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Frontal Lobe Involvement in Idiopathic Generalized Epilepsy

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Porto, junho de 2025

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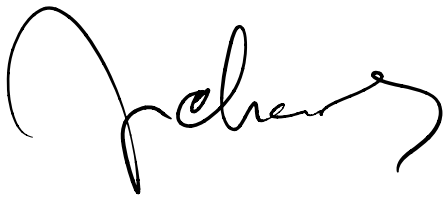
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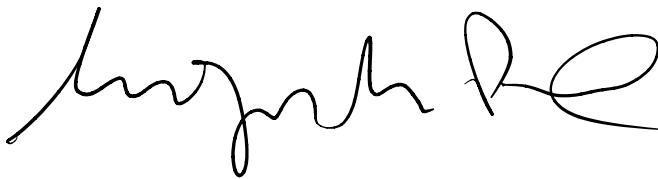
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Resumo

Enquadramento: As Epilepsias Generalizadas Idiopáticas (IGE) são um grupo de epilepsias que se caracterizam pela presença, isolada ou em combinação, de crises generalizadas: crises de ausências, mioclonias, crises tónico-clónicas ou crises mioclónica-tónico-clónicas. Tendo por base o tipo de crises presentes, a International League Against Epilepsy publicou, em 2022, a Nova Classificação para definição das IGE admitindo no grupo quatro síndromes – Epilepsia de Ausências na Criança (CAE), Epilepsia de Ausências Juvenil (JAE), Epilepsia Mioclónica Juvenil (JME) e Epilepsia só com crises tónico-clónicas (GTCSA). Ainda assim, a sua distinção nem sempre é clara, dado que pode haver sobreposição entre estas síndromes, ou mesmo evolução de uma síndrome para outra. As IGE são frequentes, correspondendo a 15-20% do total dos casos de epilepsia. Por norma, em doentes com IGE, o eletroencefalograma evidencia um padrão generalizado de ponta-onda entre 2,5 e 5,5 Hz, cuja ativação parece estar associada à hiperventilação ou fotoestimulação. Apesar de terem sido inicialmente consideradas “benignas”, dada a facilidade de controlo farmacológico das crises epilépticas, diversos estudos comprovam a presença de manifestações clínicas compatíveis com envolvimento frontal nestes doentes para além das crises. Por definição, os doentes com IGE não apresentam evidência imagiológica de lesões estruturais focais a nível cerebral em exames de ressonância magnética. No entanto, foram descritas alterações estruturais e funcionais com envolvimento predominantemente fronto-talâmico provindas de novos métodos de imagem e novos exames funcionais do estudo cerebral.

Objetivos: Esta revisão teve como objetivo descrever as evidências que apoiam o envolvimento do lobo frontal nas IGE.

Metodologia: Foi efetuada uma revisão narrativa com pesquisa e estudo abrangente da literatura em relação a alterações compatíveis com envolvimento frontal em doentes com IGE. A pesquisa foi feita nas seguintes bases de dados: PubMed e Scopus, sem restrição nas datas dos estudos analisados. As evidências descritas foram divididas em 3 secções – alterações clínicas, alterações estruturais e alterações funcionais que envolvam o lobo frontal. No que diz respeito à primeira secção, foram documentadas as alterações descritas a nível cognitivo, psiquiátrico e social dos doentes com IGE. A segunda secção diz respeito a evidências de alterações estruturais encontradas em estudos com ressonância magnética encefálica. A terceira secção versa sobre as alterações encontradas em estudos funcionais, como eletroencefalograma, ressonância magnética funcional, magnetoencefalografia, tomografia por emissão de positrões e espectroscopia por ressonância magnética.

Desenvolvimento: Foram detetados défices neuropsicológicos de predomínio frontal, nomeadamente compromisso da função cognitiva executiva, comorbilidades psiquiátricas e alterações na conduta social. A nível estrutural, estudos demonstraram alterações nos valores de anisotropia fracional na substância branca frontal, assim como alterações na substância cinzenta frontotálâmica, sugerindo degeneração microestrutural progressiva. A nível funcional, foram descritas alterações focais no eletroencefalograma destes doentes, com predomínio das descargas epiléticas a originar-se no lobo frontal. Além disso, observaram-se alterações na conectividade funcional entre o lobo frontal e outras regiões cerebrais, bem como alterações nas concentrações de metabolitos nesta área.

Conclusão: Esta revisão narrativa sublinha o envolvimento do lobo frontal nas IGE, desafiando a definição tradicional que exclui a presença de alterações estruturais. Reconhecer o envolvimento do lobo frontal para além das crises epiléticas é crucial na abordagem do doente com IGE, quer no diagnóstico, quer no tratamento, quer no manejo das comorbilidades tradutoras de uma disfunção frontal.

Palavras-chave: Epilepsia Generalizada Idiopática; lobo frontal

Abstract

Introduction: Idiopathic Generalized Epilepsies (IGE) are a group of epilepsies characterized by the presence, either isolated or in combination, of generalized seizures: absence seizures, myoclonic seizures, tonic-clonic seizures, or myoclonic-tonic-clonic seizures. Based on the types of seizures present, the International League Against Epilepsy published, in 2022, the new classification for the definition of IGE, admitting four syndromes in this group – Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME), and Epilepsy with Only Tonic-Clonic Seizures (GTCSA). Their distinction is not always clear, given that there may be an overlap between these syndromes, or even an evolution from one syndrome to another. IGE are common, accounting for 15-20% of all epilepsy cases. Typically, in patients with IGE, the electroencephalogram shows a generalized spike-and-wave pattern at 2.5 to 5.5 Hz, which activation seems to be associated with hyperventilation or photic stimulation. Although initially considered ‘benign’ due to the ease of pharmacological seizure control, several studies have demonstrated the presence of clinical manifestations compatible with frontal involvement in patients with IGE besides the seizures. By definition, patients with IGE do not present evidence of structural lesions in the brain in magnetic resonance imaging. However, structural and functional alterations predominantly involving the frontothalamic network have also been described, supported by findings from advanced imaging techniques and new functional brain studies.

Objectives: This review aimed to describe the evidence supporting frontal lobe involvement in IGE.

Methodology: A narrative review was conducted regarding changes compatible with frontal lobe involvement in patients with IGE. The research was performed using the PubMed and Scopus databases, without restrictions on the dates of the analysed studies. The described evidence was divided into three sections: clinical alterations, structural alterations, and functional alterations involving the frontal lobe. The first section documents the cognitive, psychiatric, and social changes reported in patients with IGE. The second section addresses structural alterations identified in studies using brain magnetic resonance imaging. The third section focuses on findings from functional studies, such as electroencephalography, functional magnetic resonance imaging, magnetoencephalography, positron emission tomography and magnetic resonance spectroscopy.

Development: We identified neuropsychological deficits with frontal predominance, namely impairment of executive cognitive function, psychiatric comorbidities, and alterations in social behavior. Structurally, studies have shown changes in fractional anisotropy values in the frontal white matter, as well as alterations in the frontothalamic grey matter, suggesting progressive microstructural degeneration. Functionally, focal abnormalities in the electroencephalogram of these patients have been described, with most epileptic discharges originating in the frontal lobe. Additionally, changes in functional connectivity between the frontal lobe and other brain regions were observed, along with alterations in metabolite concentrations in this area.

Conclusion: This narrative review emphasizes the involvement of the frontal lobe in IGE, challenging the traditional definition that excludes the presence of structural alterations. Recognizing the involvement of the frontal lobe beyond epileptic seizures is crucial in the management of patients with IGE, both in diagnosis and treatment and in the management of comorbidities that reflect frontal dysfunction.

