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Functional Imaging in Idiopathic/Genetic Generalized Epilepsies

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Summary

Genetic generalized epilepsies affect approximately 15 million people worldwide. Seizures can range from generalized tonic-clonic seizures to absence seizures to myoclonic seizures. They can disrupt learning, memory, and social life and lead to potentially life-threatening consequences during certain activities. Subtypes of genetic generalized epilepsy include epilepsy with generalized tonic-clonic seizures alone, juvenile myoclonic epilepsy, childhood absence epilepsy, and juvenile absence epilepsy.

This review evaluates the literature regarding functional neuroimaging in genetic generalized epilepsy, with a focus on electroencephalography and functional magnetic resonance imaging. Electroencephalography is the primary diagnostic tool. It can be combined with functional imaging techniques such as functional magnetic resonance imaging to investigate the mechanisms underlying genetic generalized epilepsy.

Our understanding of the pathophysiology of genetic generalized epilepsies has considerably improved due to recent developments in functional magnetic resonance imaging. These discoveries have shown abnormal functional connectivity across subtypes, notably within functional networks of the brain. Epilepsy with generalized tonic-clonic seizures alone shows disruptions in the default mode network and motor-related areas. Juvenile myoclonic epilepsy involves the cortex-thalamo-striato-cerebellar network, default mode network, and salience network, while childhood absence epilepsy displays changes in the prefrontal-thalamocortical circuit and attention network. The limited research on JAE indicates some functional network alterations. To develop more accurate diagnostic criteria or identify potential therapeutic targets, there is a need for further research to fully understand the pathophysiology of these disorders.

Keywords: Functional imaging; functional neuroimaging; genetic generalized epilepsy; idiopathic generalized epilepsy; fMRI; EEG; functional networks; Juvenile myoclonic epilepsy; juvenile absence epilepsy; childhood absence epilepsy; generalized tonic-clonic seizures alone.

Introduction

Epilepsy is one of the most common brain disorders in the world. It is estimated that 6.4 people out of 1,000 are affected by this disease (1). The idiopathic/genetic generalized epilepsies (IGE/GGE) account for about 20 percent of all epilepsies (2). According to this estimation, approximately 15 million people are affected worldwide.

Multiple types of seizures caused by the disease can significantly disrupt a person's life (3). GGE affects mainly young people and interferes with learning, attention, memory, and other aspects of academic and social life (3). Seizures can be dangerous and potentially life-threatening, if they occur during certain activities, such as swimming or driving (4).

A combination of electroencephalography (EEG) and clinical features is the most commonly used tool for diagnosis, but it has not been able to explain the pathophysiological basis, which is still not fully understood (5). Recent advances in other functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have revealed new insights into brain networks and mechanisms that underlie the disorder.

The objective of this review is to summarize and critically evaluate the expanding body of literature regarding functional neuroimaging in IGE/GGE, with a focus on fMRI. Since this field has grown rapidly in recent years, it is important to provide a comprehensive overview of the key findings and their implications.

Literature selection strategy

The relevant literature for this review was identified by a systematic search of electronic databases, including PubMed, ClinicalKey, and Google Scholar. A literature search was conducted in January 2023. Only studies written in English were selected. There were no restrictions with respect to the publication year. This search was conducted using the following keywords: “functional neuroimaging” OR “functional imaging” OR “fMRI” OR “EEG” OR “electroencephalography” OR “functional networks” AND “IGE” OR “idiopathic generalized epilepsy” OR “GGE” OR “genetic generalized epilepsy” OR “JME” OR “Juvenile myoclonic epilepsy” OR “JAE” OR “Juvenile absence epilepsy” OR “CAE” OR “childhood absence epilepsy” OR “GTSCA” OR “generalized tonic clonic seizures alone”. Further relevant studies were identified by reviewing the reference lists of the included studies.

Genetic Generalized Epilepsy

Genetic generalized epilepsy is a group of epileptic diseases with similar clinical symptoms and electroencephalographic signs that are thought to be caused by genetic mutations (6). The genetic involvement of these conditions is still under investigation and is therefore only an assumption at this time. The clinical picture consists of generalized seizures, such as absence seizures, myoclonic seizures, tonic-clonic seizures, or a combination of these. In addition to seizures, patients with GGE syndromes typically exhibit a generalized 2.5 to 5.5 Hz spike-

wave pattern on EEG, which can be frequently induced by hyperventilation or photic stimulation (7).

