942 by Kennedy and Hill who reported on a case of cognitive and behavioural regression in an 8-year-old boy with slow spike-wave abnormalities at EEG recording unassociated with overt seizures (incisively defined 'dementia dysrythmica infantum')[2]. In 1957 Landau and Kleffner described a series of 5 children with acquired epileptic aphasia (primarily receptive) and diffuse interictal epileptiform discharges (IEDs), prominently localised on temporal regions. Describing this epileptic syndrome, hence called Landau-Kleffner syndrome (LKS), they pointed out a possible correlation between the severity of clinical features and IEDs[3]. The importance of sleep in potentiating EEG abnormalities in children with clinically evident cognitive regression was then demonstrated by Patry, Lyagoubi and Tassinari in 1971 who defined the ensuing clinical condition as electrical status epilepticus during slow sleep (ESES)[4]. Subsequent studies of large case series supported the concept of a cause-effect relationship between IEDs and mental regression and yielded an ever-growing knowledge about the "encephalopathic" nature of this condition.

The literature has been progressively marked by some degree of confusion due to the proliferation of nosological terms used to describe the same condition, including Continuous Spike-Waves during Slow-Wave Sleep (CSWS), ESES, and Epileptic Encephalopathy with CSWS (EECSWS)[5]. Despite this terminological variability, a unified

conceptual framework has emerged around the notion of 'epileptic encephalopathy', which characterizes a group of epilepsies where epileptiform abnormalities are believed to contribute significantly to progressive neurological impairment[6]. On the other hand, the quantification of EEG abnormalities has emerged as a prominent element of debate, with various proposed thresholds for the Spike-Wave Index (SWI) during NREM sleep, ranging from 85%[7] to as low as 25%[8].

ESES/EECSWS was hence typically defined by the following features[9]:

i) epilepsy: focal and apparently generalized seizures (unilateral or bilateral clonic seizures, tonic-clonic seizures, absences), partial motor seizures, complex partial seizures or epileptic falls.
ii) encephalopathy: neurological deterioration, involving cognitive, behavioural and/or motor domains.
iii) typical EEG findings: status epilepticus during sleep (SES), defined as the appearance at sleep onset of a pattern of diffuse spike-and-waves (with different degrees of symmetry or even unilateral or focal) occurring in up to 85% of slow sleep and persisting for months or years.

Against this background, the main focus of debate and critical inquiry has remained over the complex interplay between electrical abnormalities and clinical deterioration, which can be framed either as independent epiphenomena of an underlying disorder or as strictly bonded in a causal chain giving rise to an epileptic encephalopathy. Indeed, the latter has been overshadowed ever since the early days when Landau and Kleffner speculated about a "functional ablation" of cortical areas involved in language induced by persistent convulsive discharges[3]. The iconic definition of "Penelope syndrome" issued by Tassinari reinforced this causal correlation and placed sleep in the foreground, leveraging on the analogy between sleep-activated spike-waves and the mythical wife of Odysseus, both undoing overnight what has been spun during the day[10]. Despite its clarity and straightforwardness, this pathogenetic model cannot explain in an exhaustive way the variability of atypical pictures observed as uncoupled electroclinical fluctuations in the evolutions of single cases, or in individuals harbouring marked spike-wave activation in sleep without any clinical sign of deterioration[11].

The new definition of this condition i.e. D/EE-SWAS, issued in 2022 by the ILAE Task Force on Nosology and Definitions[1], features only two mandatory criteria for the diagnosis:

i) slow (1.5–2 Hz) spike-and-wave abnormalities in N-REM sleep, with marked activation in sleep (SWAS)
ii) cognitive, behavioural, or motor regression or plateauing temporally related to SWAS on EEG

Within this framework, EE-SWAS is identified when regression or developmental plateauing occurs in individuals with pre-existing normal development. In contrast, a diagnosis of DEE-SWAS is established when a documented persistent worsening is observed in patients with pre-existing neurodevelopmental disorders (NDDs) (Figure 1). LKS has been retained as a specific subtype of EE-SWAS, characterized by regression affecting mainly the language domain due to acquired auditory agnosia.

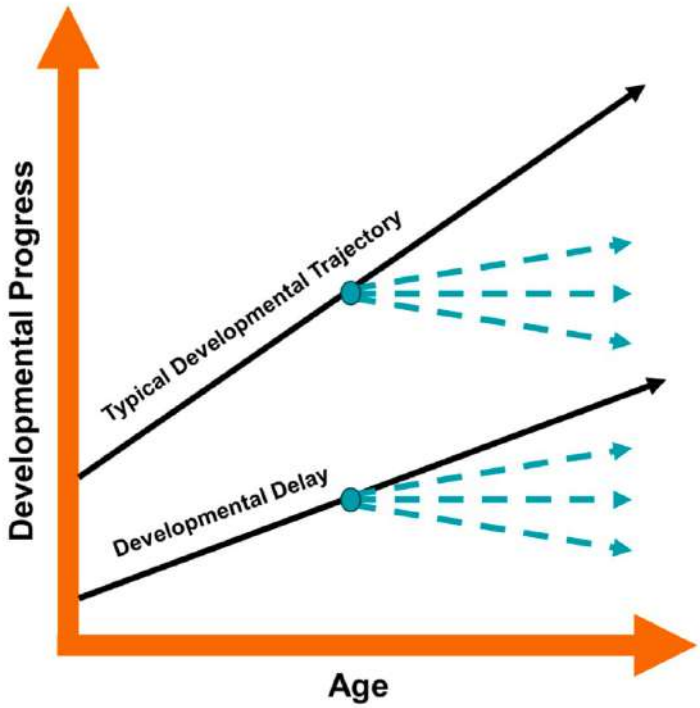

Figure 1. Potential effect of epileptic activity (dashed arrows) on developmental trajectories superimposed on normal development or pre-existing developmental delay (solid arrows) as observed in EE-SWAS and DEE-SWAS, respectively. (from Sands & Gelinas, 2024)[12]

Although some authors claimed that this latest definition by ILAE represents a step back as compared to other terminologies which hinged on the 'epileptic encephalopathy' concept (e.g. ESES, Penelope syndrome)[13], it appears to undermine the cause-effect relationship, opening to new and unexplored perspectives and viewpoints. D/EE-SWAS definition, in fact, does not take a stance on the matter, merely grounding the syndrome on the association between electrical and clinical features which need to be carefully documented in their temporal relation. On the other hand, it features less strict criteria as regards EEG pattern: this should allow to divert and orient attention towards diagnostic assessment and long-term monitoring of cognitive and/or behavioural features, given the manifest relevance of neuropsychological long-term sequelae[14]. In this respect, lack of thorough characterization of neuropsychological and behavioural profiles, including accurate description of psychiatric diagnoses, has been recently pointed out as concerns case series and drug trials involving patients with D/EE-SWAS[15].

EPIDEMIOLOGY

Epidemiological data are limited, but it is estimated that D/EE-SWAS affects approximately 0.5% to 1.9% of paediatric epilepsy patients who are treated at tertiary epilepsy referral centres[16,17]. An epidemiological survey on LKS in Japan revealed an incidence of 1/1.000.000 among individuals aged 5–14, and a prevalence of LKS ranging from 1 in 300.000 to 1 in 410.000 among individuals aged 5–19 years receiving medical care[18]. The prevalence of D/EE-SWAS appears to be similar between sexes, although a slight male predominance has been reported in some series[16,19]. Age at onset ranges from one to 14 years, with a peak between four and eight years[20].

A family history for seizures has been reported in a widely variable proportion of patients with D/EE-SWAS, ranging from 10-15% up to 50%[7,21].

About one-third of patients with D/EE-SWAS had received a previous diagnosis of SeLFEs[22,23]. Conversely, D/EE-SWAS represents an "atypical" evolution of SeLFEs in a subset of cases, most notably from SeLECTS in 6,5-20% of cases[24,25] and less frequently from SeLEAS and COVE[26–28]. Electroclinical features predicting evolution of SeLECTS into D/EE-SWAS include early onset of seizures, appearance of new seizures with increased frequency, seizure semiology (including dysarthria or somatosensory auras), EEG spike–waves, EEG without evidence of left lateralization, and EEG fronto-centrotemporal focus[25,29].

AETIOPATHOGENESIS

Aetiological investigations have allowed the identification of structural causes in 25-30% of D/EE-SWAS cases, including both developmental and early-acquired lesions. These brain abnormalities often determine *per se* a Developmental Encephalopathy (DE) featuring psychomotor delay (and, in some cases, cerebral palsy) which may be further complicated by the emergence of SWAS.

Notably, malformations of cortical development (MCDs) have been reported in patients with D/EE-SWAS, with perisylvian polymicrogyria emerging as the most frequent subtype[30–32]. Additionally, shunted hydrocephalus has been reported as a significant risk factor for D/EE-SWAS[33,34]. Early thalamic lesions also exhibit a strong association with D/EE-SWAS[35,36], particularly in case of involvement of medial and dorsal nuclei and/or association with bilateral cortical-subcortical lesions[37,38].

Genetic studies have demonstrated the association of D/EE-SWAS with monogenic variants and copy number variations (CNVs) in 15-35% of cases[39–41]. In a recent study involving a large cohort of 91 patients a brain-specific gene co-expression analysis revealed two principal genetic clusters—one encoding ionic channels and the other transcriptional regulators—whose disruption is associated with both DEE-SWAS and EE-SWAS[42]. In the same cohort, GRIN2A emerged as the most frequently identified gene variant, accounting for 23% of cases, underscoring its significant role in D/EE-SWAS, particularly within the epilepsy-aphasia spectrum encompassing LKS[43–45].

However, despite recent advancement in aetiological investigations, a large part of cases remains without a known cause, accounting for up to 40% in recent case series[46].

The pathophysiology of D/EE-SWAS remains incompletely understood, although several potential mechanisms have been proposed. The activation of spike-wave abnormalities during slow-wave sleep, frequently accompanied by secondary bilateral synchrony, has been primarily attributed to thalamic dysfunction[47]. This central role of the thalamus in SWAS pathogenesis is further supported by evidence of early thalamic lesions, which can be associated with the development of SWAS in over 80% of cases[48]. Moreover, reductions in thalamic volume have been observed in patients with D/EE-SWAS, even in the absence of macroscopic lesions[49,50], with additional evidence suggesting the presence of microarchitectural damage[51].

A potential role for inflammation in the pathogenesis of D/EE-SWAS has also been proposed. Elevated serum inflammatory markers have been identified in patients with D/EE-SWAS, with apparent correlation between levels of interleukin-6 and disease activity[52,53].

The primary unresolved challenge remains the elucidation of the mechanisms underlying the association between SWAS and neuropsychological impairments. A prominent hypothesis posits a disruption of the physiological processes that mediate synaptic plasticity during sleep. Based on Tononi and Cirelli's synaptic homeostasis hypothesis[54], wakefulness drives a progressive increase in synaptic strength as the brain learns while adapting to environmental stimuli. During sleep, slow-wave activity (SWA) promotes synaptic downscaling in order to reduce energetic and spatial demands, optimize learning, and maintain the capacity for future plasticity. SWA itself is directly linked to synaptic strength and displays a progressive decline over the course of sleep as a reflection of synaptic weakening Experimental data supporting this hypothesis include findings of localized increases in SWA within cortical areas engaged in motor learning tasks[55].
In patients with D/EE-SWAS, disruptions in sleep homeostasis and memory consolidation have been consistently demonstrated[56]. Notably, studies have demonstrated an impairment of physiological slow-wave downscaling during sleep, with renormalization following the remission of SWAS[57]. This impairment is particularly pronounced at the site of the epileptic focus and correlates with SWI[58]. Furthermore, the disruption of slow-wave downscaling during active disease has been correlated with poorer long-term neuropsychological outcomes, suggesting its potential utility as a prognostic marker[59].

Spike-related high-frequency oscillations (HFOs) have also been identified in patients with D/EE-SWAS[60,61]. These oscillations are hypothesized to contribute to cognitive deficits by directly impairing higher-order brain functions and promoting synaptic strengthening in a counter-homeostatic manner. Moreover, HFOs have been associated with higher seizure frequency[62], as well as seizure recurrence and poorer neuropsychological outcomes following steroid treatment[63].

In conclusion, these findings mark significant progress in advancing the understanding of D/EE-SWAS pathophysiology. Although they offer evidence indicative of a potential causal relationship between SWAS and encephalopathy, they are not yet sufficient to

establish definitive conclusions. A comprehensive understanding of this disorder will necessitate the integration of developmental and network-based frameworks to address its inherent complexity.

EEG FEATURES

The EEG pattern has long been recognized as a defining feature of D/EE-SWAS, prompting extensive efforts over the years to characterize its prototypical features. However, while the originally described EEG features remain central to the characterization of the D/EE-SWAS, accumulating evidence has highlighted their variability, thereby expanding the spectrum of EEG patterns associated with this electroclinical syndrome.

During wakefulness, patients may exhibit various EEG patterns, predominantly influenced by the underlying aetiology. These patterns can range from a normal background EEG to asymmetries with focal or diffuse slowing. IEDs are frequently observed, including focal or multifocal spikes and bursts of spike-wave activity, with possible diffusion. Notably, these EEG findings may resemble those seen in patients with SeLFEs, supporting the conceptualization of these conditions as part of a shared spectrum of epileptic disorders as proposed by the latest ILAE classification[1].

During drowsiness and N-REM sleep, marked activation of spike-wave abnormalities is observed, with a characteristic slow frequency in the 1.5-2 Hz, which defines the SWAS pattern (Figure 2). In REM sleep, the SWAS pattern tends to fragment and subside, with possible reappearance of focal abnormalities. Historically, a quasi-continuous pattern occupying more than 85% of N-REM sleep was defined[4] and it was considered a mandatory diagnostic criterion[7]. However, lower SWI have been documented in association with clinical regression in numerous cases[27,64], leading to a reconsideration of this strict requirement.

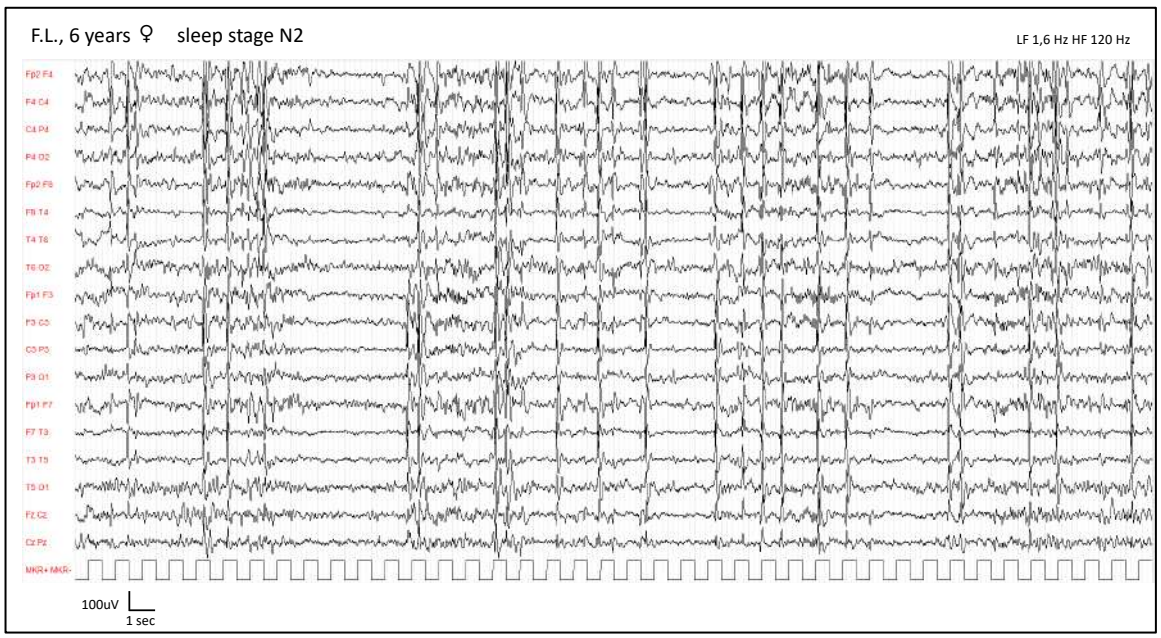

Figure 2. EEG segment from a patient included in the study showing a characteristic SWAS pattern.

In recent years, extensive research has been conducted on both quantitative and qualitative EEG parameters beyond simplistic SWI quantification[65]. Semi-automated methodologies have been introduced to extract quantitative metrics related to the evolution of spike-wave abnormalities across overnight EEG recordings[66–68].