Keywords: Idiopathic Generalized Epilepsy; frontal lobe

List of Abbreviations

BOLD: Blood Oxygenation Level–Dependent
CAE: Childhood Absence Epilepsy
Cho: Choline
Cr: Creatine + Phosphocreatine
DMN: Default Mode Network
DTI: Diffusion Tensor Imaging
EEG: Electroencephalogram
FA: Fractional Anisotropy
FDG: Fluorodeoxyglucose
fMRI: Functional Magnetic Resonance Imaging
GABA: γ -aminobutyric acid
GLX: Glutamate + Glutamine
GTCS: Generalized tonic-clonic seizures
GTCSA: Epilepsy with Tonic-Clonic Seizures Alone
IGE: Idiopathic Generalized Epilepsies
JAE: Juvenile Absence Epilepsy
JME: Juvenile Myoclonic Epilepsy
MEG: Magnetoencephalography
MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy
NAA: N-acetyl aspartate
PET: Positron Emission Tomography
PPR: Photoparoxysmal Response

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1. Introduction

Idiopathic Generalized Epilepsies (IGE) are a group of epilepsies characterized by the presence, either isolated or in combination, of generalized seizures: absence seizures, myoclonic seizures, tonic-clonic seizures, or myoclonic-tonic-clonic seizures. Based on the types of crises that are present, the International League Against Epilepsy published, in 2022, a New Classification for defining IGE, admitting four syndromes into the group – Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME), and Epilepsy with Tonic-Clonic Seizures Alone (GTCSA). Their distinction is not always clear, given that there may be an overlap between these syndromes, or even evolution from one syndrome to another ¹. IGE are common, accounting for 15-20% of all epilepsy cases ². Typically, in patients with IGE, the electroencephalogram (EEG) shows a generalized spike-and-wave pattern at 2.5 to 5.5 Hz, which activation seems to be associated with hyperventilation or photic stimulation ^{1, 3, 4}.

IGE are not monogenic diseases, but susceptibility genes with complex inheritance have been described ⁵. Supporting this genetic predisposition is the clinical analysis and electroencephalographic pattern of monozygotic twins, which showed a high concordance rate among twins ⁶⁻⁹. Despite this evidence, and considering the polygenic basis of IGE, it becomes challenging to identify which pathogenic variants are responsible for their genesis, as each individual inherits multiple susceptible and protective alleles, each conferring a specific risk, for the disease to manifest ¹⁰.

In terms of epilepsy, the vast majority of these patients are easily controlled with antiepileptic drugs appropriately chosen for these syndromes. Given the ease of pharmacological control, IGE were initially considered 'benign', but evidence has shown that the presence of comorbidities, such as executive cognitive deficits, mood disorders, anxiety and attention deficit hyperactivity disorder, is common. Additionally, a correlation has been demonstrated between patients with IGE and a poorer long-term social prognosis – difficulties in behavioral, psychiatric, and emotional management, and a greater risk of unplanned pregnancy ^{11, 12}.

1.1. Childhood Absence Epilepsy

Childhood Absence Epilepsy (CAE), being responsible for 18% of epilepsy in school aged children, is clinically characterized by daily absence seizures in children with normal cognition, development and neurological examination ^{11, 13}. CAE usually manifests in children from 4 to 10 years of age and it is more common in female patients ^{14, 15}. Febrile seizures are present in between 10% and 15% of cases ¹⁶.

Typical absence seizures last from 3 to 20 seconds, and only rarely more than 30 seconds, with an abrupt onset and offset. Children experience a complete loss of awareness that can be perceived by others as staring, loss of facial expression and interruption of activity, with an immediate return to normal activity. Most of the children also have oral and/or manual automatisms or subtle eyelid myoclonus during the seizure. The frequency of the seizures is high, occurring multiple times per day, but it can be underestimated as absence seizures can be confused with nonepileptic disorders, such as inattention or daydreaming ^{17, 18}. The occurrence of generalized tonic-clonic seizures (GTCS) is uncommon and its presence, especially after the resolution of absence seizures, should suggest the evolution from CAE to other IGE syndrome ^{18, 19}. Apart from subtle eyelid or perioral myoclonus during the absence seizure, myoclonic seizures are not present in CAE ¹⁷.

Regarding the interictal EEG, the background electrical activity is normal, but occipital intermittent rhythmic delta activity at a frequency of 2,5-4 Hz with a notched appearance is present on the EEG of 21-30% of the patients with CAE ²⁰. Generalized spike-and-wave paroxysms at 3 Hz (range: 2.5–4 Hz) are required for diagnosis. A polyspike-and-wave pattern may be seen in drowsiness and sleep only, but never in the awake period. In 21% of the patients, intermittent photic stimulation triggers a generalized spike-and-wave pattern, but it does not induce seizures ^{18, 20}. The ictal EEG is characterized by a regular 3 Hz (range: 2,5-4 Hz) generalized spike-and-wave pattern that starts in the first second of seizure onset. A slow spike-and-wave pattern (<2,5 Hz) is not seen in CAE ^{20, 21}.

Unlike the history of typical absence seizures and the characteristic interictal EEG, an ictal EEG is not mandatory to establish the diagnosis. However, if an untreated child performs hyperventilation well for 3 minutes and the EEG does not show a generalized spike-and-wave pattern, CAE can be excluded, as both the absence seizures and the ictal EEG pattern are provoked by hyperventilation in most untreated patients ¹⁹.

About its natural history, CAE responds well to drug treatment and in 60% of the patients there is remission in early adolescence ^{14, 15, 22}. However, children with CAE may have specific learning difficulties and attention deficit disorder ^{23, 24}. Higher rates of depression and anxiety were

also described in these patients ^{25, 26}. If there is no remission, CAE may evolve into other IGE syndrome ¹⁷.

1.2. Juvenile Absence Epilepsy

Juvenile Absence Epilepsy (JAE) is less common than CAE, as it is the cause of 2,4-3,1% new onset epilepsy in childhood and adolescence ²⁷. Patients present with typical absence seizures that are similar to the ones present in CAE. When compared to CAE, there are two main differences - seizures are less frequent, occurring less than daily, and the loss of awareness is usually partial. In these cases, the person may be able to respond to commands, but is not capable of completing complex tasks. This characteristic that makes seizures more subtle and hard to detect could be responsible for the underdiagnosis of JAE ^{18, 28-30}. GTCS occur in 90% of the patients, which is also a distinguishing feature from CAE, syndrome in which these seizures rarely occur. The onset of the GTCS is usually shortly after the onset of the absence seizures, but in 14-27% of cases, they may precede the absence seizures ²⁹. As in CAE, subtle myoclonus may be seen during an absence seizure, but the presence of myoclonic seizures excludes this diagnosis ¹⁷.

Typically, the age at onset is between 9 and 13 years, but it can vary from 8 to 20 years. As there is an overlap in the age at onset between CAE and JAE, in children with onset at ages close to 10 years old, the distinction between CAE and JAE depends on the frequency of absence seizures ^{29, 31}. Patients have a normal neurologic exam and development and cognition are typically normal ³². A history of febrile seizures is seen in between 6% and 33% of cases ³³.

Despite the similarities between the electroencephalographic activity in CAE and JAE, there are some distinguishing features in the EEG. In the interictal EEG, the background electrical activity is normal and paroxysms of generalized spike-and-wave discharges at frequency of 3-4 Hz (range 3-5,5 Hz) are mandatory for diagnosis. Discharges are more frequent than in CAE, being triggered by sleep deprivation in both awake and sleep recordings. The polyspike-and-wave pattern is seen mostly in drowsiness and sleep. In 25% of the patients, intermittent photic stimulation triggers generalized spike-and-wave discharges, but does not induce seizures. The ictal EEG is characterized by a regular generalized spike-and-wave pattern at a frequency of 3-5,5 Hz which is coincident with the onset of the absence seizure. Disorganized discharges, defined by brief (less than one second) or transient interruptions in the ictal rhythm or waveforms of different frequency or morphology, can occur and are significantly more common in JAE than in CAE. A slow spike-and-wave (<2,5 Hz) pattern is not seen in JAE ^{20, 34}.

Both the absence seizures and the ictal EEG pattern are provoked by hyperventilation in most untreated patients. If an untreated child performs hyperventilation well for 3 minutes and there the EEG does not show a generalized spike-and-wave pattern, JAE is not necessarily excluded, but it is unlikely. However, if a staring spell occurs and there is no EEG correlation, an absence seizure can be ruled out for that specific episode. Similarly to CAE, the presence of typical absence seizures and the characteristic interictal EEG are mandatory to establish the diagnosis ^{20, 34}.

Although seizures may be controlled with antiseizure medication, lifelong treatment may be required ^{29, 35}. Given the high likelihood of GTCS, broad spectrum antiseizure medications should be used instead of ethosuximide as the first line monotherapy ³⁶. As in CAE, attention deficit disorder and learning difficulties may occur ^{37, 38}. There were also described higher rates of depression and anxiety in these patients ²⁶.

1.3. Juvenile Myoclonic Epilepsy

Juvenile Myoclonic Epilepsy (JME) is the most common IGE syndrome in adolescence and adulthood. It accounts for approximately 9,3% of all epilepsies ³⁹. It is characterized by myoclonic and GTCS in an adolescent or adult with normal development ³⁸.

The age of onset can range from 8 to 40 years old, but most cases occur between 10 and 24 years old, with a slight female preponderance. A considerable percentage (5-15%) of patients with JME evolve from CAE, but if myoclonic seizures start before the age of 8 years, another diagnosis should be considered ^{14, 40}. A history of febrile seizures is seen in approximately 4-5% of patients⁴¹.

In JME, the presence of myoclonic seizures is mandatory for diagnosis. However, GTCS are present in more than 90% of patients and absence seizures occur in 33% of cases ^{18, 42}. Myoclonic seizures may be unilateral or bilateral, but generally with predominance in one side of the body and are more common in the first hour after awakening, being triggered by sleep deprivation. Most of the myoclonic jerks involve the upper limbs but, in some cases, lower limbs can be involved, leading to falls. When subtle, seizures can be unnoticed, being only recognized retrospectively after the first GTCS. GTCS have a later onset than myoclonic seizures, and, when they occur, are preceded by myoclonic seizures, in an increasing frequency and intensity, resulting in a myoclonic-tonic-clonic seizure ¹⁸. Absence seizures are typically subtle with incomplete loss of awareness, lasting 3-8 seconds and occur less than daily ³.

EEG findings in the interictal period, which, in association with myoclonic seizures, are mandatory for establishing the diagnosis, include generalized spike-and-wave, typically with

polyspike-and-wave, paroxysms in a normal background. The pattern is irregular with a frequency of 3,5-5 Hz and it is triggered by sleep deprivation both in the awake and sleeping periods. Focal or multifocal spikes are present in 20% of patients and even though their location varies from EEG to EEG, most of them are in the frontal region. If focal slowing and focal discharges are consistent in one area, focal epilepsy and structural brain alterations should be considered ²⁰. In more than 33% of cases there is photoparoxysmal response (PPR) to intermittent photic stimulation which may trigger seizures ^{20, 33}.

In the ictal EEG, myoclonic seizures correspond to a generalized polyspike-and-wave discharge, in which the spike coincides with the jerk. If there are no discharges associated with the myoclonus, JME is excluded, with a diagnosis of nonepileptic myoclonic jerks. In the GTCS, the EEG is often obscured by movement artifacts, but the tonic stage is characterized by fast rhythmic spikes and the clonic stage corresponds to a burst of spikes and aftercoming slow waves. The ictal EEG in absence seizures may show a generalized polyspike-and-wave or a generalized spike-and-wave discharge at a frequency of 3,5-5 Hz ^{43, 44}.

In 65-92% of patients, seizures respond to antiseizure medication ^{42, 45}. Risk factors for drug resistance are absence seizures, psychiatric comorbidities, history of CAE and younger age at epilepsy onset ⁴⁶. Even though most of the patients are drug responsive, myoclonic seizures are harder to control than GTCS. In the treatment of JME, sodium channel blockers (carbamazepine, oxcarbazepine, phenytoin) usually aggravate myoclonic and absence seizures, whereas lamotrigine can aggravate myoclonic seizures ⁴⁷. Lifelong therapy is frequently necessary ⁴⁸. In addition to the higher rates of anxiety and depression found in these patients when compared to the general population, which were also present in CAE and JAE, studies documented higher rates of impulsivity in JME patients ⁴⁹⁻⁵².

1.4. Epilepsy with Generalized Tonic-clonic Seizures Alone

Epilepsy with Generalized Tonic-clonic Seizures Alone (GTCSA) is characterized by GTCS of variable frequency, but generally infrequent, occurring yearly or less than yearly, and typically triggered by sleep deprivation. Alcohol consumption and fatigue can also trigger seizures ⁵³. In GTCSA, there are no other seizure types. It is responsible for one third of IGE in adolescence and, even though the age of onset can range from 5 to 40 years old, 80% of patients have their first seizure after 20 years of age ^{30, 35}.

Interictal findings are mandatory for diagnosis. Patients present with paroxysms of generalized spike-and-wave or polyspike-and-wave at a frequency of 3,5-5 Hz in a normal

background. This activity is typically more intense in sleep deprivation. Slow spike-and-wave discharges (<2,5 Hz) are not seen ¹.

EEG ictal findings are often obscured by movement artifacts, but they include generalized fast rhythmic spikes in the tonic stage, followed by bursts of spikes and after-coming slow waves during the clonic stage ¹.

Seizures respond to medication, but, as remission is rare, lifelong treatment is usually necessary ⁵³. Patients typically have a normal cognition, but anxiety or depression can be found ³⁸.

1.5. Focal Findings in Idiopathic Generalized Epilepsy

As IGE comprises a group of generalized epilepsies, focal features in imaging studies are not expected. In the clinical context, patients with IGE with a typical clinical presentation and characteristic EEG features, usually have no indication to perform neuroimaging studies. These should only be considered if patients present with atypical clinical features, drug resistance or persistent focal slowing on EEG ¹.

However, several studies in patients with IGE have identified focal characteristics across various domains - focal clinical features have been described, as well as anatomic and functional focal findings ⁵⁴. Clinical manifestations were suggestive of the involvement of frontal lobe networks in IGE as, frequently, patients with IGE present with subtle cognitive and behavioural symptoms, as well as a poor social outcome when compared to healthy individuals ¹. This has prompted further studies to explore this hypothesis. Although, by definition, patients with IGE do not present evidence of focal structural lesions in the brain in magnetic resonance imaging, structural and functional abnormalities predominantly involving the frontothalamic network have been described arising from new imaging methods and new functional studies of the brain. This evidence, compatible with frontal involvement, may help to explain the difficulties these patients face even when seizures are under control. In this review, we will describe the evidence supporting frontal lobe involvement in IGE ⁵⁴.

2. Objectives

This review aimed to describe the evidence supporting frontal lobe involvement in IGE.