Additionally, a key area of inquiry has been the topographic characteristics of SWAS. The prototypical EEG pattern was initially described as demonstrating widespread distribution with so-called 'secondary bilateral synchronization' (SBS)[69,70]. Subsequent studies have also provided a detailed characterization of SBS using quantitative approaches[71,72]. However, more recent findings have identified cases of D/EE-SWAS presenting with focal, multifocal, or unilateral patterns (hemi-SWAS). This has led to a recently proposed classification of SWAS patterns that includes focal SWAS and generalized SWAS (encompassing bisynchronous, focal-onset with ipsilateral diffusion, and mixed patterns)[73]. Focal SWAS, in particular, has garnered interest among proponents of a direct causal relationship between SWAS and neuropsychological symptoms[74], supported by case studies that report about selective correlations between the topographical localization of abnormalities and the associated cognitive impairments (see below in "Neuropsychological features").

SWAS resolution typically occurs around puberty, without a strict correlation to seizure remission. Following SWAS remission, a renormalization of sleep architecture is

commonly observed; however, the persistence of focal IEDs has been documented during both wakefulness and sleep[75].

Notably, SWAS undergoes natural resolution even in the absence of treatment and can thus be characterized as an age-dependent, self-limiting EEG pattern[76]. In contrast, clinical manifestations do not always exhibit full recovery, often leading to long-term disability. On the other hand, clinical features do not always show recovery, resulting in long-term disability and claiming major efforts in the investigation of neuropsychological profiles.

CLINICAL FEATURES

Seizures

Seizures are present in the majority of cases of D/EE-SWAS and may precede its clinical recognition. Age of seizure onset varies widely, ranging from 2 to 12 years, with a peak incidence observed between 4 and 5 years of age. Absences of clinical seizures has been questionably reported in rare cases[36,46], but this could be attributed to underdetection of subtle seizures by caregivers, as observed in a series of patients with LKS[70].

Semeiology and frequency of seizures show considerable variability. According to the latest ILAE guidelines there is no mandatory seizure type for diagnosis. Most patients present with focal motor seizures at onset (occasionally manifesting as status epilepticus) or, less commonly, with absences or focal to bilateral tonic-clonic seizures. Seizure patterns typically progress to include multiple seizure types, such as focal seizures with or without impaired awareness, typical and atypical absence seizures, atonic seizures, and focal motor seizures with negative myoclonus. Epileptic spasms are an exclusionary criterion, while the emergence of tonic seizures warrants careful consideration for differential diagnosis with Lennox-Gastaut syndrome.

Tassinari et al.[9] have proposed three groups, based on seizure patterns:

- Group 1: patients with rare focal motor seizures, mainly during sleep
- Group 2: patients with unilateral focal motor seizures or focal-to-bilateral tonic-clonic seizures mainly during sleep, associated with typical absences at D/EE-SWAS onset

- Group 3: patients with rare nocturnal seizures in whom atypical absences, frequently with atonic or tonic components leading to sudden falls, developed during D/EE-SWAS, after a variable period of evolution. Negative myoclonus[76] has been frequently reported during wakefulness, contributing to the development of motor impairment[77].

Seizure frequency generally increases during D/EE-SWAS. However, it demonstrates substantial variability ranging from rare occurrence in Group 1 to weekly in Group 2 and daily in Group 3.
Seizures tend to remit regardless of epilepsy severity[78], with a mean duration of approximately 12 years in historical cohorts, varying from 4 to 15 years. In 44% of cases, seizure remission was reported prior to the resolution of SWAS, concurrently with its resolution in 31%, and following its resolution in 25%.

Motor impairment

Motor abnormalities have been consistently associated with D/EE-SWAS. The most frequently reported motor disturbances include dystonia, dyspraxia, and ataxia[77,79,80], which may occasionally manifest transiently upon awakening[81]. Additionally, a possible contribution of negative myoclonus to motor impairment has also been noted.

Isolated oromotor impairment has also been documented in patients presenting with epileptiform opercular syndrome, featuring a combination of apraxic and dysarthric symptoms affecting the orofacial region[82–85]. Such manifestations have also been conceptualized as a motor variant of LKS within the epilepsy-aphasia spectrum[86].

Neuropsychological features

Since the first descriptions, great effort has been devoted to producing detailed and representative descriptions of clinical cases featuring impairments in general cognitive or specific domains, with an eye on possible clinico-pathological correlations between neuropsychological profiles and EEG focus[87]. The clinical characterization of neuropsychological profiles has become increasingly refined in parallel with the evolution

of new theoretical paradigms throughout the 20th century, reflecting a deeper understanding of the complex interplay between brain structure and function.

In this perspective, mono or bilateral temporal discharges with or without diffusion have been found in acquired epileptic aphasia, as originally described by Landau and Kleffner (hence eponymously called Landau-Kleffner syndrome, LKS). In-depth investigations about this condition have acknowledged a core deficit of high-perceptual auditory processing and phonological short-term memory leading to verbal auditory agnosia and consequent aphasia[88]. Despite relative preservation of non-verbal skills being initially defined as a hallmark of this syndrome, deficit in visuomotor integration and visuospatial perception and memory have been reported[89]. Behavioural disorders of diverse degree (oppositivity, inattention, social withdrawal, hyperactivity) can manifest primarily in LKS patients or they may stem from communicative isolation, thus being reverted by the provision of alternative means (AAC, sign language)[90].

Generalised EEG abnormalities have been associated with more global regression with behavioural and executive impairments defining an acquired epileptic dementia (or frontal syndrome), purportedly due to prefrontal involvement. Hallmark features include mood fluctuations and severe behavioural impairment. This can only partially be described in terms of ADHD (inattention, hyperactivity, impulsivity), considering the prominence of remarkable dementia-associated symptoms such as temporal disorientation, perseveration and repetitive behaviours, tangentiality, and oral exploration of objects, which highlight a striking overlap with adult frontal lobe syndrome[91]. Variable intellectual deterioration has been reported, ranging from subtle decline to massive regression, with impairment of higher verbal and non-verbal reasoning skills. On the other hand, basic perceptive, spatial and linguistic abilities are usually preserved (e.g. normal phonological-syntactic competences as opposed to semantic-pragmatic impairment)[92]. It is noteworthy that the adoption of a psychiatric point-of-view, in lieu of a strictly neuropsychological perspective, could yield different diagnostic interpretations for these behavioural disorders (see below).

Focal posterior foci affecting areas involved in sensory processing and integration have been observed in a small subset of patients featuring impairment of specific functions. In particular, deficit in object recognition (i.e. visual agnosia) has been described in patients

with predominantly left occipito-temporal SWAS with a major dysfunction of the ventral stream[93,94]. Impairment of graphomotor skills resulting in Kanji dysgraphia has also been reported in two patients showing focal SWAS on the occipito-temporal regions[95].

Finally, psychiatric cases have also been reported in association with EEG abnormalities activated by sleep. Psychotic features have been described in the context of significant cognitive and behavioural regression in patients who also showed transient but complete loss of language[96,97]. This could also be regarded as a severe instance of acquired epileptic dementia, where behavioural impairment was more prominent and/or emphasised in the description. This unexplained pervasive regression, leading to loss of communicative competences and behavioural regulation, can also be framed as a specimen of ASD-like regression, raising questions on the interplay between epilepsy and autism[98–100].

These presentations reflect a localizationist and modularist perspective that posits that cognitive functions are localised within distinct brain modules, each responsible for specific mental processes and behaviours. This conceptual framework has served as a crucial instrument in advancing the neuropsychology of epilepsy, allowing for more precise correlations between domain-specific cognitive impairments and specific epilepsy syndromes.

However, despite their historical significance and representativeness, these classical lesion-based profiles inadequately account for substantial clinical heterogeneity. Prototypical neuropsychological syndromes related to SWAS are seldom seen in clinical practice, where patients display diverse mixtures of symptoms affecting multiple neuropsychological and behavioural domains to varying degrees. Moreover, contrasting evidence has been produced about correlations between EEG focus and specific symptoms, arguing against definite localization-related neuropsychological syndromes[64,101].

On the other hand, nowadays neuropsychological phenotyping in D/EE-SWAS remains predominantly reliant on traditional prototypes and neurodevelopmental syndromes (e.g., ASD, ADHD), running the risk of oversimplification and exclusion of unexpected features. In pharmacological trials primary clinical outcomes are still largely represented by changes in full-scale IQ measures, which may fail to capture the complexity of the neurobehavioral impairment associated with D/EE-SWAS. In the RESCUE-ESES trial, an alternative metric was proposed: the cognitive sum score, a composite measure derived from z-scores

across six major cognitive domains (i.e., intelligence, language, memory, attention, visuospatial functions, and executive functions)[102]. While this measure offers a promising approach to synthesising a multi-component cognitive profile, it could inadequately reflect changes in clinical performance due to the attenuating effect of averaging the individual scores.

To the same end, an essential yet valuable way to describe and summarise clinical characteristics associated with D/EE-SWAS has been lately proposed, featuring a reduction to three main groups (pervasive, combined, selective) on the basis of the extent of cognitive functions impairment[103]. This straightforward approach, in line with IC-CODE proposals, could allow to collect and combine data on the patient's neuropsychological profile in its evolutive and fluctuating course, moving beyond prototype-based descriptions and paving the way for an enhanced integration with neurobiological data in a network-based perspective.

In this respect, the development of a refined, high-granularity taxonomy for the description of neuropsychological profiles associated with epilepsy would be crucial for enabling more precise correlations between cognitive and behavioural deficits and brain networks disruptions[104]. Indeed, ILAE and the International Neuropsychological Society (INS) have recently called attention on the lack of a consensus-based taxonomy for cognitive phenotypisation in epilepsy, and a collaborative initiative has been therefore launched in order to develop an International Classification of Cognitive Disorders in Epilepsy (IC CODE)[105]. The main goal is the harmonisation of the approach to cognitive diagnosis which must be based on a shared conceptual framework, guiding the exploration of cognitive domains and the systematic description of neuropsychological profiles[106]. Although still in its prime and currently focused only on adults, this initiative offers a new perspective and lays the groundwork for developing similar models for paediatric conditions.

LONG-TERM PROGNOSIS

The SWAS pattern is typically age-related, with remission occurring in the majority of cases before adolescence. However, the prognosis for intellectual functioning and language abilities remains highly variable. While language deficits, intellectual impairments, and psychiatric disturbances generally show improvement, most affected

children do not achieve complete recovery, particularly in areas such as verbal skills and attention[91,107]. For example, persistent deficits in verbal short-term memory have been observed in patients who have recovered from LKS[108], as evidenced by functional imaging studies demonstrating decreased activation in the posterior superior temporal gyri during immediate serial word recall tasks[109].

Residual impairments significantly affect the lives of children with D/EE-SWAS, with approximately half of the patients experiencing severe limitations in independent functioning[110].

A considerable body of research has focused on identifying factors that may influence the long-term prognosis of patients with this complex condition[111]. In particular, factors such as aetiology, age of onset, duration of SWAS, and EEG features have been extensively investigated.

Aetiological factors, when identified, significantly influence prognosis, as they define a pathological background against which SWAS exerts its additional effects. In some cases, the underlying aetiology may dominate, resulting in no clinical improvement even when the EEG pattern normalizes[112]. On these grounds, idiopathic cases have been associated with better long-term outcomes and a higher likelihood of full remission without sequelae[27,113,114]. Better outcome has also been associated with normal psychomotor development before clinical regression

Younger age at onset has been associated with scarce long-term prognosis[14,115], with worse neuropsychological outcome in children with onset before 6-8 years. In a developmental perspective, a persisting overnight damage to growing neural networks in their sensitive timeframes does not only disrupt their functions, but it may also irretrievably divert their developmental trajectories. For the same reasons, shorter duration of SWAS and greater reduction in response to therapy have been correlated with better outcome[27,116,117]. Cases with normal pre-existing psychomotor development (i.e. EE-SWAS) has also been associated with a more favourable outcome as compared with cases with DEE-SWAS[116].

EEG features have also been suggested as potential prognostic factors. A normal EEG background, generalized spikes, and a lower SWI have been associated with greater

improvement in verbal competencies during follow-up[118]. The persistence of interictal HFOs has been linked to lower IQ[63], while greater reductions in HFOs and spikes after steroid treatment have been observed in idiopathic D/EE-SWAS cases compared to those with structural aetiologies[62]. Additionally, poor long-term outcomes have been reported in association with slow EEG background at the time of D/E-SWAS diagnosis[119]. Finally, impaired slow-wave downscaling has been proposed as a prognostic factor, as discussed in the "Aetiopathogenesis" section[59].

A NEW FRAMEWORK TO ADDRESS COMPLEXITIES

D/EE-SWAS emerges as an inherently complex condition, and understanding complexities requires advanced methods for precise analysis and interpretation. Among the most promising tools emerging over the last decades, computational modelling has catalysed a paradigm shift towards an integrative approach of brain functioning based on graph theory[120]. This contemporary/breakthrough view, referred to as the network or connectome perspective, emphasises the brain's complex web of interconnected regions whose dynamic interactions underlie macroscale functions[121]. An essential component of networks are the *hubs*, key nodes playing a critical relay function thanks to their extensive connectivity and/or their strategic location at the intersection of significant fibre pathways essential for efficient network communication.

Brain networks exhibit a hierarchical organisation that can be explored through the lens of graph theory, providing different centrality measures (i.e. degree centrality, eigenvector centrality, betweenness centrality) with a focus on distinct facets of network communication (Figure 3). Consequently, analysing the community structure within the network allows for the classification of significant nodes as either *provincial hubs* or *connector hubs*, with highly interconnected core *hubs* forming an exclusive group known as *rich club*. These act as the primary conductors for signal transmission, integrating inputs from more isolated nodes with hyperspecialized functional roles[122]. This 'small-world topology', characterised by highly clustered sub-networks, promotes both modular segregation and integration by enabling widely distributed yet interconnected information processing in a hierarchical mode.

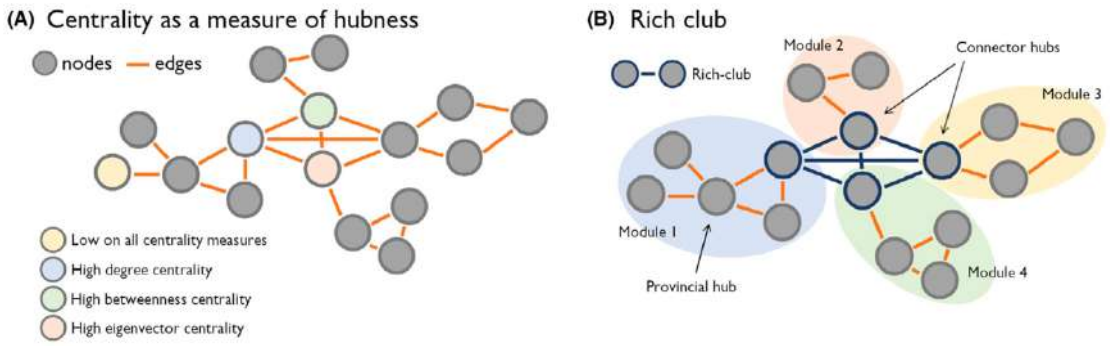

Figure 3. Network *hubs*. **A**. Characterization of network using topological parameters of a graph, comprising nodes (brain regions) and edges (connections). **B**. High-degree nodes with dense interconnections form a 'rich club' supporting information flow across peripheral nodes and modules in the network (from Royer 2022[123])

Key features of brain networks are thus represented by a genetically determined hierarchical structure which combines with elevated age-specific plasticity and significant adaptability to internal and external influences, giving rise to highly specialised functions that are optimally aligned with environmental demands. During brain development, networks are in fact structured through continuous interaction between genetic and environmental factors, following defined trajectories from small-scale to larger integrated systems, with critical developmental windows influencing their formation[124]. Emerging seminal insights are elucidating the developmental timelines of critical neural networks in the maturing brain, from early visual and sensorimotor through higher order networks[125]. In particular, during the first months of life, there emerge the Default Mode Network (DMN) and the Salience Network (SN), higher-order cortico-subcortical networks characterised by anticorrelated activity, with the DMN primarily associated with internal, self-referential processes and the SN responding to prominent external stimuli. The Control Executive Network (CEN), a fronto-parietal network crucial for complex executive functions, begins to develop later in childhood. These large, intrinsically connected networks are considered vital for cognitive and behavioural processes, thus playing a significant role in typical developmental patterns and potential deviations associated with neurodevelopmental disorders, as outlined in the triple networks model proposed by Menon[126].