3. Methodology

A narrative review was conducted regarding changes compatible with frontal lobe involvement in patients with IGE. The research was performed using the PubMed and Scopus databases, without restrictions on the dates of the analysed studies. The described evidence was divided into three sections: clinical alterations, structural alterations, and functional alterations involving the frontal lobe. The first section documents the cognitive, psychiatric, and social changes reported in patients with IGE. The second section addresses structural alterations identified in studies using brain magnetic resonance imaging. The third section focuses on findings from functional studies, such as electroencephalography, functional magnetic resonance imaging, magnetoencephalography, positron emission tomography and magnetic resonance spectroscopy.

4. Development

4.1. Clinical Evidence of Frontal Lobe Involvement in Idiopathic Generalized Epilepsy

4.1.1. Cognitive Impairment

Growing evidence describing cognitive impairment in IGE, particularly involving frontal lobe functions, has emerged in recent years. Several studies have explored cognitive function in patients with IGE. In specific cognitive domains assessed by neuropsychological tests, mild impairments in attention tasks were observed as well as mild deficits in language-related domains^{55, 56}. Furthermore, studies indicate that patients with IGE experience deficits in executive functions, primarily governed by the prefrontal cortex, specifically in complex tasks involving short-term memory⁵⁷.

Moreover, research involving unaffected siblings of IGE patients has shown that they may share some of these cognitive deficits, suggesting that these impairments are genetically influenced and may function as endophenotypes. In a study comparing the neuropsychological performance of patients with IGE, their unaffected relatives, and healthy controls, both patients with IGE and their siblings exhibited similar profiles of cognitive deficits. Impairments were noticed in domains

of attention and working memory. However, the deficits were more pronounced in patients with IGE, potentially due to a stronger genetic contribution or disease-related factors ⁵⁸.

Neuropsychological assessments in children with CAE have shown mild impairments in attention and executive functions, particularly in problem-solving and phonemic fluency ⁵⁹⁻⁶⁴.

A study with epilepsy patients showed that cognitive performance in individuals with JAE was significantly lower than in healthy controls across domains of attention, psychomotor speed, language, and executive function. Patients with ongoing seizures exhibited lower working memory scores. Furthermore, among JAE participants, those with a later age of onset performed better in attention and psychomotor speed tasks. It was hypothesized that the timing of disease onset in JAE, which occurs during an important period of the frontal lobe development, may be responsible for a disruption in the maturation of frontal networks. This disruption could lead to cognitive function impairment and executive dysfunction, highlighting the significant impact of epilepsy onset on frontal lobe development ⁶⁵.

However, the study found that response inhibition remained intact in patients with JAE, unlike in patients with JME. This suggests that not all aspects of executive function are uniformly impaired in IGE syndromes, with executive function subdomains potentially being differentially affected across the IGE spectrum ⁶⁵.

Additionally, both patients with JAE and their unaffected siblings exhibited similar language impairments, suggesting a familial trait ⁶⁵.

Regarding patients with JME, neuropsychological assessments have consistently revealed that JME is associated with significant impairments in cognitive functions, particularly those with involvement of frontal lobe ⁵⁴. Tests such as the Frontal Assessment Battery and the Executive Interview revealed significantly lower scores in patients with JME, indicating executive dysfunction. Specific difficulties have been identified in mental flexibility - impaired ability to switch between or simultaneously manage multiple concepts - and task planning and sequencing - challenges in organizing tasks and understanding their appropriate order ⁶⁶. Prospective memory, which is closely tied to executive functioning, has also been found to be significantly impaired in patients with JME and their unaffected siblings compared to healthy controls. Additionally, deficits in visual working memory have been observed in JME and they were similar to the deficits observed in patients with frontal lobe epilepsy ^{67,68}. Researchers have also explored decision-making abilities in patients with JME using the Iowa Gambling Task. Results showed worse performance in patients with JME compared to controls, with a trend toward poorer outcomes in those with inadequate seizure control ^{69,70}.

There are no studies documenting cognitive impairment in patients with GTCSA.

4.1.2. Psychiatric comorbidities

IGE are commonly associated with specific behavioral traits and psychiatric comorbidities, such as mood disorders, anxiety, attention deficit hyperactivity disorder ^{11, 12}. However, it remains unclear whether psychiatric symptoms are part of the IGE endophenotype or are secondary to the chronic disease burden ⁷¹.

A study was conducted to investigate the temporal sequence of psychiatric symptoms and epilepsy onset in patients with IGE. The results revealed that in the five years prior to their IGE diagnosis, patients had an increasing frequency of hospital visits and general practitioner consultations, along with a higher rate of psychiatric medication prescriptions, compared to controls. At the end of the study, patients exhibited a significantly higher rate of psychiatric comorbidities than controls. These findings suggest a prodromal phase of IGE that can be detected approximately five years before the first seizure, characterized by increased healthcare utilization and greater use of prescription medications for psychiatric symptoms ⁷¹.

A study compared child behavior in patients with IGE, patients with localized epilepsy, which consisted in a group of patients with temporal lobe epilepsy and frontal lobe epilepsy, and healthy controls. The findings revealed that children with epilepsy exhibited similar deficits in most evaluated domains, indicating minimal evidence for syndrome-specific behavioral problems. The only significant difference between IGE and the localized epilepsy groups was in social competence, where children with IGE had lower scores compared to controls, a finding not observed in the localized epilepsy group. The study concludes that while individual epilepsy syndromes may have distinct features, behavioral and cognitive issues in children with epilepsy predominantly overlap, emphasizing the importance of addressing these challenges irrespective of specific syndrome diagnoses ⁷².

Furthermore, a comparative study between patients with IGE, frontal lobe epilepsy, temporal lobe epilepsy, and healthy controls showed that epilepsy patients, particularly those with IGE and frontal lobe epilepsy, were more likely to have high impulsivity scores ⁷³.

Studies in patients with IGE with absence seizures, CAE and JAE, have reported a higher prevalence of attention deficit disorder ^{74, 75}. Symptoms—namely inattention, impulsivity, and hyperactivity—are consistent with frontal lobe dysfunction ⁷⁶. Increased rates of impulsivity have also been observed in these patient groups ⁶².

Clinical observations have linked JME to a characteristic sleep-wake rhythm and a specific personality profile, which has been interpreted as features of a mild frontal lobe behavioral syndrome. Subsequent studies validated the distinctive circadian rhythm associated with JME, characterized by a tendency to go to bed later at night, wake up later in the morning, and feel alert

later in the day, compared to patients with temporal lobe epilepsy. However, attempts to confirm a distinctive personality profile in JME using standardized psychological tests have been inconclusive. One possible explanation for this discrepancy is the study's focus on an older age group as behavioral abnormalities may have been more pronounced earlier in the disease course. Notably, the mean duration of epilepsy in the studied JME cohort was 19 years, suggesting that some patients may have 'outgrown' the behavioral traits initially associated with the syndrome ^{77, 78}.

Although a distinct personality profile was not confirmed, research on patients with JME has identified behavioral and neuropsychological impairments similar to those observed in individuals with frontal lobe epilepsy ⁷⁹.

Another study with patients with JME reported a negative correlation between microstructural changes in the cingulum, strongly connected to the frontal cortex, and the personality trait of agreeableness, indicating that frontal lobe alterations may impact emotional regulation and personality traits in JME. Additionally, patients exhibited a tendency toward alexithymia - difficulty recognizing and describing emotions. JME patients also demonstrated significantly higher levels of depression compared to controls ⁵⁷.

These findings underscore the role of frontal lobe dysfunction as a critical feature of JME, contributing to the neuropsychiatric and emotional challenges experienced by these patients. This dysfunction may also underlie the psychiatric comorbidities frequently observed in JME, including anxiety and impulsivity, further highlighting the complex interplay between neurological and psychological factors in this condition ⁵⁷.

There are no studies assessing psychiatric comorbidities in patients with GTCSA.

4.1.3. Social Cognition Impairment

Social cognition is a high-level cognitive function encompassing the processes used to understand and store information about interactions within a social context ⁸⁰. Perceiving social signals related to others' mental states is a fundamental prerequisite for formulating appropriate responses. Additionally, correctly processing these signals and attributing independent mental (knowledge, beliefs, motives) or emotional states to others is essential for understanding and predicting their behavior ⁵⁵.

A study examining empathy and eye emotion recognition in patients with IGE revealed that while affective empathy - the ability to share or resonate with another person's emotional state - remained intact, both eye emotion recognition and cognitive empathy - the capacity to understand another person's perspective or mental state through reasoning and mentalizing - were impaired ⁸¹.

The prefrontal cortex plays a critical role in both affective empathy, involving the orbital and ventromedial prefrontal cortices, and cognitive empathy, involving the medial and the dorsolateral prefrontal cortex. It is also implicated in eye emotion recognition. In the examined patients with IGE, cognitive empathy performance was found to correlate with their ability to recognize sadness, verbal fluency, and Stroop test scores. These results suggest that the observed empathy deficits in patients with IGE may be attributed to impairments in frontal lobe function ⁸¹.

There is an established complex relationship between empathy and morality ⁸². However, it remains unclear whether patients with IGE exhibit moral abnormalities compared to healthy individuals. Additionally, the potential link between frontal lobe dysfunction and moral behavior in IGE is not well understood ⁸³.

Morality has traditionally been conceptualized as a code of values that guides decision-making and behavior, ensuring cohesion and functionality within social groups. Immoral behavior can violate ethical norms and civil rights, posing risks to individual liberty and, in some cases, leading to aggression or violence. The frontal lobe plays a critical role in moral reasoning. Research indicates that different areas of the frontal lobe contribute distinctively to moral decision-making. The orbital and ventromedial prefrontal cortices primarily facilitate emotionally-driven moral decisions, while the dorsolateral prefrontal cortex acts as a rational 'super-ego' filter. Furthermore, brain regions associated with emotional processing demonstrate greater activation during personal dilemmas (e.g., 'me hurt you'), whereas regions linked to rational processing exhibit heightened activation during impersonal dilemmas (e.g., 'not me hurt you') ⁸⁴.

An exploratory study by the same authors who studied empathy in patients with IGE assessed moral decision-making in these patients after evaluating their frontal lobe function. Using 50 hypothetical scenarios encompassing personal, impersonal, and non-moral dilemmas, the study found that both patients with IGE and healthy controls made similar choices in non-moral judgments. However, patients with IGE were more likely to choose utilitarian options in impersonal moral judgments compared to controls. No significant differences were observed between the two groups regarding personal moral judgments. These findings suggest that patients with IGE exhibit atypical impersonal moral decision-making, which may be influenced more by cognitive impairments than by deficits in social-emotional processing. Correlation analysis further supported that the observed abnormalities in moral decision-making were associated with frontal lobe dysfunction in patients with IGE ⁸³.

However, other studies documented opposite results. In a study involving patients with IGE, patients with temporal lobe epilepsy and healthy controls, the participants underwent a basic neuropsychological battery alongside two experimental tasks designed to evaluate social cognition. The tasks included the Ekman-60-Faces test, which assesses emotion recognition from facial

expressions, and the Story-based Empathy Task, a psychological task designed evaluate cognitive empathy through evaluating the ability to infer others' intentions and emotions ⁵⁵. Given the neural correlates of socioemotional processing, which involve specific frontotemporal and limbic networks ⁸⁵, it was hypothesized that social cognition would be impaired in both IGE and temporal lobe epilepsy, with more extensive deficits in temporal lobe epilepsy. While patients with temporal lobe epilepsy showed lower performances on both tasks, patients with IGE showed selective impairments in recognizing anger, but did not exhibit deficits on the Story-based Empathy Task that evaluated cognitive empathy ⁵⁵. These findings contrast with the previous study, which documented deficits not only in eye emotion recognition but also in cognitive empathy ⁸¹.

Regarding facial emotion recognition, previous research supports the presence of deficits in negative emotion recognition IGE. Studies have demonstrated that fear and disgust recognition are impaired in these patients. It has been proposed that dysfunction in thalamofrontal pathways, and disrupted communication between these regions and limbic structures (primarily the amygdala), underlies deficits in recognizing fear and disgust in patients with IGE ⁸⁶.

Social impairments have been described in all major IGE syndromes, with the most pronounced difficulties reported in patients with JME ⁸⁷⁻⁸⁹.

4.2. Structural Evidence of Frontal Lobe Involvement in Idiopathic Generalized Epilepsy

By definition, brain MRI is normal in IGE, not revealing focal abnormalities. However, studies using advanced neuroimaging techniques have uncovered structural changes, particularly in the thalamocortical regions ⁵⁴.

Diffusion tensor imaging (DTI) is an advanced MRI technique that characterizes the microstructural integrity of white matter in the brain by measuring the movement of water molecules along white matter tracks. One of its key metrics is fractional anisotropy (FA), which quantifies the degree of directional water diffusion. FA values range from 0 to 1, with higher values indicating more organized and directionally coherent white matter, and lower values suggesting microstructural disruption, such as demyelination or axonal damage ⁹⁰.

Several studies using DTI have described abnormalities in the microstructural integrity of the frontal white matter in patients with IGE as decreased FA has been reported in prefrontal white matter in both adults ^{91, 92} and untreated children ⁹³ with IGE. The medial prefrontal regions are known to play a critical role in the spreading and generalization of epileptic discharges in IGE. Therefore, abnormalities in this area were not unexpected ⁹⁴⁻⁹⁶. Studies in patients with JME also reported decreased FA values in frontal white matter regions, particularly those underlying the

dorsolateral prefrontal cortex, the supplementary motor area, and the middle frontal gyrus. The FA values were negatively correlated with cognitive function abnormalities ^{97,98}. Moreover, a study in patients with CAE documented lower myelin-water content in the frontal cortex in patients when compared to controls ⁹⁹.

However, these findings were not concordant with the findings observed in other studies. A more recent study, which investigated microstructural abnormalities of the white matter in children with new-onset, untreated IGE showed an opposite finding - it was observed an increased FA in the right white matter of the superior and middle frontal gyri ¹⁰⁰. Additionally, another study identified no FA abnormalities in patients with new-onset epilepsy, but longer illness duration than the children in the previous study ¹⁰¹. Studies with patients with GTCSA also showed variable results - while a study found significantly increased FA in the left superior frontal lobe and the bilateral supplementary motor area of the brains of children with GTCSA ¹⁰², other studies described reduced ¹⁰³ or normal ¹⁰¹ FA.

The differing findings in FA at various stages of the disease suggest that brain microstructural changes in IGE may be dynamic, with increased FA in specific brain areas in the early stages that progresses to decreased FA in the chronic stage. It was hypothesized that increased FA may occur in the early stages of the condition, potentially as part of a compensatory mechanism to maintain normal cognitive function (as the study found that patients with increased FA had normal cognition) or a microstructural alteration contributing to the development of epileptogenic networks. Conversely, the decreased FA observed in chronic IGE could reflect microstructural degeneration potentially contributing to cognitive impairment. ¹⁰⁰.