Nowadays, brain networks and *hubs* can be mapped using non-invasive methods, especially neuroimaging and neurophysiological techniques that allow to investigate in-vivo structural and functional connectivity. Structural connectivity refers to anatomical pathways (mainly white matter fibre associative and commissural tracts) linking distinct brain regions and it can be documented with advanced neuroimaging techniques, including diffusion MRI tractography and co-variance analysis of morphological MRI markers. Conversely, functional connectivity refers to the temporal correlations between activity patterns in different brain regions, which reveal the lasting effects of past learning and synaptic modifications driven by Hebb's rule ("Neurons that fire together, wire together"). It can be investigated using fMRI or EEG/MEG, providing insights into dynamic network interactions during both resting-state and task-related conditions[127].

This network-based approach has enhanced our understanding of the relationship between brain activity and behaviour, as well as how dysfunctions in connectivity can underlie

disorders of brain functioning[102]. Although graph theory has primarily been applied to the study of the brain's physiological functions, this perspective could also be pivotal in advancing our understanding of the neurocognitive aspects of neurodevelopment disorders and epilepsy syndromes, allowing correlations between network connectivity metrics and quantitative measures of cognitive functions. Indeed, this approach aligns with the RDoC framework, which advocates for a neurobiological and network-based view of mental disorders and promotes the study of neuropsychological/behavioural domains through dimensions of functioning rather than mere diagnostic label[128,129].

In this context, epilepsy has been framed as resulting from the dysfunction of specific neural systems[130] and investigations in a network perspective have highlighted prominent involvement of *hub* regions, with structural and functional alterations possibly due to atypical reorganisation[123]. Although in its early stages, this research avenue has set a promising step in the direction of a more comprehensive understanding of childhood epilepsy syndromes, with potential implications for the development of more refined prognostic measures and new therapeutic tools[131].

To date, research on D/EE-SWAS has primarily focused on its distinctive features, including genetic and structural etiological factors, EEG patterns, and cognitive phenotypes, often tentatively connected through direct cause-effect relationships. Embracing a network perspective rooted in neurodevelopmental trajectories may be essential for capturing the inherent complexity of this condition as it evolves over time, thereby providing a more comprehensive point of view to "grasp the whole picture" (Figure 4).

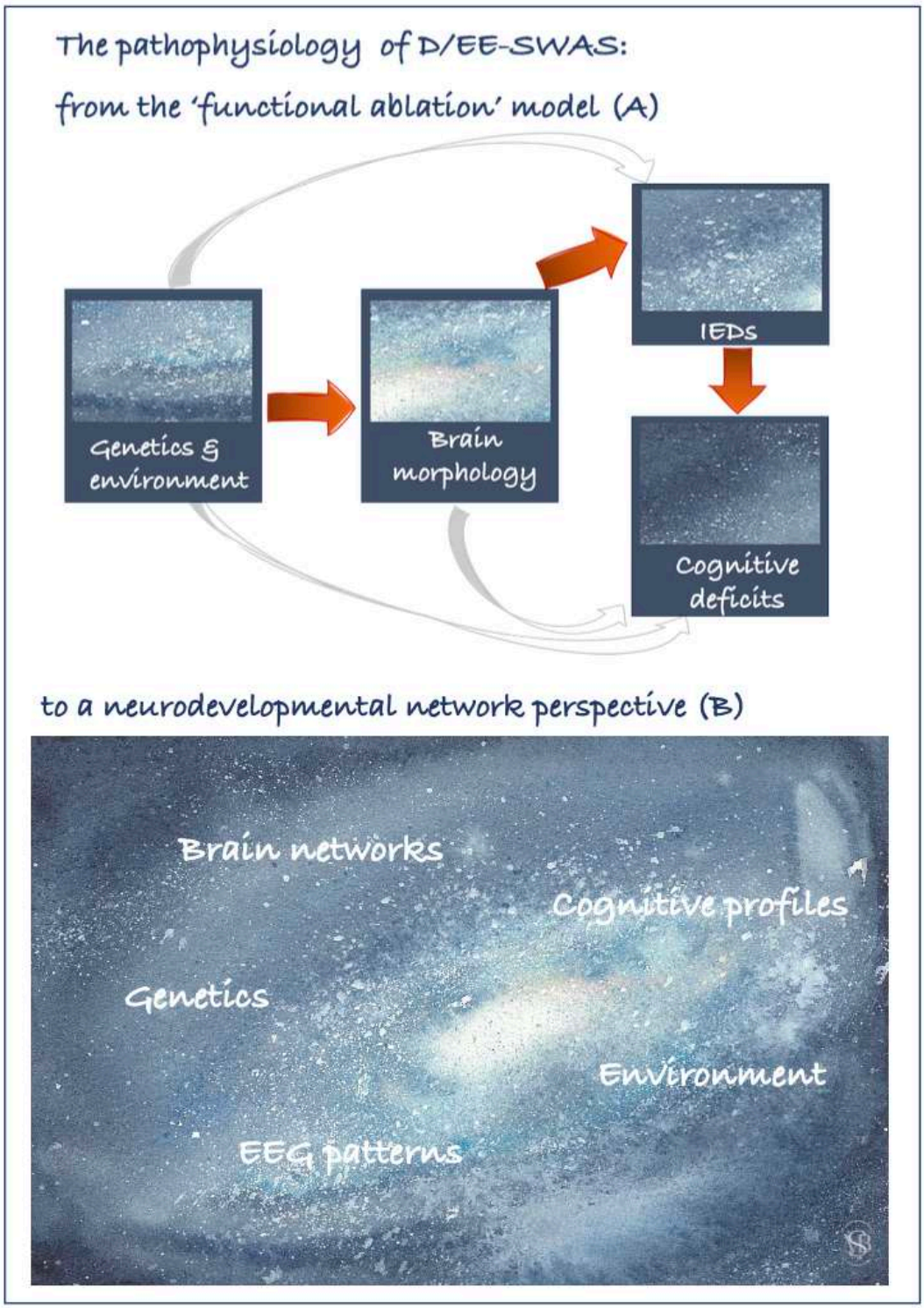

Figure 4. A. The pathophysiology of Developmental/Epileptic Encephalopathy with Spike Wave Activation in Sleep (D/EE-SWAS) has been investigated over the years through an in-depth analysis of its aetiological underpinnings and electroclinical features. The emerging "frames" have been connected in a cause-effect chain, starting from the combined influence of genetics and environment on brain morphology which in turn determines the activation of interictal epileptiform discharges (IEDs) in sleep, hence causing cognitive decline.

B. In order to "grasp the whole picture" underlying this complex condition, individual features should be re-framed and observed through a network-based perspective wherein each element contributes to the global system through multidirectional dynamics that unfold over time.

EVIDENCE IN D/EE-SWAS FROM A NETWORK PERSPECTIVE

D/EE-SWAS can be regarded as a sophisticated yet powerful model that offers a framework for understanding how brain networks are shaped during developmental phases. In particular, this model could highlight the interplay of structural and functional noxae, as well as genetic and environmental influences, which can modify developmental trajectories at various critical periods by affecting the maturation and organisation of brain networks. Analysing this complex condition through the lens of graph theory is thus highly intriguing, as it allows for a deeper exploration of how disruptions in structural and functional processes contribute to neurodevelopmental and neurocognitive disorders, providing valuable insights into the intricate dynamics of brain development and function. A substantial body of historical and widely accepted evidence suggests that network theory may provide a viable framework for the comprehension of D/EE-SWAS through the lens of neural development. Indeed, this condition features a strong and age-dependent temporal connection with the development of brain networks subserving high-order functions such as language and behaviour[110,132]. Moreover, evidence concerning genetic underpinnings corroborates this strong association, given the involvement of genes that are differentially expressed during subsequent neurodevelopmental phases. Proposed correlations between gene variants and average age of D/EE-SWAS onset could further substantiate this hypothesis, although additional evidence is required[41]. Moreover, recent research has identified a shared genetic basis underlying both DEE-SWAS and EE-SWAS[42]. This DEE-EE continuum could reflect shared underlying mechanisms that drive maladaptive interactions between neurodevelopmental and epileptogenic processes, which together shape genetically determined brain networks through their epigenetic vulnerability to environmental stimuli. Lastly, from a clinical viewpoint the onset and natural resolution of SWAS are closely tied to critical periods during which the brain demonstrates heightened plasticity and vulnerability to external stimuli that shape its structural and functional maturation. This temporal intersection can lead to dysfunctional plasticity within cortico-cortical and thalamocortical circuits, particularly through the disruption of NREM slow-wave activity, which is vital for synaptic homeostasis and network stability. Indeed, in analogy with other childhood epilepsies, the localization of epileptic foci in D/EE-SWAS exhibits an age-related posterior-anterior progression, paralleling maximal cortical thickness and slow wave activity, thereby suggesting a close association with brain maturation[59]. Moreover, when cortical structures are thus shaped by

aberrant electrical activity during these critical periods, they may become misaligned with the actual sensory environment. As these maladapted structures are then effectively "cemented" at the end of the developmental window of opportunity, they can result in long-term impairments[133].

In recent years, advanced neuroimaging and neurophysiological techniques have been therefore employed to characterise brain networks in D/EE-SWAS and to elucidate disruptions in functional connectivity, providing valuable insights into the underlying pathomechanisms[134,135].

Thalamo-cortical networks have been implicated in the etiopathogenesis of DEE/EE-SWAS, largely due to their significant role in sleep-related mechanisms and generation of IEDs[47,136] and the strong aetiological link between D/EE-SWAS and thalamic lesions[35,36]. Significant activation in thalamus has been observed in association with bilateral and generalized epileptic discharges in patients with D/EE-SWAS[137]. Moreover, altered thalamic glucose metabolism has been reported, despite the absence of a clearly defined pattern[138].

The **Perisylvian Network** has been specifically indicated as a critical component in the pathophysiology of D/EE-SWAS. Initial evidence for its involvement arose from its association with perisylvian polymicrogyria[30] as well as sporadic findings of structural abnormalities in this region in patients with LKS[139]. Subsequent support for the role of the Perisylvian Network has emerged from source reconstruction analyses[137,140–143]. These findings have provided grounds for theories positing that D/EE-SWAS exists on a spectrum continuum with SeLFEs, collectively conceptualised as a developmental disorder of the perisylvian network[144]. In this framework, epileptogenesis could be driven by derangement of sleep-related homeostatic plasticity affecting a physiological neural network during its critical developmental phase.

Disrupted activity and connectivity in the **Default Mode Network** (DMN) has been also pointed out as a potential contributory factor to cognitive dysfunctions in individuals affected by D/EE-SWAS, as already observed in various neuropsychiatric conditions including neurodevelopmental disorders[145,146]. Building on previous PET studies demonstrating metabolic changes in patients with DEE/EE-SWAS[132], a distinctive functional fingerprint has been indeed identified, characterised by hypermetabolism in

centroparietal regions, mainly co-localized with epileptic foci, and hypometabolism in DMN-related structures (including prefrontal areas, posterior cingulate cortices, parahippocampal gyrus, and precuneus), during both sleep and wakefulness[147,148]. This metabolic pattern has consequently been linked to the potential remote inhibition of the DMN[149], with further corroboration by EEG-fMRI studies demonstrating negative Blood Oxygen Level Dependent (BOLD) signal changes in DMN structures in patients with D/EE-SWAS, regardless of aetiology[137]. Remote cortical inhibition mechanisms have also been proposed as critical factors underlying reduced motor cortex excitability observed in D/EE-SWAS patients through transcranial magnetic stimulation (TMS). Notably, the resolution of these inhibitory effects appears to parallel clinical recovery (as measured by Vineland Social Maturity subscale and CBCL) and reduction in SWI after steroid treatment[150]. Ultimately, a complex network of coherent sources involving DMN structures has been demonstrated using coherence analysis applied to sleep EEGs in D/EE-SWAS patients, irrespective of the aetiology and severity of epilepsy, with resolution after successful treatment. These central *hubs* appear to direct information flow to other regions, particularly the temporal cortex where epileptic activity originates, prompting the question of whether the DMN induces changes in the epileptic network rather than the reverse[151].

Lastly, it would be of particular interest to explore the application of Menon's **triple network model** to D/EE-SWAS. In this context, a recent resting-state fMRI study on patients diagnosed with BECTS featuring SWI >85% has demonstrated reduced functional connectivity in both CEN and SN[152], providing a valuable conceptual framework that could serve as a foundation for future research.

FUTURE DIRECTIONS AND PRACTICAL CONSIDERATIONS

Future investigations on D/EE-SWAS in a network-based perspective should delve more deeply into the complex relationship between neurobiological and clinical measures.
Few studies have so far investigated correlations between neuropsychological features and functional neuroimaging data. Recent evidence has demonstrated a moderate yet significant correlation between Child Behavior Checklist (CBCL) scores, but not IQ scores, and the total number of hypometabolic brain regions identified through FDG PET-CT[153]. In a more innovative network-based approach, a resting state-fMRI study on patients with BECTS-ESES reported altered variability in functional connectivity

involving key SN structures, i.e. the anterior cingulate cortex and anterior insula, which was associated with deficits in executive function and attention[154].

Another promising avenue for future research would involve longitudinally examining alterations in functional connectivity during interictal periods, both during wakefulness and sleep, to evaluate the enduring effects on neural networks. For instance, current applications of EEG coherence analysis in D/EE-SWAS are relatively limited and have primarily demonstrated increased coherence during spike-wave epochs in D/EE-SWAS patients, which is interpreted as a manifestation of hypersynchronization[155]. Nevertheless, these methods could prove to be a valuable tool due to the extensive and readily available tracing records throughout the patients' histories, with further potential for correlation with neuropsychological measures.

From a more practical standpoint, advancing the understanding and management of D/EE-SWAS necessitates the collection of data from a network-based perspective across multiple domains, producing multimodal datasets within the same cohort of participants. Neuropsychological data must be collected using standardised and shared protocols to ensure consistency and comparability across studies, enabling more precise correlations between cognitive and behavioural deficits and brain network disruptions. To this end, a consensus has indeed been proposed to develop a shared protocol of neurocognitive tests covering major neuropsychological domains[15]. To advance beyond lesion-based models and conventional neurodevelopmental syndromes, there is a crucial need for a refined, high-granularity taxonomy for the description of neuropsychological profiles associated with epilepsy[104]. In line with the IC-CoDE framework[106], evaluation protocols for patients with D/EE-SWAS should encompass a comprehensive assessment of key domains, including language, memory, executive, visuospatial, and attention. Given their critical relevance in the developmental age, a multidimensional cognitive evaluation, with careful consideration of the patient's cognitive profile, alongside an assessment of academic, social and adaptive skills, should be routinely included as well.

Concurrently, neuroimaging and neurophysiology data should therefore be gathered with a focus on connectomics to elucidate the complex neural connections and network disruptions associated with this condition. Along with conventional and more recent quantitative EEG-derived measures (SWI, slow wave downscaling), shared protocols

should be implemented to gather comprehensive data on both structural and functional connectivity. This includes leveraging advanced MRI techniques (DTI, resting state-fMRI) to investigate the intrinsic functional networks and their potential alterations, and EEG coherence studies to identify global and local network disruptions that may underlie the pathophysiology of the disorder. Furthermore, multimodal integration of these data, including simultaneous EEG-fMRI studies, could offer a more detailed understanding of the spatiotemporal characteristics of the epileptic networks involved. Given the transient and dynamic nature of the epileptiform activity in D/EE-SWAS, it is also crucial to incorporate longitudinal neuroimaging and neurophysiological assessments, which would allow for the tracking of network changes over time.

Ultimately, genetic information is crucial to the study of D/EE-SWAS due to the significant role it plays in shaping and determining the developmental trajectories of neural networks. Incorporating genetic data can therefore provide deeper insights into the underlying mechanisms and individual variability of neural connectivity patterns.

The implementation of standardized, cross-centre data collection protocols would facilitate the creation of large, harmonized datasets, which should subsequently undergo rigorous analysis and be integrated into sophisticated models to promote a holistic understanding of this complex condition. Towards this end, the integration of artificial intelligence (AI) tools holds significant promise, particularly in leveraging the extensive datasets that encompass multimodal data and combining features from each modality through the use of algorithms. Applications of these advanced computational methods have already been underway in the epilepsy field, but also in the study of neurodevelopmental conditions and psychiatric disorders[156,157]. This emerging field of computational neuroscience represents a promising avenue for future research, particularly through the development of multiscale, data-driven brain models that integrate microscopic features into mesoscopic and macroscopic frameworks, while also incorporating task-driven models[158]. AI and the implementation of machine learning/deep learning algorithms could therefore be the key factor to bridge the existing gaps in understanding the complex interplay among the multifaceted dimensions of D/EE-SWAS, potentially guiding the development of targeted interventions and the identification of biomarkers predictive of disease progression or treatment response.

STUDY

D/EE-SWAS: Neuropsychological profiles with IC-CoDE and analysis of the functional connectivity in a two-centre cohort

STUDY OBJECTIVES

- to comprehensively describe a cohort of patients with idiopathic D/EE-SWAS (clinical, neurophysiological, neuroradiological, and genetic characteristics)

- to analyse their neuropsychological profiles through a multidomain model, inspired by the IC-CoDE framework

- to investigate functional connectivity in a subcohort of patients, with the application of Partial Directed Coherence to IEDs-free epochs of EEG recorded during phase II sleep

PATIENTS AND METHODS

Patients

The study involved patients with idiopathic D/EE-SWAS followed at two neuropediatric centres in Milan: Fondazione IRCCS Istituto Neurologico "Carlo Besta" and Ospedale dei Bambini "Vittore Buzzi". These patients have been selected among patients with an established diagnosis of D/EE-SWAS or with clinical suspicion of D/EE-SWAS, followed in both ward and outpatient care units in the last 11 years (starting from 2014 up to the end of 2024). We identified a total of 28 patients which have been included in the study, of whom 1 has already been described previously (in a published original article by Siri et al.[159]).

Inclusion criteria are as follows:

- diagnosis of DEE-SWAS or EE-SWAS reflecting the ILAE diagnostic criteria, namely:
  a) slow (1.5–2 Hz) spike-wave abnormalities in N-REM sleep, markedly activated in sleep
  b) cognitive, behavioural, or motor regression or plateauing temporally related to SWAS on EEG
- absence of structural abnormalities at brain MRI
- availability of comprehensive neuropsychological data obtained at the time of maximum disease activity (clinical nadir)

Clinical evaluation

All patients have undergone detailed clinical examination at disease diagnosis, carried out by neuropediatricians expert in epileptology. Data concerning clinical history have been collected, including: gender, family history for epilepsy and neurodevelopmental disorders, psychomotor development before D/EE-SWAS onset (to discriminate between DEE and EE), neurological examination, age at first seizure and seizure semiology, age at the onset of cognitive/behavioural/motor regression and features of regression (as indicated in medical records), antiseizure medications, follow-up duration. Each patient underwent 1-11 neuropsychological evaluations (mean: 3.5).

EEG studies, including at least one overnight sleep registration, was performed in all patients to confirm SWAS at the time of diagnosis. EEG was recorded by scalp electrodes placed over the scalp according to the 10–20 International system. No quantitative measures have been used to establish D/EE-SWAS diagnosis, in line with recent ILAE recommendations. EEG recordings obtained during periods of maximum disease activity were collected and systematically reviewed. The analysis focused on key features, including background activity, spike-eave and slow-wave activity during wakefulness, SWAS distribution, and the presence of sleep spindles. The main lateralization and main localization on an anterior-posterior axis of abnormalities was determined by integrating these findings.

Aetiological investigations were carried out including brain MRI to exclude structural lesions. Genetic tests were also executed (including array CGH, NGS panels for epilepsy-related genes, WES).

All patients have been periodically evaluated through clinical, neuropsychological and EEG assessments in order to monitor the response to antiseizure and immunosuppressive therapy and possibly consider the need for treatment adjustments.

Neuropsychological study

All participants underwent at least one comprehensive neuropsychological assessment during the period of maximum disease activity, as per the inclusion criteria. Time of maximum disease activity was defined as the period of greatest clinical regression in association with SWAS.

Additionally, when available, neuropsychological data obtained prior to the onset of cognitive, behavioural, or motor regression were collected to better characterize neurodevelopmental trajectories.

Follow-up neuropsychological evaluations have been collected to define long-term outcome (for patients with at least one year of follow-up after nadir), which was categorized as follows:

- 0 = normal cognition
- 1 = mild deficit (learning disorder, ADHD, mild behavioural disorder)
- 2 = severe deficit (ID, severe behavioural disorder, severe language difficulties/minimal verbal language)

The neuropsychological test batteries employed varied significantly to accommodate the diverse ages of participants. These batteries predominantly included assessments of:

- Psychomotor development: Griffiths-R, Griffiths-III
- Multidomain cognitive skills: Wechsler scales (WPPSI-III/IV, WISC-IV, WAIS-IV)
- Non-verbal cognitive skills: Raven Progressive Matrices, Leiter-R, Leiter-3
- Executive functions: selected subtest from NEPSY-II, and BVN 5-11/12-18 batteries
- Language skills: BVL 4-12

To synthesize these heterogeneous data and facilitate the characterization of syndromic profiles at the time of maximum disease activity, a multidomain framework was adopted. This approach was inspired by IC-CoDE, a recent initiative aimed at developing and validating a harmonized cognitive taxonomy for epilepsies. Within this framework, five cognitive domains have been selected by field experts: Language, Visuospatial ability, Executive Function, Memory, Attention/Processing Speed. For each domain, a limited number of specific cognitive abilities has been identified together with requisite core test characteristics. Standardized scores based on demographically corrected normative data are used to determine the presence or absence of deficits in each domain. Appropriate threshold for impairment should be identified for each study population after examination of multiple cutoffs. Domains with 2 or more impaired test are then defined as “impaired”, while those with 0 or 1 impaired test scores are classified as “intact.” Based on the number

of impaired cognitive domains, patients are then classified into different phenotypes ranging from cognitively intact to generalized impairment.

Since no IC-CoDE guidelines for the paediatric age have been thus far published, the five original cognitive domains have been retained in this study, and suitable tests were selected to evaluate the presence of impairment. Specifically:

- Language: Verbal Comprehension subtests (Wechsler scales), Naming test, Comprehension test
- Visuospatial: Matrices, Block Design test, Rey-Osterrieth Complex Figure
- Executive: Tower of London, Phonemic/Semantic Fluency
- (Working) Memory: Digit Span backwards, Letter Number Sequencing, Corsi Test backwards
- Attention/Processing speed: Cancellation test, Symbol Search test, Digit Symbol Substitution test, Auditory and Visual Attention tests

The Memory domain was further refined to specifically focus on Working Memory, due to its critical importance in the developmental age.
To allow for the inclusion of younger children who had been tested with developmental scales, measures of Language and Visuospatial competencies were derived from Griffiths' scales and classified as intact or impaired based on the single scales' standard score.
In cases where formal assessment of attention was unavailable or infeasible due to significant impairments, data from direct clinical observations by experienced child neuropsychologists were utilized.
Data concerning these five domains, if available, were used to classify each domain as intact or impaired using three different thresholds (-1.0 SD, -1,5 SD, and -2.0 SD).
Phenotype classification has been implemented following IC-CoDE: cognitively intact (0 = no domains impaired), single domain impairment (1 = one cognitive domain impaired), bi-domain impairment (2 = two cognitive domains impaired), or generalized impairment (≥3 = three or more cognitive domains impaired). Based on previously published IC-CoDE guidelines[106], cognitive phenotypes were generated for all patients who had available data for at least two cognitive measures within at least four of the five domains.

In the context of D/EE-SWAS, Behavior and Motor domains hold critical importance. Consequently, data from clinical records and standardized assessments (parents/teachers' questionnaires as CBCL and Conners' Rating Scales for the Behavior domain; Movement-ABC 2 and APCM-2 for Motor domain) were used to determine the presence or absence of impairment in these domains. A dichotomic score was therefore assigned: 0 = intact; 1 = altered.
Cognitive phenotypes were then delineated using five domains: Language, Visuospatial, and Attention domains (using the -1,5 SD threshold) as well as Behavior and Motor. Executive and Working Memory domains were not included, due to insufficient data (particularly for younger patients). However, impairment in the domain of Attention was usually observed alongside deficits in these two domains, and it was therefore deemed sufficiently indicative of global executive dysfunction.

In order to provide a more detailed classification of impairment (for Language, Visuospatial, and Attention domain), a four-point scale was also developed as follows: 0 = no impairment; 1 = 2 or more impaired tests at -1.0 SD; 2 = 2 or more impaired tests at -1.5 SD; 3 = 2 or more impaired tests at -2.0 SD.
Cluster analysis was utilized to identify clinical subgroups within the patient cohort based on neuropsychological data. Initially, an analysis was performed using a three-domain model comprising Language, Visuospatial skills, and Attention, with impairment severity categorized according to the previously described four-point scale. Subsequently, a second cluster analysis was conducted, incorporating the Behaviour and Motor domains. The additional contribution of these domains to the definition of clusters was then evaluated.

Connectivity study

Subjects

The study involved a total of 27 subjects: 13 D/EE-SWAS patients (8 females, mean age: 6.7±2.8 years) and 14 age-matched healthy controls (8 females, mean age: 7.3±1.4 years) referred to the Fondazione IRCCS Istituto Neurologico "Carlo Besta" in Milan and Ospedale dei Bambini "Vittore Buzzi".
The patients underwent diagnostic EEG recordings at the time of maximum disease activity (clinical nadir). At the time of EEG recording, 4 patients were not receiving any

pharmacological treatment, whereas the remaining 9 patients were taking ASMs (including VPA, ETS, CLB, STM, TPM and BRV, in different combinations).

EEG acquisition

For all subjects, EEG was acquired during early afternoon nap (8 subjects) or nocturnal sleep (5 subjects) at the time of maximum disease activity. Recordings were made using 19 Ag-AgCl electrodes placed according to the International 10-20 System with a common reference, with a sampling rate of 256 Hz.

Signals acquired during the stable phase II sleep were analysed. Two experienced neurologists selected artifact-free and IEDs-free epochs lasting at least 2 seconds each for analysis and agreed on the selection (see example in Figure 5).

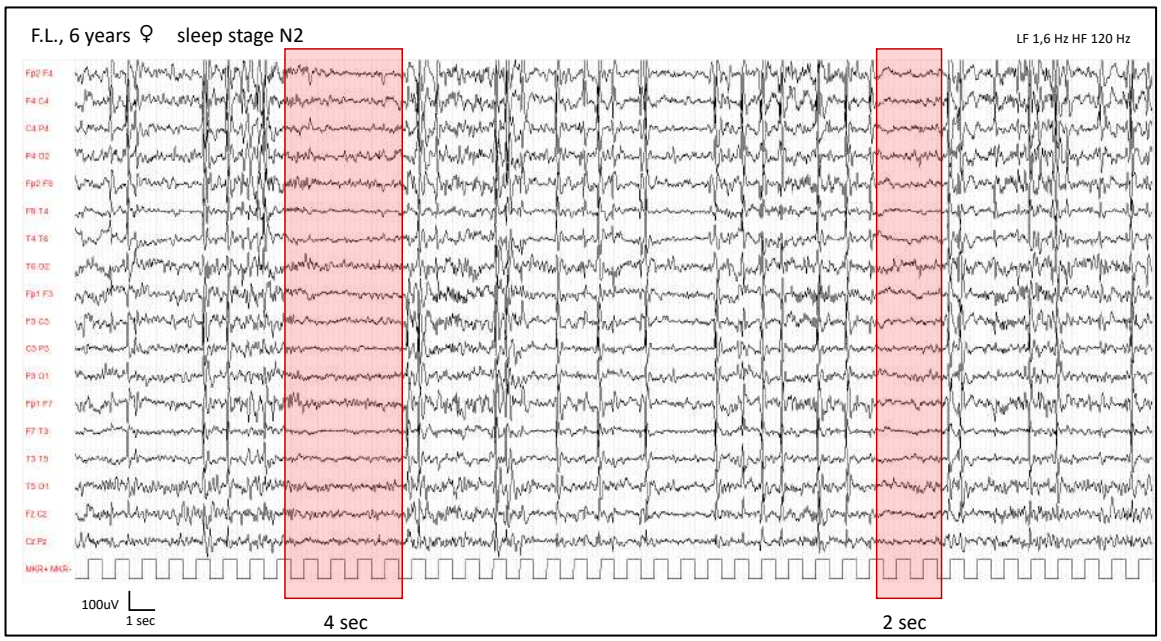

Figure 5. EEG segment from a patient included in the study showing a characteristic SWAS pattern. IEDs-free epochs during stable phase II sleep selected for PDC analysis are highlighted (red).

EEG analysis

In order to ensure reference-free and spatially accurate data, a surface Laplacian estimate was applied to the EEG channels[160]. Next, the EEG data were normalized by subtracting the mean value and dividing the result by the standard deviation and were then then divided into nonoverlapping 2-second epochs. Sixteen channels (Fp2, F4, C4, P4, O2, F8, T4, T6,

Fp1, F3, C3, P3, O1, F7, T3 and T5) and 5 canonical bands (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-13 Hz, beta: 13-30 Hz, gamma: 30-40 Hz) were selected for spectral and functional connectivity (FC) analyses.

For the spectral analysis, the Fast Fourier Transform (FFT) was applied to each 2-second segment of EEG data windowed using a Hamming window to reduce spectral leakage. The power spectral density (PSD) for each frequency band was computed by averaging the squared magnitude of the FFT over the relevant frequency range. Relative power within each of the canonical frequency bands was calculated by dividing the power within each band by the total power of the signal across all frequencies (1-40 Hz). This normalization allows for comparisons of power across individuals.

Connectivity analysis by Partial Directed Coherence (PDC) and connectivity indices were calculated in 5 canonical bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-40 Hz). Statistical significance of PDC values in each frequency band was assessed by a bootstrap approach with phase randomization, applied based on Theiler's method[161,162].

To allow comparison of the topological properties of the network between subjects and to ensure that the proportion and overall spatial distribution of connections between brain regions were similar between subjects, the total degree of the graph must be the same. For each band, we then defined a fixed threshold defined as the minimum number of connections needed to ensure a fully connected graph for each subject and each population and then selected the maximum of these values as the optimal common threshold. To study the regional properties of the network, we calculated the following connectivity indices: out-degrees, in-degrees, out-strength, in-strength, clustering coefficient (CC) and betweenness centrality (BC) at the node level, considering each EEG electrode as a node[163]. Out/in-degree are the number of efferent/afferent connections to the node (electrode) and measures the centrality of a node in the network. Out/in-strength refers to the magnitude of the outgoing/incoming connections from/to a specific node. The clustering coefficient measures how interconnected a node's neighbours are within the network; a high clustering coefficient suggests that a node is part of a dense, tightly interconnected group of regions implying a more synchronized or specialized local network structure in brain activity. Betweenness centrality measures the importance of a node in mediating connections between other nodes, facilitating the flow of information

between other nodes; a high betweenness centrality indicates that a node occupies a strategic position in the network, functioning as *hubs* for global communication.

The signals were pre-processed and analysed using a custom-written toolbox in MATLAB (MathWorks Inc., Natick, MA, U.S.A.) containing modified functions from Biosig[164] and ARFIT[165].

Statistical analysis

Neuropsychological study

To classify clinical groups according to the neuropsychological scores, a two-step cluster analysis with Schwarz's Bayesian Criterion was performed. The analysis employed a hierarchical clustering algorithm for the pre-clustering step and a k-means algorithm for the final clustering. The differences between the resulting clusters were tested using Pearson's chi-squared test and ANOVA or Kruskall-Wallis test, if the normality of the data can not be assumed.

Connectivity study

Personal data and analysis parameters were analysed using an independent samples Student t-test. Prior to conducting the t-test, we assessed the assumption of homogeneity of variances using Levene's test.

FC indices data were evaluated separately for each frequency band (delta, theta, alpha, beta and gamma) and for each index (out and in-degree, out and in-strength, BC, CC) by repeated-measures ANOVA (rmANOVA) using the with-in factor for each electrode (ELEC: Fp2, F4, C4, P4, O2, F8, T4, T6, Fp1, F3, C3, P3, O1, F7, T3 and T5) and the between factor for the patient group (GROUP: CTRL, ESES). The sphericity hypothesis was evaluated using Mauchley's test and Greenhouse-Geisser degree of freedom correction was applied when appropriate.

When RMANOVA showed a significant main effect or interaction, post-hoc pairwise comparisons were conducted using Tukey's Honest Significant Difference (HSD) test to explore the effect of electrode location within each group and the differences between patient groups at each electrode, using the Bonferroni correction to multiple comparison.

Correlation between FC indexes and neuropsychological scores were performed by Spearman correlation.

All statistical analyses were performed using SPSS 28 with significance set at $p<0.05$.