Supporting this notion, a longitudinal study, which examined the two-year developmental progression of the frontal lobe in pediatric patients with new-onset IGE (diagnosed within 12 months), provides additional insights into the timing and progression of these abnormalities. Compared to healthy controls, who showed an increase in frontal white matter volume, IGE patients showed no significant increase in frontal white matter volume over the two-year period, indicating impaired white matter development, which is compatible with the hypothesis of microstructural degeneration over time in IGE ¹⁰⁴.

Regarding brain grey matter, volumetric analyses in IGE have yielded mixed results, with abnormalities in the thalamus being the most frequently reported. Findings vary widely, with studies identifying reduced ^{105, 106}, increased ¹⁰⁷, or inconsistent ¹⁰⁸ changes in thalamic volumes.

Thalamic abnormalities but also changes in regional cortical grey matter have been identified in studies with voxel-based morphometry, an automated quantitative MRI analysis technique. The most consistent finding is a reduction in thalamic volumes, reported across numerous studies ^{67, 106, 108-118}. Specifically concerning the frontal lobe, abnormalities in frontal

cortical grey matter have also been observed, with reports of both increased^{112, 115, 116, 118} and decreased^{106, 109, 111, 113} volumes. Despite the variability of results, these findings highlight the involvement of the frontothalamic network in IGE.

Moreover, a study in recent-onset, drug-naïve IGE patients with voxel-based morphometry, that measures cortical volumes, and surface-based morphometry, which measures cortical thickness, revealed that, compared to controls, patients with IGE showed decreased cortical volume in the left superior frontal gyrus, particularly the medial frontal region, and decreased cortical thickness in the left rostral middle frontal gyrus, in the dorsolateral prefrontal cortex¹¹⁹.

The longitudinal study which examined the two-year developmental progression of the frontal lobe in pediatric patients with new-onset IGE (diagnosed within 12 months) also observed decreased frontal grey matter volumes. Contrary to results observed in white matter, differences in frontal grey matter volume between controls and patients with IGE were already evident at baseline, with lower volumes in IGE patients, but persisted throughout the study, suggesting that grey matter loss may begin early in the disease and subsequently follows the same grey matter loss trajectory as healthy controls¹⁰⁴.

Regarding the specific syndromes, findings were also variable. In CAE patients, voxel-based morphometry studies found different results regarding frontal grey matter - one study described increased superior medial frontal grey matter¹¹², while two other studies revealed a grey matter decrease, particularly in the subcallosal gyri of the frontal lobe and in the left orbital frontal gyrus^{113, 120}. In a study with patients with JAE, when compared to healthy controls, patients revealed decreased grey matter volume in bilateral frontal regions¹²¹.

A pioneering study using an incipient model of voxel-based morphometry demonstrated an increase in medial frontal grey matter volume in patients with JME when compared to controls¹¹⁸. Subsequent studies replicated the finding of increased grey matter volume in the frontal cortex, especially in the medial frontal region^{112, 115, 116, 118, 122}. Studies also reported increased grey matter, specifically in the frontobasal region, and in the superior frontal, orbital frontal and medial frontal gyri^{112, 116, 123}. However, other studies found different results: three studies found a reduction in grey matter volume in the prefrontal cortex, precentral cortex, or supplementary motor area^{109, 111, 124} whereas two studies did not find any differences in frontal grey matter volume between patients and controls^{67, 125}.

Thalamic involvement was also documented in patients with JME. Voxel-based morphometry revealed findings of anteromedial thalamic volume reduction in patients with JME^{110, 114-116, 126, 127}. The anteromedial thalamus, including the anterior nucleus, ventral anterior nucleus, and mediodorsal nucleus, exhibits strong structural and functional connectivity with the cingulate, premotor, and prefrontal cortices, as shown in DTI and resting-state functional connectivity MRI

studies ¹²⁸⁻¹³⁰. Therefore, the volume reduction of this area supports the hypothesis of thalamofrontal network dysfunction in JME.

A recent meta-analysis of 7 published voxel-based morphometry studies with a total of 211 patients with JME and 241 healthy controls revealed increased grey matter volume in the bilateral medial frontal gyrus and anterior cingulate cortex, and reduced grey matter volume in the bilateral thalamus in JME patients, supporting the notion of structural abnormality of the thalamofrontal circuitry in the pathogenesis underlying JME ¹³¹. Another meta-analysis study using 7 voxel-based morphometry studies also found increased grey matter volume in the medial frontal in a JME cohort ¹³². Unlike voxel-based morphometry studies, that found cortical grey matter volume changes primarily in the frontal lobe, surface-based morphometry studies in patients with JME revealed cortical thickness changes in both the extrafrontal and frontal cortex ¹³³⁻¹³⁸.

Quantitative analysis of the cerebral grey matter volumes indicated that in GTCSA there was a relative increase of grey matter, compared with a control population ¹³⁹. However, two posterior voxel-based morphometry studies described a decrease in frontal lobe grey matter in patients with GTCSA ^{106, 140}. In a different study, GTCSA patients showed significant decreases in grey matter volume in the thalamus and frontal lobe, corroborating the essential role of the thalamocortical network in these patients. In addition, grey matter volume in the thalamus and left medial frontal gyrus had a negative correlation with duration of epilepsy, suggesting that progressive grey matter volume changes may be due to seizures, indicating that epilepsy can directly impair these brain regions ¹⁴¹.

However, it remains largely unknown whether the observed frontal grey matter abnormalities reflect histopathological changes ¹⁴². A few postmortem studies have identified cortical dystopic neurons and other microscopic structural abnormalities, such as excessive or misplaced neuronal and glial cells (referred to as 'microdysgenesis') and increased neuronal density in the frontal cortex in a small number of patients with IGE ^{143, 144}. Histological abnormalities, such as microdysgenesis, could lead to an increase in grey matter volume, potentially explaining some of the morphological changes observed ¹¹⁸. However, such abnormalities can also appear in neurologically normal controls ¹⁴⁵. Additionally, a controlled, blinded histological study did not replicate findings of microdysgenesis or increased frontal neuronal density in IGE ¹⁴⁶.

Apart from the evidence supporting the frontothalamic involvement in IGE, volumetric abnormalities were also described in other brain areas that are connected to the frontal lobe, such as the putamen. A reduced putaminal volume was described in JME patients' MRI studies when compared to healthy controls ^{147, 148}. Considering the strong connections between the putamen and the frontal lobe, this suggests the involvement of striatalthalamofrontal networks in JME ^{79, 148-151}.

4.3. Functional Evidence of Frontal Lobe Involvement in Idiopathic Generalized Epilepsy

4.3.1. Electroencephalogram

A study that used EEG to investigate epileptic discharges in patients with IGE identified that, even though there is not a common focal source for generalized spike-and-wave discharges, the frontal lobe is the principal source of discharges, accounting for 70% of the identified sources. Specifically, the anterior cingulate cortex was identified as a significant anatomical source, contributing to 36% of the discharges, followed by the medial frontal gyrus with 23% ¹⁵². Another study with IGE patients observed that the prefrontal cortex was the principal source of discharges in IGE ¹⁵³.

However, a posterior study with patients with IGE observed that the thalamus, particularly the mediodorsal nuclei, was the primary source of generalized spike-and-wave discharges ¹⁵⁴. The mediodorsal nuclei of the thalamus is known to be strongly functionally connected to the prefrontal cortex ¹⁵⁵⁻¹⁵⁷. The study also identified that a stronger connectivity between the anterior cingulate cortex and the thalamus was correlated with more frequent generalized spike-and-wave discharges. The authors hypothesized that the thalamus initiates the discharges, while the frontal cortex is involved in their spread, highlighting a dynamic corticothalamic network in IGE ¹⁵⁴.