RESULTS

28 patients diagnosed with idiopathic D/EE-SWAS at the two centres in the 2014-2024 period have been identified. The gender composition of the sample comprised 12 males (43%) and 16 females (57%). A positive family history for epilepsy was identified in 8/28 subjects (29%), while family history for NDDs, such as DLD and specific learning disorder, was found in 3/28 (11%), with one subject exhibiting a family history for both epilepsy and NDDs.

Early psychomotor development was reported as typical in 22/28 subjects (79%) who subsequently received a diagnosis of EE-SWAS. The other 6/28 subjects (21%) exhibited developmental delay and were therefore diagnosed with DEE-SWAS. Among these, five patients presented with mild delay mainly limited to the language domain, while one patient had a history of moderate psychomotor delay associated with ASD traits.

Neurological examination was largely unremarkable, with the exception of macrosomia observed in 1/28 subjects (4%) and abnormalities in head circumference, including microcephaly in 1 subject (4%) and macrocephaly in 2 subjects (8%).

Aetiological investigations

All patients underwent brain MRI which yielded normal findings, except for mild ventricular dilatation observed in two subjects.

Genetic screening was performed in 20/28 patients (71%) and identified presumed disease-causing gene variants/CNVs in 4 individuals (20%). Two patients (10%) harboured a pathogenetic variant in GRIN2A, which in both cases was inherited from a parent with a history of seizures and/or DLD. In one patient (5%) a CACNA1A variant was identified which was paternally inherited and present in a sibling. Notably, the variant co-segregated with epilepsy and NDDs in all family members who carried it. Additionally, one patient (5%) was found to carry a microduplication in the 15q13.3 region encompassing the CHRNA7 gene, with a likely contributory role in the pathogenesis of the patient's epileptic condition.

EEG features

EEG recordings conducted recordings at the time of maximum disease activity were analysed. Normal background activity was evident in all patients. Focal or multifocal IEDs, predominantly with spike-wave morphology, were detected during wakefulness across the entire patient cohort. Focal left CT abnormalities were observed in 3/28 patients (11%), with one case showing a tendency for contralateral propagation to homotypic regions. Right CT foci were identified in 7/28 patients (25%), with contralateral spread observed in three of these cases. Multifocal abnormalities were present in 18/28 patients (64%), with propensity for diffusion and synchronization in five cases. Multifocal IEDs predominantly involved bilateral CT regions in 8 patients, frontal regions in 5 patients, and posterior regions in 2 patients. Abnormal foci of slow-wave activity were noted in 15/28 patients (54%), frequently co-localized with focal IEDs (4 left CT, 7 right CT, 2 bilateral frontal, 1 right frontal, 1 bilateral occipital). Sleep spindles were recorded in most of the cohort patients (23/28, 82%).

During sleep, diffuse SWAS was observed in 25/28 patients (89%), either with symmetric amplitude across the hemispheres (10 cases) or with asymmetric amplitude (8 right>left, 7 left>right). The remaining 3 patients exhibited hemi-SWAS restricted to the right hemisphere. Near-continuous SWAS was identified in 7/28 patients (25%), with diffuse involvement. Mean age at first SWAS detection was 5 years and 1 month (range: 2 years-8 years and 5 months). Age at first SWAS detection was not significantly different between patients with EE-SWAS and patients with DEE-SWAS.

Main lateralization of abnormalities was found in 20 patients (8 left, 11 right), while 9 patients featured equal involvement of both hemispheres. Main localization on an anterior-posterior axis was found in 27 patients (6 anterior, 18 central, 2 posterior), while it was not identifiable in 2 patients with multifocal abnormalities.

Seizures

Epileptic seizures were reported in 26/28 patients (93%). Mean age at epilepsy onset was 4 years and 7 months (range: 2 years–7 years and 10 months). The majority of patients

experienced focal seizures (24/26, 92%), which were the only seizure type in 10/24 subjects (42%). Other seizure types included generalized seizures, absences, negative myoclonus, and non-convulsive status epilepticus. Most patients (21/26, 81%) exhibited a low seizure frequency at the time of maximum disease activity, with less than one episode per month, primarily occurring during the onset period. In contrast, a higher seizure frequency was observed in the remaining patients, with one patient experiencing monthly episodes, one reporting weekly seizures, and three demonstrating daily or multiple daily episodes.

Two subjects never showed overt seizures and EEG study was prompted by cognitive/behavioural/motor regression (one patient exhibited ADHD symptoms and dyspraxia, while the other displayed behavioural and affective regression).

In 13/26 (50%) patients, epilepsy onset preceded first SWAS detection. Eight of these patients had received a definite epileptic syndrome diagnosis prior to evolution towards EE-SWAS (3 SeLECTS, 3 SeLEAS, 1 CAE, 1 EMAtS), while the others had received a provisional diagnosis of "atypical focal epilepsy". Mean duration of epilepsy prior to SWAS detection was 7 months (range: 1 month–1 year and 7 months). In 10/26 patients (38%) seizure onset and first SWAS detection coincided. 3 out of 26 subjects (8%) presented with a first overt epileptic seizure within 6 months from the first identification of SWAS.

Cognitive/behavioural/motor regression

Mean age at first clinical symptom of regression was 5 years and 1 months (range: 2 years and 6 months – 11 years). For 6/28 (21%) patients regression onset coincided with first seizure. 14/28 (50%) displayed symptoms of cognitive/behavioural/motor regression after first seizure (mean interval 1 year and 2 months, range: 3 months – 4 years), while 6/28 patients had presented with a first epileptic seizure after the onset of regression (mean interval 11 months, range: 2 months – 2 years and 3 months). Age at first clinical symptom was not significantly different between patients with EE-SWAS and patients with DEE-SWAS.

In our cohort, behavioural issues were the main neuropsychological symptom at D/EE-SWAS onset 11/28 patients (39%), who presented with emotional dysregulation, aggressive conducts and difficulties in interpersonal interactions. Caregivers reported

symptoms of inattention and/or hyperactivity at onset in 12/28 patients (in 8 associated with behavioural disturbances), while isolated learning difficulties were identified in 4/28 patients (14%). Language deterioration was noted in 7/28 patients (25%), including three cases presenting with acquired aphasia. Of these, two exhibited verbal auditory agnosia and were diagnosed with LKS, while one demonstrated mixed anarthria-aphasia. Two patients (2/28, 7%) with previously diagnosed developmental delay exhibited a stagnation and/or deterioration in skills previously acquired.

Motor dysfunctions were observed in the course of D/EE-SWAS in 14 patients (50%), manifesting as clumsiness or dyspraxia in nine cases (two of which included loss of previously acquired handedness), orofacial apraxia with drooling in one case, stagnation or regression in motor skill acquisition in two cases (1 associated with unilateral fine distal tremor), and dystonia and negative myoclonus in one case.

Throughout the progression of D/EE-SWAS, various combinations of cognitive, behavioural, and motor disturbances were evident in the study population, particularly pronounced during the peak of disease activity (or nadir).

Mean age at the time of clinical nadir was 6 years and 4 months (range: 2 years and 7 months – 13 years and 8 months). Time at maximum disease activity immediately preceded corticosteroid administration for all patients who underwent immunomodulatory therapy.

Mean time from disease onset (first clinical symptom, either seizure or regression) to clinical nadir was 1 year and 9 months, ranging from cases of apparently concomitant onset and nadir (7 patients) to a maximum of 6 years and 9 months.

First detection of SWAS coincided with clinical nadir in 5/28 patients, while for other patients apparent SWAS duration to clinical nadir was had a mean of 1 year and 7 months (range: 1 month – 5 years and 5 months).

Cognitive evaluations with Wechsler scales were possible in 18/28 (64%) patients and yielded a mean full score IQ of 83 (range: 51-118; IQ >85: 50%, IQ 70-85: 22%, IQ <70: 28%). 7/28 (25%) patients underwent developmental evaluations with Griffiths scales revealing a mean Developmental Quotient of 59 (range: 43-93). 3/28 (11%) with acquired aphasia underwent non-verbal cognitive assessment, which showed normal functioning.

In 11/28 patients (39%) with a prior cognitive evaluation available for comparison, an average decline of 21 IQ points was observed.

The neuropsychological profile characterizing this phase is the focus of the detailed neuropsychological study (see below).

Therapy

In our cohort population, an average of 2.9 ASMs per patient (range: 1–6) was used, including clobazam (CLB), ethosuximide (ETS), valproate (VPA), levetiracetam (LEV), sulthiame (STM), lamotrigine (LTG), topiramate (TPM), brivaracetam (BRV), and carbamazepine (CBZ). Immunomodulatory therapy with corticosteroid was implemented in 15/28 patients (54%), either with oral hydrocortisone (8/15, 53%) or cycles of intravenous methylprednisolone (7/15, 47%). One patient diagnosed with LKS who was unresponsive to corticosteroid therapy received treatment with intravenous immunoglobulins (IVIg), resulting in electroclinical improvement.

Follow-up

Follow-up was available for 27/28 patients (96%), with at least one neuropsychological evaluation for 19/27 patients (70%). Mean follow-up duration from the time of maximum disease activity was 4 years (range: 7 months – 9 years and 5 months).
SWAS resolution with EEG renormalization was achieved only in 6/28 patients (21%).
Cognitive evaluations with Wechsler scales at last follow-up were available for 14/28 (50%) patients and yielded a mean full score IQ of 88 (range: 64-116; IQ >85: 50%, IQ 70-85: 36%, IQ <70: 14%). 10 patients showed an increase in IQ as compared to clinical nadir (mean 18 points), while 2 patients featured a decline (mean 11 points). One patient with LKS, who had previously undergone a non-verbal cognitive assessment, was now able to undertake an evaluation with WISC-IV, indicating overall intellectual functioning within the average range (full score IQ 87).

Outcome measures were derived for patients with at least 1 year of follow-up from the time of maximum disease activity (25/28, 90%). For these patients mean duration of follow-up was 4 years and 4 months (range: 1 year and 4 months – 9 years and 5 months). Three out of 25 patients (12%) showed complete recovery and normal adaptive functioning. Mild deficits were observed in 15/25 patients (60%), while severe deficits persisted in 7/25 patients (28%).
Outcome groups were not significantly different for age of first clinical symptom and age of first SWAS detection. No correlations were found between clinical outcome and localization of epileptic abnormalities.

Gender	12 M/16 F
Developmental delay (DEE)	6 (21%)
Aetiology	
Genetic analysis	20 (71%)
Genetic diagnosis	4 (GRIN2A in 2 pts, CACNA1A in 1 pt, 15qdup in 1 pt)
EEG features	
IEDs in wake	Focal 10, multifocal 18
Focal slow activity	15 (54%)
SWAS	Diffuse 25, hemispheric 3
Age at first SWAS detection	5 y 1 mo (2 y – 8 y 5 mo)
Main lateralization	Left 8, right 11, not identifiable 9
Main localization (ant/post)	Anterior 6, central 18, posterior 2, not identifiable 2
Seizures	
Presence	26/28 (93%)
Types	Focal (24), generalized (7), absences (5), negative myoclonus (1), atonic (1), SE (4: 2 focal, 1 CSE, 1 NCSE)
Frequency	Sporadic (21), monthly (1), weekly (1), daily/multiple daily (3)

Therapy	
ASMs	CLB (27), ETS (17), VPA (16), LEV (8), STM (4), LTG (2), TPM (1), BRV (1), CBZ (1)
Immunomodulatory treatment	Steroid 15 (8 oral hydrocortisone, 7 methylpredisolone i.v.), IvIG 1
Clinical regression	
Age at first symptom	5 y 1 mo (2 y 6 mo – 11 y)
Main symptom	Behavioural issues (39%), ADHD symptoms (43%), learning difficulties (14%), language deterioration (25%), developmental stagnation (7%)
Clinical nadir	
Age at clinical nadir	6 y 4 mo (2 y 7 mo – 13 y 8 mo)
IQ at clinical nadir	83 (51-118)
Follow-up	
Time from clinical nadir	4 y (7 mo – 9 y 5 mo)
Outcome	Complete recovery (3), mild deficit (15), severe deficit (7)

Table 1. Main characteristic of the patient cohort; age and follow-up duration are expressed as: mean (range).

Neuropsychological study

A study of the neuropsychological profile was conducted for all 28 patients on data from evaluations performed around the time of maximum disease activity

The application of a multidomain model encompassing 5 domains (Language, Visuospatial, Executive, Working Memory, Attention) was performed with the application of three different thresholds (-1.0 SD, -1,5 SD, and -2.0 SD) (Table 2).

Pt	- 1,0 SD					- 1,5 SD					- 2,0 SD				
	Lang	Vis	Exe	WM	Att	Lang	Vis	Exe	WM	Att	Lang	Vis	Exe	WM	Att
1	D	I	NA	D	D	D	I	NA	D	D	D	I	NA	I	I
2	I	D	D	D	D	I	I	D	I	D	I	I	I	I	D
3	D	I	D	D	D	D	I	D	D	D	D	I	D	D	I
4	D	I	NA	D	D	D	I	NA	D	D	D	I	NA	D	D
5	I	D	NA	I	I	I	D	NA	I	I	I	I	NA	I	I
6	D	D	NA	NA	D	D	I	NA	NA	D	D	I	NA	NA	I
7	D	D	NA	NA	D	D	D	NA	NA	D	D	D	NA	NA	D
8	D	D	I	I	D	I	I	I	I	I	I	I	I	I	I
9	I	I	I	D	D	I	I	I	I	D	I	I	I	I	I
10	D	D	D	D	D	D	D	D	D	D	I	D	D	D	D
11	D	D	NA	NA	D	D	D	NA	NA	D	D	D	NA	NA	D
12	I	I	D	D	D	I	I	I	D	D	I	I	I	I	I
13	D	D	NA	NA	D	D	D	NA	NA	D	D	D	NA	NA	D
14	D	D	NA	NA	D	D	D	NA	NA	D	D	D	NA	NA	D
15	D	I	NA	NA	D	D	I	NA	NA	D	I	I	NA	NA	D
16	D	D	NA	NA	D	D	D	NA	NA	D	D	I	NA	NA	D
17	D	D	NA	D	D	D	D	NA	D	D	I	D	NA	I	D
18	D	I	NA	NA	D	D	I	NA	NA	I	D	I	NA	NA	I
19	D	I	I	NA	D	I	I	I	NA	D	I	I	I	NA	D
20	I	I	NA	NA	D	I	I	NA	NA	D	I	I	NA	NA	D
21	D	I	D	I	I	I	I	I	I	I	I	I	I	I	I
22	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
23	I	I	I	I	D	I	I	I	I	I	I	I	I	I	I
24	D	D	D	D	D	D	D	I	D	D	D	I	I	D	D
25	D	I	I	D	D	D	I	I	D	D	I	I	I	I	I
26	D	I	I	I	I	D	I	I	I	I	I	I	I	I	I
27	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
28	I	I	D	D	D	I	I	I	D	D	I	I	I	I	D

Table 2. Codification of neuropsychological data across five domains (Language, Visuospatial, Executive, Working Memory, Attention) using three different thresholds. I = intact, D = deficient, NA = not available

For 19/28 patients (68%) data for at least four domains were available and cognitive phenotypes were hence derived (Figure 6).

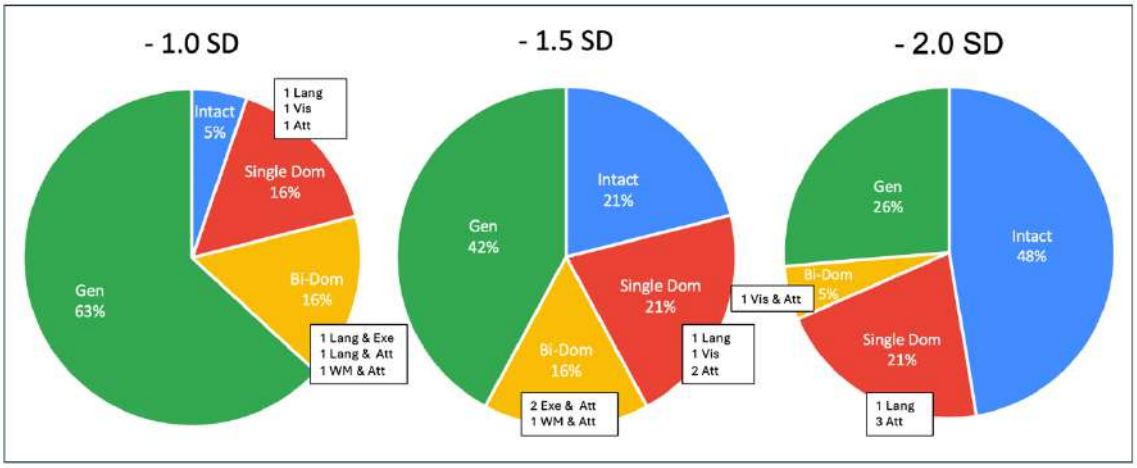

Figure 6. Cognitive phenotypes derived from data in Table 2, with impairment degree classified as Single-Domain, Bi-Domain or Generalized (if ≥ 3 domains are involved).