A different EEG study evaluating the correlation between mental activation and epileptic discharges found that the rate of epileptiform activity in the frontal lobe significantly increased during engagement in cognitive tasks, such as the Stroop test, suggesting a potential link between frontal lobe activation in cognitive processing and the modulation of epileptic activity in IGE ¹⁵⁸.

The frontal lobe has also been consistently identified as a principal source of epileptic discharges across specific IGE syndromes as revealed by various EEG studies. A study that aimed to evaluate the origin of epileptiform discharges in CAE observed that 69.4% of epileptic activity originates in the frontal lobe, particularly in the superior frontal gyrus and the middle frontal gyrus and the medial frontal gyrus ¹⁵⁹.

Focal discharges were also identified in a study involving patients with JAE and JME - 53% presented with focal epileptiform discharges. The discharges were most often multifocal and localized essentially in frontal and temporal regions ¹⁶⁰.

Several studies have also described the frontal cortex as the principal source for generalized spike-and-wave discharges in JME ¹⁶¹⁻¹⁶³. In particular, one study observed that, during the ascending phase—representing the initial rise in brain electrical activity prior to a larger discharge—58.6% of the maximal current source density was located in the frontal lobe ¹⁶³. Similar findings have already been reported in earlier studies. One EEG study showed that the spike components of

polyspike-and-wave complexes were associated with prefrontal medial current sources, while the wave components were linked to diffuse sources across multiple cortical regions. These findings support the hypothesis that JME seizures originate primarily in the prefrontal medial cortex and rapidly propagate to other areas ¹⁶⁴.

A source localization analysis in patients with GTCSA estimated that most sources of generalized spike-and-wave discharges were located in the superior frontal gyrus and anterior cingulate cortex ¹⁶⁵.

4.3.2. Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that measures brain activity by detecting changes in cerebral blood flow based on the ratio of oxygenated to deoxygenated hemoglobin, relying on a blood oxygenation level-dependent (BOLD) contrast. When a specific brain area is activated, there is an increased demand of oxygen that is met by increasing the blood flow in that area. The variation in the blood flow alters the ratio of oxygenated to deoxygenated hemoglobin, increasing the BOLD signal ¹⁶⁶.

Several EEG-fMRI studies have been performed in patients with IGE to evaluate the correlation between epileptic discharges and brain activation. Most of them demonstrated thalamic increased BOLD signal with generalized spike-and-wave discharges ^{95, 150, 167-170}, even though in some cases there was a decreased signal in the thalamus ¹⁶⁷. However, the results regarding cortical BOLD signal were more variable - generalized spike-and-wave discharges were associated with increased BOLD signal in some cortical areas, mainly frontal, parietal, temporal and insular ^{95, 167, 169, 170}, but there was described a decreased BOLD signal in certain cortical regions recognized as the Default Mode Network (DMN) ^{95, 150, 167, 169}. The DMN is a complex and heterogeneous network anatomically defined by certain key regions such as the prefrontal cortex - particularly the superior frontal gyrus and the anterior cingulate cortex - the inferior frontolateral cortex, the middle temporal cortex, the inferior parietal lobe, the parahippocampal cortex, the precuneus and the posterior cingulate cortex ¹⁷¹. This network is bilaterally activated at rest. It typically shows decreased activity during attention-demanding tasks, but increased activity during complex cognition processes, many of which are linked to memory, abstract thought or introspection ¹⁷². The increase in BOLD signal in patients with IGE can be explained by the epileptic activity, but the reasons for decreased BOLD signal in the DMN are less clear. They were postulated to be a reflection of interruptions in the default state of the brain by epileptic discharges ⁹⁵.

fMRI findings in patients with CAE were similar to findings in unspecified IGE. One study observed activation of the orbitofrontal medial frontal and medial and lateral parietal cortices 5 seconds before seizure onset, which was followed by thalamic activation¹⁷³. Activation in thalamus and frontal and parietal cortices was also described in other studies during generalized-spike-and-wave discharges^{174, 175}, such as deactivation in DMN¹⁷⁵.

fMRI can also be used to evaluate functional connectivity between different brain areas - if two areas have synchronized BOLD signals in resting-state fMRI, it means they are functionally connected¹⁶⁶.

Decreased functional connectivity between specific brain areas was described in patients with IGE. Resting-state fMRI studies have shown a reduction in functional connectivity inside the DMN - specifically between the prefrontal cortex and the posterior cingulate cortex - and between the prefrontal cortex and the thalamus. In both cases, the duration of epilepsy correlated negatively with the functional connectivity, indicating that epilepsy could compromise communication between the brain areas^{176, 177}. A more recent meta-analysis corroborated these findings as it found decreased functional connectivity in specific frontal regions, particularly in the dorsal anterior cingulate cortex and medial prefrontal cortex, which are part of the DMN¹⁷⁸. Additionally, a recent study that evaluated functional connectivity in children with IGE described significantly reduced functional interhemispheric connectivity between regions in the DMN such as the bilateral hippocampus, bilateral precuneus and bilateral fusiform gyrus. Even though frontal lobe alterations were not described in this study, as the frontal region is part of the DMN, it may be indirectly affected¹⁷⁹.

Functional connectivity analysis in patients with GTCSA described decreased functional connectivity between the cingulate cortex and the frontal cortex¹⁴⁰.

However, hyperconnectivity was described in frontothalamic networks in resting-state fMRI in patients with JME¹⁸⁰, in opposition to the frontothalamic hypoconnectivity described in the study with unspecified IGE¹⁷⁷. It was hypothesized that the thalamus may show heightened activity or coordination with the frontal cortex possibly as a compensatory mechanism to maintain the communication between the areas. Increased functional connectivity was more evident in patients with more severe disease and active seizures¹⁸⁰.

A different fMRI study comparing patients with refractory and non-refractory IGE found significantly increased functional connectivity between the ventral lateral posterior nuclei of the thalamus and regions of the frontal motor cortex in patients with refractory IGE, indicating a potential contribution of this hyperconnectivity and the frontal lobe for the mechanisms of pharmacoresistance in epilepsy¹⁸¹.

Beyond resting-state analyses, fMRI studies evaluating brain activation during cognitive tasks have also provided insights into frontal lobe involvement. A study that aimed to evaluate cortical activation in patients with CAE during cognitive tasks described decreased activation in the medial frontal cortex during the performance of attentional vigilance tasks, indicating a possible impairment of this area in patients with CAE, which could relate with clinical cognitive deficits ¹⁸².

In a study that performed fMRI evaluation while performing working memory paradigms in JME patients, the patients performed well cognitively and there was no difference in fMRI activation between JME and controls. To explain these findings that were inconsistent with previous results, the authors suggested that frontal lobe dysfunction could be present only in a JME subgroup or that the cognitive task was not sufficiently challenging ⁶⁷. A posterior study with fMRI done with more challenging spatial working memory paradigms showed that an increase in cognitive demand was associated with coactivation of the primary motor cortex and supplementary motor area in patients with JME, particularly in those still suffering from seizures, which did not happen in controls ¹⁸³. It also described a hyperconnectivity between the frontoparietal cognitive networks and the motor cortex that could explain how cognitive effort can be responsible for causing myoclonic jerks ¹⁸³. A posterior study that evaluated that the pattern of coactivation of the primary motor cortex and supplementary motor area during cognitive tasks was present not only in JME patients but also in unaffected siblings, indicating a shared trait. This suggests that altered motor system activation and hyperconnectivity is not related to seizures or medication ¹⁸⁴.

There are no studies with fMRI in patients with JAE.

4.3.3. Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive neuroimaging technique that measures the magnetic fields produced by neuronal electrical activity in the brain ¹⁸⁵.

Based on the hypothesis that the network function in the resting-state without epileptiform discharges was more representative of the underlying pathophysiology in IGE, MEG was used to study the brain of patients with IGE. It was described a widespread increase in brain connectivity when compared to controls. These changes were most pronounced in the motor network, the medial frontal and temporal cortex. This increased resting-state connectivity could be a determinant factor for seizure spread and possible generation of seizures ¹⁸⁶.

A study using MEG in patients with CAE observed that most of the participants had more active source activity locations in the ictal-onset period rather than in the interictal period, being

the frontal lobe, the temporoparietal junction and the parietal lobe the main active areas of source activity during the ictal period ¹⁸⁷.

In JAE, a study used MEG to evaluate if the DMN was involved in generalized spike-and-wave discharges. Results showed strong medial prefrontal activation in all patients, with activation in the posterior cingulate and precuneus in three of five patients simultaneously or slightly after medial prefrontal activation ¹⁸⁸.

However, a study using MEG to localize the sources of epileptiform discharges JME at three different time instances (onset, peak, offset) challenges the idea that the discharges originate in the frontal cortex. The study observed that, at onset, discharges were most commonly localized in sublobar regions, while at peak they were mostly localized in the frontal lobe. This suggests that discharges may start in deeper brain regions and then spread to the frontal cortex. The restricted cortical involvement suggests that discharges may not rapidly spread throughout the entire cortex but only in specific areas, such as the frontal cortex ¹⁸⁹.

There are no studies with MEG in patients with GTCSA.

4.3.4. Positron Emission Tomography

Positive Emission Tomography (PET) is not frequently used in patients with IGE, but there are some results from this imaging method in JME patients. A study evaluated fluorodeoxyglucose uptake with visual working memory paradigms in JME patients compared to controls. Only the controls demonstrated increased uptake in frontal regions during the task. The absence of uptake in JME was interpreted as 'cortical disorganization' in the region ¹⁹⁰.

4.3.5. Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a non-invasive technique of *in vivo* quantification of brain metabolites¹⁹¹.

Several studies have been carried out in patients with IGE analysing glutamate + glutamine (GLX), N-acetyl aspartate (NAA), creatine + phosphocreatine (Cr), Choline (Cho), and γ-aminobutyric acid (GABA) levels¹⁶⁶. The most consistent findings are reduced NAA levels in the thalamus and the frontal lobe ^{192, 193}. There are conflicting results on GLX levels in the frontal lobe, with studies showing both increased ¹⁹³ and reduced ¹⁹² concentrations. It was hypothesized that the elevation of GLX may infer increased neuronal excitability and/or increased numbers of glutamatergic neurons, whilst reduced NAA may suggest neuronal dysfunction or loss ¹⁹³.

A study that aimed to identify metabolic differences between photosensitive IGE patients, non-photosensitive IGE patients and healthy subjects by using MRS observed that photosensitive IGE patients showed significantly decreased concentrations of NAA in the right frontal lobe and left thalamus, decreased NAA/Cr ratio in left thalamus, significantly increased Cho/Cr ratio in the right frontal lobe and increased NAA/Cr ratio in the left occipital lobe when compared to normal controls. Frontal lobe involvement was consistent with previous results, but this study suggests an asymmetrical nondominant frontal lobe involvement along with the involvement of the left thalamus ¹⁹⁴.

Another study showed that patients with IGE have increased frontal glutamine and GABA levels when compared with controls, particularly in the left dorsolateral prefrontal cortex, which indicates altered excitatory and inhibitory neurotransmission in frontal regions. Glutamine is a precursor to glutamate, which is the primary excitatory neurotransmitter in the brain. After its action of facilitating communication between neurons in the synaptic cleft, glutamate is taken up by glial cells and converted back into glutamine, which can then be transported back to neurons for reuse. Glutamate itself can be difficult to measure directly due to its rapid turnover and the complexities of MRS techniques, therefore the measurement of glutamine levels may be a more sensitive measure for excitatory neurotransmission than GLX (glutamine plus glutamate). The elevated levels of glutamine are concordant with an increased brain activity in patients with IGE ¹⁹⁵. Regarding the elevated GABA levels, it was suggested by a previous study that pre- and post-synaptic GABA-mediated inhibitory mechanisms were altered in IGE. The findings of this study performed in patients with IGE support evidence from experimental models and *in vitro* studies of human epileptic brain tissue, suggesting that GABA may have a paradoxical excitatory role in the motor cortex, contributing to ictogenesis ¹⁹⁶.

A MRS study with patients with JAE, observed that there were not significant differences in NAA/Cr ratios between JAE patients and controls in frontal and hippocampal regions. However, thalamic NAA/Cr ratios were significantly lower in JAE, even in early stages of the disease ¹⁹⁷.

Multiple MRS studies revealed that some patients with JME had lower concentrations of NAA in the frontal cortex when compared to controls ^{79, 115, 198-201}. The findings were interpreted as a reflection of neuronal dysfunction and not neuronal loss as there was no increase in tissue water content or decrease in other metabolites. Patients with reduced frontal NAA concentrations performed worse in executive function evaluation tests than patients with normal frontal NAA levels, that had similar results in the tests as healthy controls. However, the studies did not establish a correlation between the frequency of seizures and the NAA levels. This suggests that metabolic changes may be responsible for cognitive alterations, but not related to seizures ^{79, 115, 198, 199}. Reduced NAA/Cr ratios were also observed in the frontal cortex in MRS studies, specifically in the

motor cortex and medial prefrontal cortex ^{149, 202}. A more recent meta-analysis corroborated previous results as it revealed decreased NAA/Cr levels in the frontal lobe and it found no significant difference in the NAA/Cr ratios between patients with seizure control and those with refractory seizures. This concept is important to comprehend that treatment should focus not only in controlling seizures but also in potential cognitive deficits that can occur even in well controlled patients ⁷⁹.

Additionally, one study identified reduced GLX/Cr ratio in the motor cortex and medial prefrontal cortex of patients with JME ¹⁴⁹. However, two different studies noted that JME patients had elevated glutamine levels in the frontal lobe, indicating hyperexcitability in JME patients ^{195, 203}. Regarding GABA levels in the frontal cortex, one study observed increased GABA concentrations in JME patients ²⁰³.

Contrary to the results in JME patients, NAA values in patients with GTCSA did not differ from those of the controls. This may indicate a more pronounced frontal lobe involvement in JME than in GTCSA ¹⁹⁹. Another study also observed that these patients had increased GABA and glutamine levels in the frontal cortex, suggesting a compensatory increase in inhibitory neurotransmission in response to the excitatory processes occurring during seizures ¹⁹⁵.

There are no studies with MRS in patients with CAE.

Conclusion

The evidence analysed in this narrative review strongly supports the notion that frontal lobe involvement is a key feature of IGE. This challenges the traditional definition of IGE, which excludes structural brain abnormalities and does not explicitly acknowledge the role of the frontal lobe in these syndromes. The presence of cognitive, psychiatric, and social dysfunctions, as well as structural and functional abnormalities identified in neuroimaging studies, suggests that the frontal lobe plays a more significant role in IGE than previously recognised.

Understanding frontal lobe involvement in IGE is crucial not only to improve diagnostic accuracy, but also to ensure that cognitive, psychiatric and social comorbidities are addressed when patients are treated. This holistic approach that does not focus only on seizure control would contribute to improve long-term outcomes for patients with IGE and consequently their quality of life.

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