All 28 patients had complete data for Language, Visuospatial and Attention domains. When an intermediate cut-off was adopted (- 1.5 SD), Language domain was impaired in 17/28 patients (61%), Visuospatial domain in 10/28 patients (36%), and Attention in 21/28 (75%) (Figure 7A). Specifically, 9/28 patients (32%) presented tri-domain impairment, 6/28 patients (22%) showed bi-domain impairment (all have combined Language and Attention impairment), while 9/28 (32%) patients had mono-domain impairment (6 Attention, 2 Language, 1 Visuospatial). Additionally, 4 out of 28 patients (14%) showed no apparent impairment across the domains. (Figure 7B)

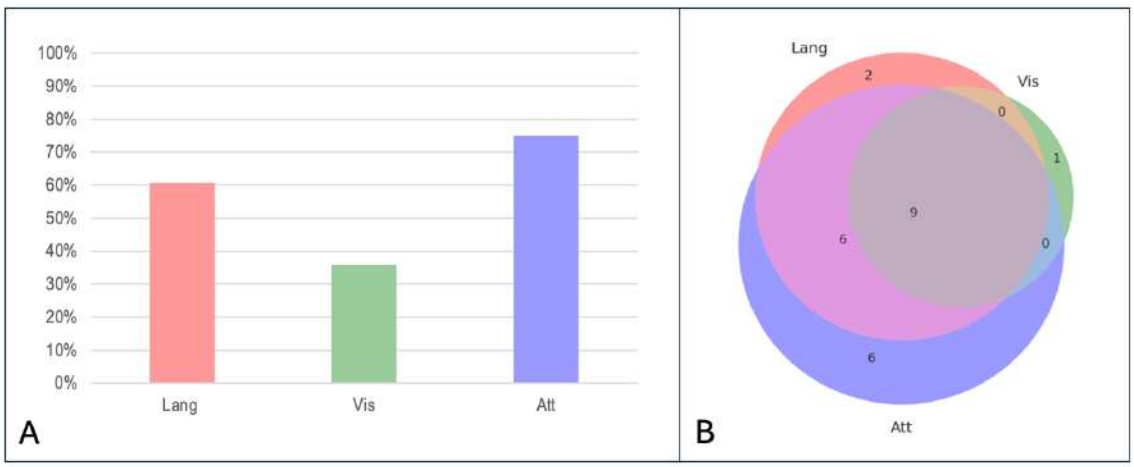

Figure 7. **A.** Impairment of Language (Lang), Visuospatial (Vis) and Attention (Att) domains in the study cohort. **B**. Distribution of cognitive phenotypes showing either single-domain, bi-domain or generalized impairment.

Clinical data regarding Behavior and Motor domains were available for all 28 patients. Impairment in the Behavior domain was present in 21/28 patients (75%), while Motor domain was affected in 14/28 (50%).

A cognitive phenotype was then derived for all patients using five D/EE-SWAS-related domains: Language, Visuospatial, and Attention domains (using the -1,5 SD threshold) as well as Behavior and Motor. (Table 3 and Figure 8)

Pt	Lang	Vis	Att	BV	Mot
1	D	I	D	D	D
2	I	I	D	I	I
3	D	I	D	I	I
4	D	I	D	D	I
5	I	D	I	I	I
6	D	I	D	D	D
7	D	D	D	D	D
8	I	I	I	I	D
9	I	I	D	D	I
10	D	D	D	I	I
11	D	D	D	D	D
12	I	I	D	D	D
13	D	D	D	D	D
14	D	D	D	D	D
15	D	I	D	D	D
16	D	D	D	D	D
17	D	D	D	D	D
18	D	I	I	D	D
19	I	I	D	D	D
20	I	I	D	D	I
21	I	I	I	I	I
22	D	D	D	D	I
23	I	I	I	D	I
24	D	D	D	D	I
25	D	I	D	D	D
26	D	I	I	I	D
27	I	I	I	D	I
28	I	I	D	D	I

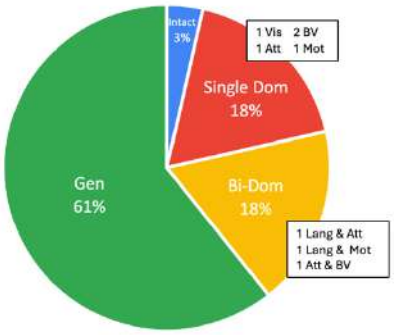

Table 3 (left) and Figure 8 (right). On the left side, codification of neuropsychological data across five domains: Language, Visuospatial, Attention, Behavior, Motor. (I = intact, D = deficient). On the right side, derivation of a cognitive, with impairment degree classified as Single-Domain, Bi-Domain or Generalized (if ≥ 3 domains are involved).

Impairment in the Language, Visuospatial, and Attention domains was also classified on a four-point scale according to degree of impairment, as previously explained in the Methods section. (Table 4)

Pt	Lang	Vis	Att
1	3	0	2
2	0	1	3
3	3	0	2
4	3	0	3
5	0	2	0
6	3	1	2
7	3	3	3
8	1	1	1
9	0	0	2
10	2	3	3
11	3	3	3
12	0	0	2
13	3	3	3
14	3	3	3
15	2	0	3
16	3	2	3
17	2	3	3
18	3	0	1
19	1	0	3
20	0	0	3
21	1	0	0
22	3	3	3
23	0	0	1
24	3	2	3
25	2	0	2
26	2	0	1
27	0	0	1
28	0	0	3

Table 4. Classification of impairment for Language, Visuospatial, and Attention domains on a four-point scale (0 = no impairment; 1 = 2 or more impaired tests at -1.0 SD; 2 = 2 or more impaired tests at -1.5 SD; 3 = 2 or more impaired tests at -2.0 SD).

A correlation analysis was conducted to examine the potential prognostic value of neuropsychological features on clinical outcome. If a 3-domain model is adopted, with impairments described on a 4-point scale, a significantly worse outcome was associated with greater impairment in the Attention domain. A similar trend, albeit without statical significance, was observed for the Language domain (Table 5). Alternatively, adopting a 5-domain model with impairments categorized dichotomously, a significantly worse outcome was correlated with impairment in the Language domain. (Table 6)

	Good outcome	Mild deficit	Severe deficit	
Language				
Normal	1	4	1	$\chi^2(6) = 11.57$, p=0.072
Mild	2	3	0	
Moderate	0	3	0	
Severe	0	5	6	
Attention				
Normal	2	0	0	**$\chi^2(6) = 19.65$, p=0.003**
Mild	0	2	1	
Moderate	0	5	0	
Severe	1	8	6	
Visuospatial				
Normal	2	10	1	$\chi^2(2) = 8.11$, p=0.230
Mild	0	1	1	
Moderate	1	1	1	
Severe	0	3	4	

	Good outcome	Mild deficit	Severe deficit	
Language				
Normal	3	7	1	**$\chi^2(2) = 6.37$, p=0.041**
Pathological	0	8	6	
Attention				
Normal	2	2	1	$\chi^2(2) = 4.64$, p=0.098
Pathological	1	13	6	
Visuospatial				
Normal	2	11	2	$\chi^2(2) = 4.05$, p=0.132
Pathological	1	4	5	
Behaviour				
Normal	2	2	1	$\chi^2(2) = 4.64$, p=0.098
Pathological	1	13	6	
Motor				
Normal	3	6	2	$\chi^2(2) = 4.59$, p=0.101
Pathological	0	9	5	

Table 5 (left) and 6 (right). Correlation between neuropsychological impairment at the time of maximum disease activity and long-term clinical outcome

No significant correlation was found between age at first clinical symptom or age at first SWAS detection and degree of impairment in each neuropsychological domain.

A correlation analysis was conducted to highlight possible correlations between degree of impairment in each neuropsychological domain and EEG features. A significant correlation was found between degree impairment in the Language domain and both lateralization ($\chi(6)=14.19$, $p=0.028$) and localization ($\chi(6)=20.95$, $p=0.013$). In particular, greater language dysfunction was correlated with main localization of abnormalities in the left central area.

A two-step cluster analysis was carried out to identify distinct clinical groups based on neuropsychological scores.

A first-tier analysis was performed using a three-domain model comprising Language, Visuospatial, and Attention domains. This analysis identified three clusters: cluster 1 grouped 10 subjects (36%), cluster 2 grouped 11 subjects (39%), cluster 3 grouped 7 subjects (25%). Patients in Cluster 1 predominantly exhibited a severe and widespread deficit encompassing all three cognitive domains. In contrast, individuals in Cluster 2 were distinguished by preserved Visuospatial functioning, accompanied by varying degrees of impairment in both Language and Attention domains. Lastly, patients in Cluster 3 were primarily characterized by marked impairment in the Attention domain, while Language and Visuospatial abilities remained intact or demonstrated only mild deficits. (Figure 9)

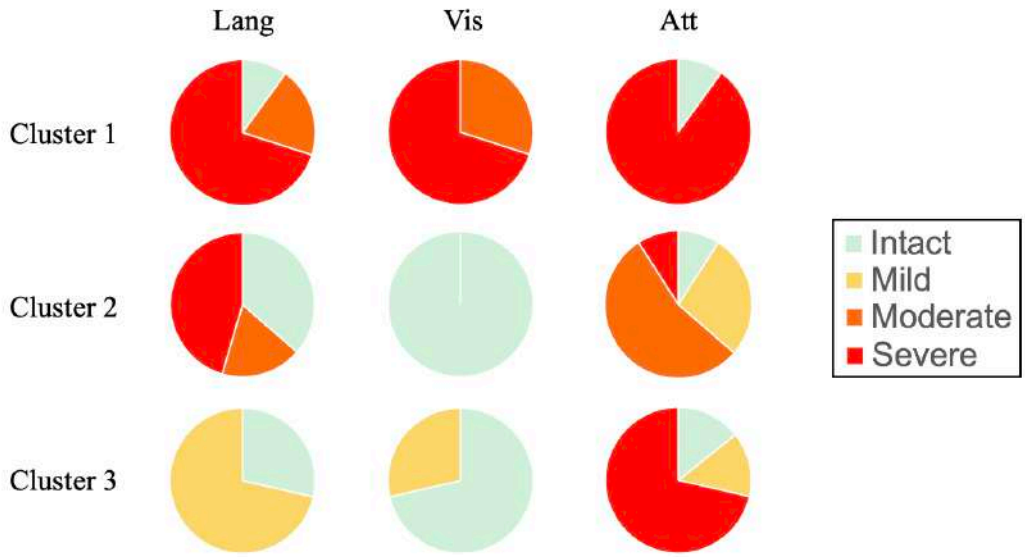

Figure 9. Clusters based on neuropsychological scores in the Language (Lang), Visuospatial (Vis), and Attention (Att) domains.

Comparing the clusters showed a significant difference in all considered domains. No significant differences between the subjects in the clusters in terms of IQ, age at regression onset and age at clinical nadir. (Table 7)

	Cluster 1	Cluster 2	Cluster 3	
N° of subjects	10 [35.7%]	11 [39.3%]	7 [25.0%]	
Language				
Normal	1	4	2	
Mild	0	0	5	**$\chi^2(6) = 22.59$, $p<0.001$**
Moderate	2	2	0	
Severe	7	5	0	
Attention				
Normal	1	1	1	
Mild	0	3	1	**$\chi^2(6) = 19.07$, $p=0.004$**
Moderate	0	6	0	
Severe	9	1	5	
Visuospatial				
Normal	0	11	5	
Mild	0	0	2	**$\chi^2(6) = 33.50$, $p<0.001$**
Moderate	3	0	0	
Severe	7	0	0	

	Cluster 1	Cluster 2	Cluster 3	
N° of subjects	10 [35.7%]	11 [39.3%]	7 [25.0%]	
IQ				
>85	1	4	4	
78-85	0	2	1	$\chi^2(6) = 12.19$, $p=0.058$
70-78	2	1	2	
<70	7	2	0	
Age at regression onset	4.57±1.21	4.80±1.85	6.47±2.3	$H(2) = 1.69$, $p=0.429$
Age at clinical nadir	5.84±1.32	5.72±1.91	8.14±3.0	$H(2) = 0.80$, $p=0.671$

Table 7. Distribution of patients in different clusters and correlation with other variables.

Following the integration of data pertaining to Behavioural and Motor domains, a second-tier analysis was conducted, identifying three distinct clusters. Cluster 1 grouped 19 subjects (32%), cluster 2 grouped 12 subjects (43%), and cluster 3 grouped 7 subjects (25%). Cluster 1 was characterized by severe, generalized regression, including pronounced deficits in the Language, Attention, and Behavioural domains, frequently accompanied by impairments in Visuospatial functioning. Cluster 2 was defined by significant impairments in the Attention and Behavioural domains, often co-occurring with Language deficits, while Visuospatial skills remained preserved. Lastly, Cluster 3 was distinguished by the absence of deficits in the Behavioural domain and the presence of varying degrees of impairment across cognitive domains (Language, Visuospatial, Attention) while the Motor domain was less frequently affected. (Figure 10)

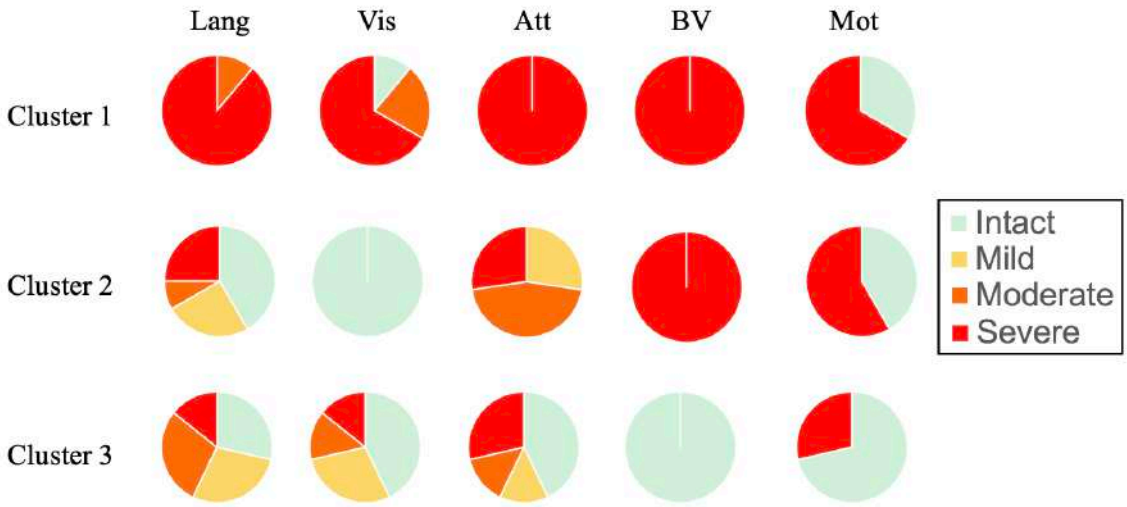

Figure 10. Clusters based on neuropsychological scores in the Language (Lang), Visuospatial (Vis), Attention (Att), Behaviour (BV), and Motor (Mot) domains.

Comparing the clusters showed a significant difference all considered domains, with the exception of Motor domain. Patients belonging to Cluster 1 had lower IQ on average than those in Cluster 2 and Cluster 3. There was no difference between the subjects in the clusters in terms of age at regression onset and age at clinical nadir. (Table 8)

	Cluster 1	Cluster 2	Cluster 3	
N° of subjects	9 [32.1%]	12 [42.9%]	7 [25.0%]	
Language				
Normal	0	5	2	**$\chi^2(6)=14.06$, p=0.029**
Mild	0	3	2	
Moderate	1	1	2	
Severe	8	3	1	
Attention				
Normal	0	0	3	**$\chi^2(6)=20.99$, p=0.002**
Mild	0	3	1	
Moderate	0	5	1	
Severe	9	4	2	
Visuospatial				
Normal	1	12	3	**$\chi^2(6)=25.50$, p<0.001**
Mild	0	0	2	
Moderate	2	0	1	
Severe	6	0	1	
Behaviour				
Normal	0	0	7	**$\chi^2(2)=28.00$, p<0.001**
Pathological	9	12	0	
Motor				
Normal	3	5	5	$\chi^2(2)=1.49$, p=0.288
Abnormal	6	7	2	

	Cluster 1	Cluster 2	Cluster 3	
N° of subjects	9 [32.1%]	12 [42.9%]	7 [25.0%]	
IQ				
>85	0	7	2	**$\chi^2(6)=14.41$, p=0.025**
78-85	0	1	2	
70-78	2	2	1	
<70	6	1	2	
Age at regression onset	4.57±1.21	4.80±1.85	6.47±2.3	H (2) =3.69, p=0.158
Age at clinical nadir	5.84±1.32	5.72±1.91	8.14±3.0	H (2) =4.41, p=0.110

Table 8. Distribution of patients in different clusters and correlation with other variables.

A significant difference in age at first SWAS detection between clusters (H(2)=6.69, p=0.035). Post-hoc comparison showed that Cluster 3 patients had a significantly higher age at first SWAS detection than Cluster 1 patients (6.7 ± 2.0 vs 4.1 ± 1.2 years).
No correlation was found between cluster membership and main localization of IEDs.

Additionally, a correlation analysis was performed to evaluate the potential prognostic significance of cluster membership on clinical outcomes. The analysis revealed that patients classified within Cluster 1 had significantly poorer outcomes, with none demonstrating substantial recovery at follow-up. In contrast, Cluster 2 was primarily associated with mild deficits at follow-up, while membership in Cluster 3 correlated with more favourable clinical outcomes. (Table 9)

	Good outcome	Mild deficit	Severe deficit	
Cluster				
1	0	4	5	**$\chi^2(4) = 9.953$, p=0.041**
2	1	9	1	
3	2	2	1	

Table 9. Correlation between clusters derived from neuropsychological data and long-term clinical outcome.

Connectivity study

The ages of the CTR and D/EE-SWAS groups did not significantly differ (t(25)=0.70, p=0.488). The number of epochs per subject was variable and ranged from 30 to 87. The difference in epochs between patient groups was not statistically significant (t(25)=1.09, p=0.286).

All D/EE-SWAS patients featured diffuse SWAS and main lateralization of abnormalities was heterogeneous (right in 6 cases, left in 5 cases and absent in 2 cases). Focal or multifocal slow wave activity was found in 9/13 patients.

D/EE-SWAS group was also representative of different phenotypes of neuropsychological impairment (6 patients belonging to Cluster 1, 5 patients to Cluster 2 and 2 patients to Cluster 3).

Spectral analysis

The number of epochs per subject was variable and ranged from 30 to 87. The difference in epochs between patient groups was not statistically significant (t(25)=1.09, p=0.286).

Delta

RmANOVA showed a main effect of GROUP (F(1,25)=11.91, p=0.002). After Bonferroni correction for multiple comparison, significance survived for Fp1 (F(1,26)=12.22, p=0.002), F8 (F(1,26)=14.88, p<0.001), T3 (F(1,26)=14.66, p<0.001), C3 (F(1,26)=11.51, p=0.002) and T4 (F(1,26)=20.14, p<0.001).

Theta

RmANOVA showed a main effect of GROUP (F(1,25)=5.83, p=0.023). After Bonferroni correction for multiple comparison, significance survived for T3 (F(1,26)=13.32, p=0.001).

Alpha

RmANOVA showed a main effect of GROUP ($F(1,25)=6.49$, $p=0.017$). After Bonferroni correction for multiple comparison, significance survived for T3 ($F(1,26)=13.09$, $p=0.001$) and T6 ($F(1,26)=12.81$, $p=0.001$).

Beta

RmANOVA showed a main effect of GROUP ($F(1,25)=5.26$, $p=0.031$). After Bonferroni correction for multiple comparison, no significance survived.

Gamma

RmANOVA showed no significant difference.

	Delta		**Theta**		**Alpha**		**Beta**		**Gamma**	
	CTRL	*D-EE/SWAS*	*CTRL*	*D-EE/SWAS*	*CTRL*	*D-EE/SWAS*	*CTRL*	*D-EE/SWAS*	*CTRL*	*D-EE/SWAS*
Fp1	**0.47±0.05**	**0.56±0.08**	0.18±0.02	0.17±0.02	0.14±0.04	0.12±0.03	0.16±0.03	0.11±0.03	0.05±0.01	0.04±0.02
Fp2	0.47±0.06	0.54±0.07	0.18±0.02	0.15±0.02	0.14±0.03	0.12±0.04	0.16±0.03	0.12±0.04	0.05±0.02	0.03±0.02
F7	0.47±0.05	0.53±0.07	0.19±0.02	0.18±0.03	0.13±0.03	0.12±0.03	0.17±0.03	0.13±0.05	0.04±0.01	0.04±0.02
F3	0.46±0.07	0.53±0.06	0.20±0.04	0.18±0.03	0.14±0.04	0.12±0.02	0.17±0.03	0.13±0.05	0.03±0.01	0.04±0.02
F4	0.45±0.06	0.53±0.09	0.21±0.04	0.18±0.03	0.14±0.04	0.12±0.03	0.17±0.03	0.13±0.06	0.03±0.01	0.04±0.02
F8	**0.45±0.01**	**0.55±0.09**	0.19±0.02	0.17±0.02	0.15±0.04	0.11±0.03	0.17±0.03	0.13±0.05	0.04±0.01	0.04±0.02
T3	**0.46±0.04**	**0.56±0.09**	**0.21±0.03**	**0.17±0.03**	**0.13±0.01**	**0.10±0.02**	0.15±0.03	0.12±0.05	0.04±0.01	0.04±0.02
C3	**0.47±0.05**	**0.55±0.07**	0.22±0.04	0.18±0.03	0.15±0.03	0.11±0.02	0.15±0.03	0.12±0.04	0.03±0.01	0.04±0.02
C4	0.46±0.03	0.53±0.08	0.22±0.04	0.19±0.02	0.13±0.02	0.11±0.03	0.15±0.03	0.13±0.06	0.03±0.01	0.04±0.02
T4	**0.45±0.04**	**0.55±0.07**	0.21±0.03	0.19±0.03	0.13±0.02	0.11±0.02	0.16±0.03	0.12±0.04	0.04±0.01	0.04±0.02
T5	0.46±0.04	0.53±0.07	0.23±0.03	0.20±0.03	0.13±0.01	0.11±0.03	0.14±0.03	0.12±0.04	0.04±0.01	0.04±0.02
P3	0.47±0.06	0.52±0.09	0.21±0.03	0.19±0.03	0.13±0.02	0.12±0.03	0.15±0.03	0.12±0.05	0.04±0.01	0.04±0.02
P4	0.46±0.04	0.52±0.09	0.21±0.02	0.19±0.02	0.13±0.01	0.12±0.04	0.15±0.03	0.13±0.05	0.04±0.01	0.04±0.02
T6	0.46±0.04	0.54±0.07	0.22±0.03	0.20±0.02	**0.13±0.01**	**0.11±0.02**	0.14±0.03	0.11±0.04	0.04±0.01	0.04±0.02
O1	0.48±0.04	0.54±0.09	0.21±0.03	0.20±0.02	0.13±0.01	0.11±0.03	0.12±0.02	0.11±0.04	0.04±0.01	0.04±0.02
O2	0.48±0.04	0.53±0.08	0.22±0.03	0.21±0.02	0.14±0.01	0.11±0.03	0.12±0.02	0.11±0.04	0.03±0.01	0.04±0.02

Table 10. Power Spectral Density values

Functional Connectivity indices

Delta

RmANOVA on out-degree showed a main effect of GROUP ($F(1,25)=13.10$, $p=0.001$). After Bonferroni correction for multiple comparison, significance survived for F8 ($F(1,26)=45.53$, $p=0.001$), F3 ($F(1,26)=15.04$, $p<0.001$) and C3 ($F(1,26)=17.01$, $p<0.001$).

RmANOVA on BC showed a main effect of GROUP ($F(1,25)=10.55$, $p=0.003$). No significance survived after Bonferroni correction.

RmANOVA on CC showed a main effect of GROUP ($F(1,25)=11.41$, $p=0.002$). After Bonferroni correction for multiple comparison, significance survived for Fp2 ($F(1,26)=15.66$, $p<0.001$), F7 ($F(1,26)=11.20$, $p=0.003$) and C3 ($F(1,26)=11.08$, $p=0.003$).

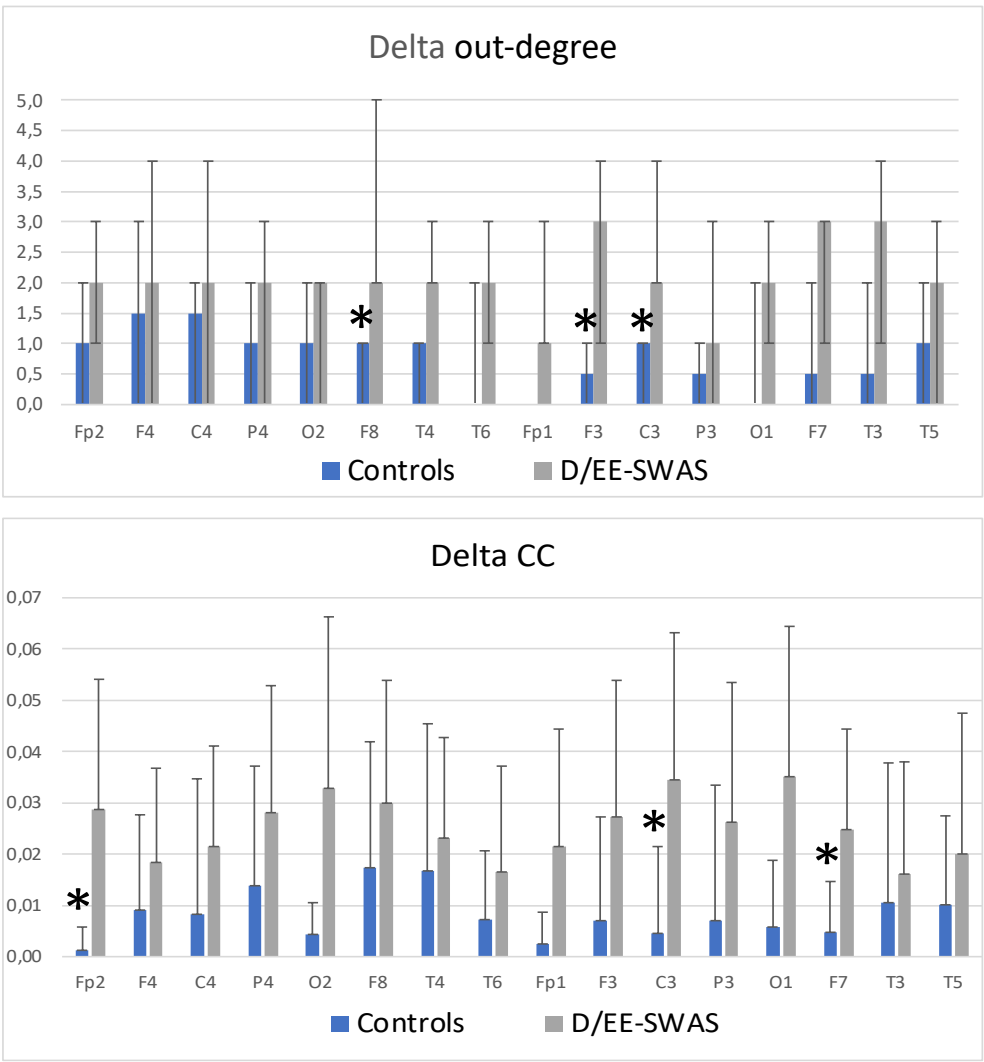

Figure 11. Functional connectivity indices in the delta band showing differences between patients and controls. Out-degree measures exhibit significant differences for electrodes F8, F3 and C3 (above); Clustering Coefficient demonstrate significant differences for electrodes Fp2, C3 and F7 (below).

Theta

RmANOVA showed on out-degree a main effect of GROUP ($F(1,25)=73.63$, $p=0.004$) and ELEC ($F(8.03,200.70)=1.9$, $p=0.004$) and on BC a main effect of GROUP ($F(1,25)=10.62$, $p=0.004$), but no significance survived the Bonferroni correction.

Alpha

RmANOVA on out-degree showed a main effect of ELEC ($F(7.47,186.72)=4.63$, $p<0.001$); no significance survived after Bonferroni correction.

Beta

RmANOVA on out-degree showed a main effect of GROUP ($F(1,25)=5.66$, $p=0.025$) and ELEC ($F(15,375)=8.02$, $p<0.001$) and a significant interaction ELECxGROUP ($F(15,375)=2.11$, $p=0.009$). No significance survived after Bonferroni correction.

RmANOVA on out-strength showed a main effect of ELEC ($F(7.83,195.69)=7.66$, $p<0.001$) and a significant interaction ELECxGROUP ($F(7.83,195.69)=2.11$, $p=0.014$). After Bonferroni correction for multiple comparison, significance survived only for C3 ($F(1,26)=13.19$, $p=0.002$).

RmANOVA on BC showed a main effect of GROUP ($F(1,25)=5.99$, $p=0.022$) and ELEC ($F(8.14,203.37)=3.07$, $p=0.003$) and a significant interaction ELECxGROUP ($F(8.14,203.37)=3.48$, $p<0.001$). After Bonferroni correction for multiple comparison, significance survived only for F3 ($F(1,26)=22.58$, $p<0.001$).

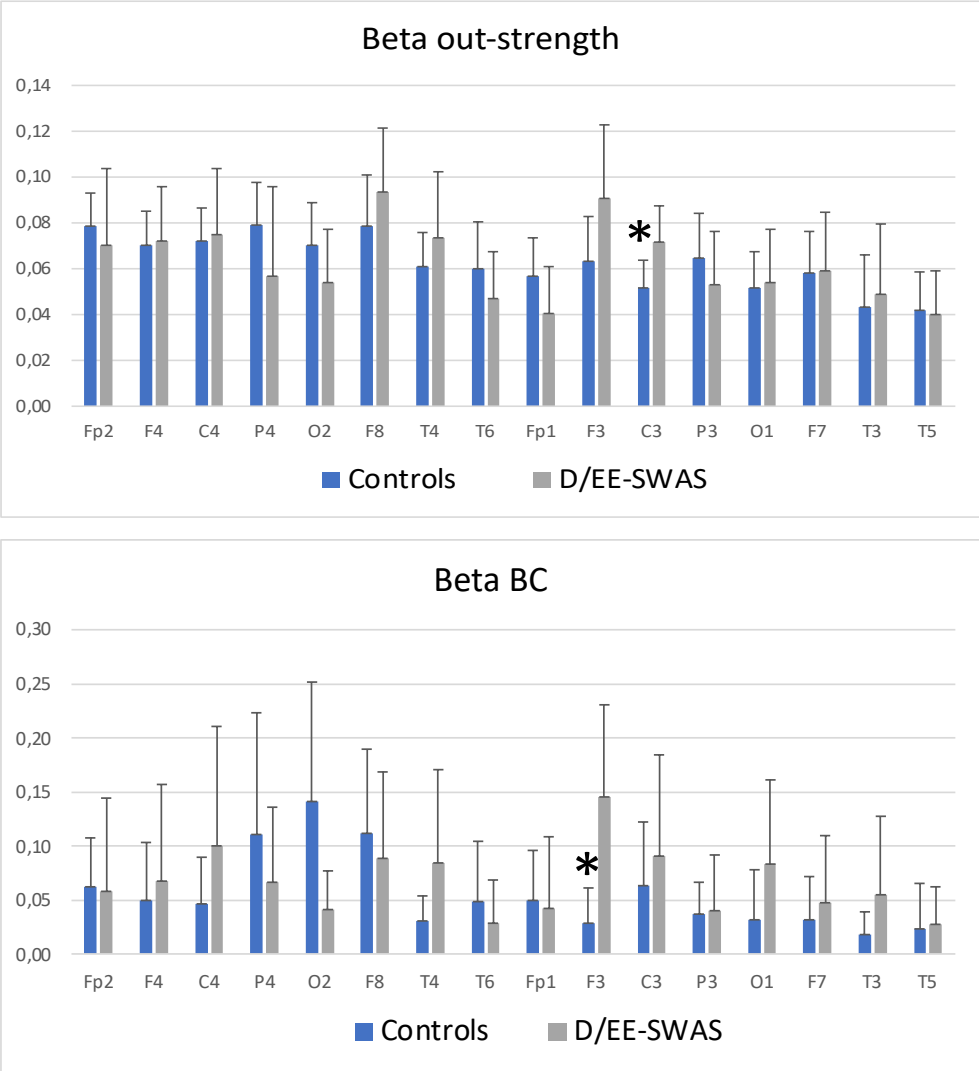

Figure 12. Functional connectivity indices in the beta band showing differences between patients and controls. Out-strength measures exhibit significant differences for electrode C3 (above); Betweenness Centrality measures demonstrate significant differences for electrode F3 (below).

Gamma

RmANOVA on CC showed a main effect of ELEC ($F(6.00,149.92)=3.86$, $p=0.001$) and a significant interaction ELECxGROUP ($F(6.00,149.92)=2.93$, $p=0.010$), but no significance survived the Bonferroni correction.

Correlation analysis

An exploratory analysis was performed to investigate potential correlations between measures of functional connectivity and neuropsychological impairment across various domains (Language, Visuospatial, Attention, Behavior, Motor). The analysis did not reveal any significant correlations.

DISCUSSION

This retrospective observational study analysed data from 28 patients with idiopathic D/EE-SWAS, collected at two neuropediatric centres. The cohort was relatively homogenous, predominantly consisting of EE-SWAS patients (79%), while DEE-SWAS patients mainly featured mild pre-existing psychomotor delay. Furthermore, the exclusion of patients with structural abnormalities removed a critical variable with a significant impact on electroclinical features.

From a aetiological point of view, genetic studies revealed a high diagnostic yield (20%) within the patient cohort, consistent with recent literature, supporting the integration of genetic testing into routine diagnostic workflows[40,41].

Seizures were reported in all but two patients, aligning with existing reports indicating the rarity of patients without overt seizures. However, we concur with other researchers in hypothesizing an under-detection of subtle seizures in this population, emphasizing the importance of careful EEG analysis for identifying subclinical epileptic activity[9,70]. Seizure frequency was notably low for the greater part of the study population and generally restricted to the early phases of epilepsy, consistent with prior findings. Evolution to D/EE-SWAS in patients with previous diagnosis of other epileptic syndromes, particularly SeLFEs, was observed in approximately half of the cohort, further substantiating the nosological continuum proposed by ILAE[1]. These findings underscore the need for close clinical monitoring and comprehensive neuropsychological assessments in patients with SeLFEs.

On the other hand, nearly one third of the patient cohort displayed signs of cognitive/behavioural/motor regression before the onset of clinical seizures. This highlights the necessity of sleep EEG recordings in children exhibiting plateauing or regression in neuropsychological or motor skills, even in the absence of seizures.

EEG findings were consistent with literature data, showing normal background activity with foci of spike-wave and/or slow activity during wakefulness. Focal abnormalities were predominantly observed in centrotemporal derivations, with less frequent involvement of anterior or posterior regions, without clear hemispheric predominance. While SWAS patterns were mostly bisynchronous and diffuse, three cases exhibited hemi-SWAS, consistent with similar cases reported in the literature[22].

Behavioural, attentive and linguistic deterioration were mainly reported by caregivers and variously characterized the phase of clinical regression. Data about SWAS-related dysfunctions in the motor domain showed high prevalence (50%), supporting the need for close evaluation of these often-neglected features. Thorough neuropsychological assessments conducted at the nadir of clinical impairment were available for all patients (in accordance with inclusion criteria) and were employed to describe neuropsychological profiles within a framework inspired to the IC-CoDE model[106]. This allowed the integration and comparison of retrospective data featuring high heterogeneity in scales and measures due to use of tailored use for different patients' ages and characteristics, but also different availability of tests in different times and centres.

In the absence of IC-CoDE guidelines for the paediatric age, an adapted version was employed featuring the original domains (Language, Visuospatial, Executive, Working Memory, Attention). Different thresholds (- 1,0 SD, -1,5 SD, and -2,0 SD) were tentatively adopted to define impairment, yielding varying sensitivity and specificity. This approach revealed a diverse range of cognitive phenotypes, including single-domain, bi-domain, and generalized impairments, consistent with historical accounts[87]. A similar classification in three groups based on the number of impaired domains (selective, combined, pervasive) was recently proposed for D/EE-SWAS; nonetheless, it has not yet been applied to the characterization of patient data[103].
However, the adapted IC-CoDE model proved incomplete for describing the cohort due to the lack of data concerning Executive and Working Memory domains in a subgroup of younger or most impaired patients, and these two measures were therefore excluded from the analysis. However, deficits in these domains (where data were available) were consistently associated with impairments in the Attention domain, which was hence considered indicative of global executive dysfunction in the patient population. Moreover, we deemed useful to incorporate data concerning Behavioural and Motor domains in our model, in order to fully capture the possible clinical presentations associated with D/EE-SWAS.

The findings highlighted prominent impairments in the Language and Attention domains (respectively in 61% and 75% of patients, when a - 1,5 SD threshold was adopted), mirroring descriptions of classically SWAS-related syndromes such as LKS and "acquired

epileptic dementia"[86,92]. Recent studies have similarly demonstrated that greater deficits in receptive vocabulary and working memory differentiate patients with high SWI (either in the context of SeLECTs or EE-SWAS) from controls, further underscoring the significance of linguistic and executive domains in the SeLFEs-D/EE-SWAS spectrum[154].

In contrast, visuospatial impairments were less frequently observed, in virtually all cases in the context of generalized regression. Only one case exhibited mild, isolated visuospatial impairment linked to epileptic foci in the right centrotemporal region, diverging from prior findings correlating visuospatial deficits with posterior SWAS[94,95].

A greater degree of impairment in the language domain was associated with the predominant localization IEDs in the left central region, consistent with the established role of this area in language processing. In contrast, no other correlations were found between impairment in single neuropsychological domain and focus of epileptic activity, in line with other recent studies[64,101].

A cluster analysis was conducted on the collected data, leading to successful identification of three distinct subgroups based on cognitive and behavioural impairment profiles (see Figure 10), while impairment in the Motor domain did not significantly contribute the definition of clusters.

In particular, Cluster 1 is characterized by severe, generalized cognitive-behavioural regression, prominently involving language and attention deficits and often accompanied by visuospatial impairment. This cluster represents the most severe phenotype, resembling historically reported cases of ESES/EECSWS with marked cognitive and behavioural regression,

Cluster 2 is characterized by combined executive-behavioural impairments. Language deficits of varying degrees are frequently observed in association, whereas visuospatial impairments are always absent. This phenotype was the most prevalent in patients with prior SeLFE diagnoses, consistent with findings in SeLECTs[166,167].

Lastly, Cluster 3 is defined by the absence of behavioural dysfunction, despite various combinations of cognitive impairments (Language, Visuospatial, Attention). These patients likely represent a milder phenotype, where intact behavioural skills may facilitate better adaptation to environmental and interpersonal demands, potentially mitigating additional deterioration.

Patients with LKS were categorized into distinct clusters (specifically, cluster 1 and cluster 2) based on the extent of impairment in Visuospatial and Attention domains. This highlights the heterogeneity of the neuropsychological profile linked to this syndrome, as well as the variable involvement of additional cognitive domains beyond the linguistic core deficit[168].

Further analysis showed significantly lower age at first SWAS detection in cluster 1 as compared with cluster 3. This finding suggests that the early onset of D/EE-SWAS is associated with a more generalized disruption of neuropsychological development, resulting in a more severe clinical presentation. Abnormal formation of brain networks during early critical periods may lead to a misalignment with the sensory environment. These maladaptive neural structures become consolidated at the conclusion of the developmental phase, resulting in persistent functional impairments[133], as observed in patients classified within cluster 1.

To our knowledge, this study is the first to comprehensively profile neuropsychological domains in D/EE-SWAS, providing valuable insights into the condition's diverse presentations. The findings highlight the limitations of traditional and newer measures (such as full-scale IQ and cognitive sum score[102], respectively) in capturing nuanced deficits, advocating for domain-specific analyses. Prior studies often compounded verbal and performance IQ data from all patients, potentially obscuring distinct cognitive profiles[14]. In contrast, the current cluster analysis successfully categorized patients into clinically meaningful groups based on cognitive and behavioural data, presenting a potential framework for future research.

While this study was not specifically designed to evaluate long-term outcomes due to the relative recency of many cases, clinical outcomes were systematically assessed in all patients with a minimum follow-up period of one year following the peak of their clinical impairment. A correlation analysis revealed that greater impairments in the Language and Attention domains were predictive of poorer clinical outcomes. Clusters were also significantly associated with outcomes: Cluster 1 correlated with severe deficits, Cluster 2 with mild impairments, and Cluster 3 with favourable outcomes or minimal deficits.

These findings underscore the utility of neuropsychological profiling and cluster analysis in advancing the understanding and management of D/EE-SWAS.

In the second part of this study, we investigated functional connectivity in a subcohort of 13 patients on IEDs-free epochs selected during stable phase II sleep.
Numerous studies have documented the relative preservation of sleep macroarchitecture in patients with D/EE-SWAS, as confirmed by the presence of N-REM and REM phases and of physiological sleep elements such as sleep spindles, also in our study cohort[169]. This allows a comparison between IEDs-free EEG epochs from D/EE-SWAS patients and healthy controls (selected during the same sleep stage) to investigate the impact of abnormal electrical activity reflects on network connectivity.

Preliminary power spectral analysis revealed an increase in delta activity (DA), predominantly localized to the left central regions (Fp1, C3, T3) and the right frontotemporal regions (F8, T4). This finding is likely attributable to the presence of focal slow-wave activity observed during both wakefulness and sleep in the majority of our cohort.
Focal slow wave activity has been reported in patients with D/EE-SWAS, with a potential contributory role to neuropsychological symptoms[170]. Increased DA has indeed been proposed as a potential predictor of progression to D/EE-SWAS in patients with SeLECTs or perinatal stroke[171,172]. Moreover, altered DA has been observed in D/EE-SWAS patients compared to controls[57]. Specifically, impairments in the physiological reduction of slow-wave activity throughout sleep cycles[54] have been correlated with focal spike-wave activity, leading to a maladaptive increase in synaptic density[58]. Additionally, focal abnormalities during wakefulness have been shown to result in heightened slow-wave activity at the onset of sleep[58]. Enhanced DA in our cohort was observed outside of spike-wave IEDs, in regions predominantly affected by focal abnormalities during wakefulness, further supporting this association.
Lastly, the localization of increased DA in our cohort suggests a potential role of fronto-centrotemporal regions in the genesis and propagation of IEDs, possibly implicating the involvement of a physiological network, the perisylvian network (PN), consistent with Halász's theoretical framework[144].

Prior studies investigating functional connectivity in D/EE-SWAS patients through coherence analysis demonstrated hyperconnectivity during IEDs compared to IED-free intervals[155]. However, this finding was relatively expected given the hypersynchronous and diffuse signal observed across all recording electrodes during IEDs. Moreover, the selection of IEDs-free epochs in this study was confounded by the inclusion of post-spike slow waves, which are an intrinsic component of the IED itself.

We therefore performed a functional connectivity analysis on IED-free epochs and compared the results with data from healthy controls to identify differences in functional connectivity that may underlie neuropsychological dysfunction. Differences in connectivity measures were identified within the delta and beta frequency bands, with a predominant localization on central and frontal regions. These findings are consistent with a similar study featuring the application of PDC to patients with SeLECTs, which demonstrated altered connectivity in centrotemporal regions compared to controls[173]. In that study, connectivity differences were mainly observed in the beta frequency band and localized at the sites of IEDs. The authors interpreted these findings as evidence for a role of the centrotemporal regions in the pathogenesis of SeLECTs. Similarly, our results further support the involvement of the Perisylvian Network across the SeLECTs-D/EE-SWAS spectrum. Moreover, this pattern of connectivity alteration was observed in a cohort of patients presenting different profiles of neuropsychological impairment (and belonging to different clusters). This finding argues against a direct correlation between the localization of IEDs and specific cognitive deficits, supporting instead the framing of D/EE-SWAS as a "perisylvian developmental epilepsy"[144]. Within this framework, idiopathic D/EE-SWAS could be conceptualized as a genetically determined transient developmental failure of the Perisylvian Network, leading to both IEDs and disruption of human-specific cognitive functions. These observations are consistent with earlier studies indicating significant involvement of the bilateral perisylvian regions in the initiation and propagation of IEDs[174], while also aligning with evidence of regional disruptions in glucose metabolism in patients with D/EE-SWAS[132,147,149]. Combined fMRI study and electrical source analysis in a small group of patients with either idiopathic or structural D/EE-SWAS confirmed IEDs propagation to perisylvian regions with consequent BOLD increase in all patients, regardless of aetiology and localization of initial epileptic activity[137].

Furthermore, altered connectivity within the frontal regions was identified in our cohort, in agreement with previous findings that highlighted abnormal activation in the prefrontal

cortex in relation to D/EE-SWAS[137]. These disruptions in the connectivity of the perisylvian and prefrontal regions may account for the complex neuropsychological deficits characteristic of D/EE-SWAS, particularly impacting linguistic and executive functions. The pronounced involvement of these cortical areas may stem from their extended developmental timeline, which spans childhood and adolescence[175,176]. This prolonged maturation process likely renders these regions particularly susceptible to both environmental factors and intrinsic physiological disturbances during critical developmental windows.

Notably, in our cohort significantly altered measures of connectivity were consistently localized to the left hemisphere, regardless of the main lateralization of abnormalities, which varied across the patient cohort. The predominant involvement of the left Perisylvian Network may be attributed to its dominance in the majority of the population, particularly concerning linguistic functions. Conversely, left-sided epileptic foci have been linked to reduced non-verbal abilities in patients with idiopathic EE-SWAS, suggesting a complex role of neuroplasticity in the developing brain[177].

Limitations

The limitations of this study include the small sample size. D/EE-SWAS is a rare condition, and the exclusion of patients with structural lesions further narrowed the study cohort. Nonetheless, we believe that the homogeneity of the patient population strengthened the findings and enhanced the robustness of the results related to functional connectivity.

The retrospective design of the study posed an additional limitation due to the heterogeneity and incomplete availability of data from neuropsychological assessments. However, variability in measures and scales is an inherent challenge, particularly in paediatric populations. The application of the IC-CoDE model for neuropsychological characterization proved highly effective in addressing these limitations, enabling a structured and comprehensive analysis of the available data. Furthermore, this approach has demonstrated significant strengths, characterized by its originality and innovation, along with its ability to effectively delineate clusters with potential prognostic significance.

The relatively short follow-up duration limited the availability of data regarding SWAS resolution and constrained the evaluation of prognostic correlations. Further follow-up periods with comprehensive assessments could provide more robust insights and further validate the observed associations between neuropsychological profiles and clinical outcomes.

The analysis of functional connectivity was primarily constrained by the limited electrode array. Although high-density EEG would undoubtedly yield more comprehensive and accurate information on functional connectivity measures, the use of standard EEG recordings have allowed for the extraction of valuable insights from retrospective data acquired at the time of maximum disease activity.

Another limitation lies in the lack of overnight EEG recordings for all patients, primarily due to technical challenges in epoch selection in presence of abundant IEDs. While nap EEG recordings are now considered sufficient for the diagnosis of D/EE-SWAS, we posit that nocturnal sleep recordings would be more suitable for the neurophysiological study of homeostatic sleep processes.

Lastly, the reduced sample size in the connectivity study limited the ability to detect significant correlations between functional connectivity and neuropsychological measures. Future research involving larger cohorts is essential to further investigate these relationships and to identify potential biomarkers with prognostic significance.

CONCLUSIONS

Our study aimed to provide a detailed characterization of a cohort of patients with idiopathic D/EE-SWAS, and to investigate neuropsychological and neurophysiological features in a network-based perspective.

The IC-CoDE model has proven effective in characterizing the features of cognitive and behavioural regression at the time of maximum disease activity, enabling the identification of clusters with potential prognostic value. Further studies on larger populations are required to validate these clusters, which may serve as a valuable tool to guide clinical-therapeutic decisions for D/EE-SWAS patients.

The application of advanced neurophysiological techniques enabled the detection of functional connectivity alterations in D/EE-SWAS patients as compared to healthy controls. Despite the small sample size, our findings provide seminal evidence supporting a pivotal role of the perisylvian region in the pathogenesis of D/EE-SWAS, highlighting a consistent pattern of altered connectivity irrespective of the primary localization of IEDs.

Further research is required to examine the longitudinal progression of these findings and to identify reliable long-term prognostic biomarkers. Moreover, this research framework could be extended to patients with D/EE-SWAS associated with structural lesions and to those exhibiting SWAS-like abnormalities in the absence of neuropsychological impairment, offering an opportunity to enhance our understanding of this complex and intriguing condition.

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