According to the "International League against Epilepsy" the terms genetic generalized epilepsy and idiopathic generalized epilepsy can be used synonymously. This review will focus on the most common types of GGEs which include epilepsy with tonic clonic seizures alone (GTCSA), childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME) (5).

As the name suggests, GTCSA is characterized by recurrent generalized tonic-clonic seizures (GTCS) in the absence of other seizure types. It usually manifests in adolescence or early adulthood and can have a significant impact on daily life (8). CAE is a subtype of GGE that typically manifests between the ages of four and ten (9). Brief episodes of staring and unresponsiveness are common in children with CAE, and they can last up to 30 seconds. Often, those absence seizures are misinterpreted as daydreaming or inattention. Seizures often occur multiple times daily. CAE can rarely cause generalized tonic-clonic seizures (5). JAE is an epilepsy with predominant absence seizures and is very similar to CAE. JAE can be diagnosed from 8 to 20 years of age. It can be difficult to differentiate it from CAE in the overlapping years because both the clinical picture and the appearance on EEG can be similar (5). Patients with JAE typically experience fewer seizures than those with CAE (8). JME is the most common type of IGE. It typically occurs during adolescence or early adulthood. Symptoms of JME include myoclonic jerks, which are sudden, brief contractions of the arms, legs, or face. Certain stimuli may trigger these jerks, such as sleep deprivation or photic stimulation. Additionally, other types of seizures can occur, including generalized tonic-clonic seizures and absence seizures (10).

The diagnosis of GGE typically involves a detailed history to determine which seizure type was experienced and electroencephalography, which will be discussed in greater detail in a later section.

Genetic generalized epilepsy is frequently associated with mood disorders, anxiety, and attention-deficit hyperactivity disorder. The presence of these comorbidities is not always the case (11).

IGE syndromes can be treated with anti-seizure medication. Diagnosing the subtypes of IGE to manage it effectively is crucial since each subtype may require different treatment approaches. In approximately 80% of cases, anti-seizure medications are effective in treating IGE syndromes. Individual therapeutic outcomes can vary depending on the syndrome (5).

Functional neuroimaging

Functional neuroimaging is used to measure changes in brain activity, whereas structural neuroimaging assesses the brain's anatomy and physical structure. Functional neuroimaging is based on the idea that alterations in neural activity are associated with alterations in local blood flow, metabolism, and oxygenation. Various techniques, including electroencephalography, functional magnetic resonance imaging (fMRI), positron emission tomography, single photon emission computed tomography, and magnetoencephalography, can detect these alterations (12). Using electrodes positioned on the scalp, electroencephalography measures the electrical activity of the brain. Typically, EEG is not considered a neuroimaging technique, but a neurophysiological technique. However, it can be combined with other neuroimaging techniques, to overcome some of their disadvantages. EEG has a high temporal resolution while its spatial resolution is poor. Moreover, it is susceptible to artifacts caused by motion or other factors (13). While EEG alone is used to diagnose GGE, fMRI is a tool for research purposes. Functional magnetic resonance imaging measures changes in blood oxygen levels in the brain. These changes occur in response to neuronal activity. In contrast to EEG, it has a higher spatial resolution but a relatively poor temporal resolution (14).

When fMRI and EEG are used together, researchers can measure both the changes in blood flow and electrical activity in the brain that happen at rest or when performing certain tasks (15). EEG is great for measuring quick changes in the brain because it has a high temporal resolution. On the other hand, fMRI is better at identifying where brain activity is happening than EEG (16). When these methods are used together, researchers can look at the fMRI data that is collected either during or between seizures or generalized spike-wave discharges.

Functional neuroimaging can provide valuable insight into the functions of the human brain and has been used to study the underlying processes of GGE and other neurologic diseases.

Electroencephalography

Electroencephalography measures the electrical activity in the brain. The electrical activity is caused by a group of neurons that are active at the same time. When an action potential is generated, it eventually reaches the pre-synaptic part of the synapse. This causes the release of neurotransmitters. The neurotransmitters then attach to receptors on the post-synaptic neuron. Depending on the type of neurotransmitter and receptor, either positively or negatively charged ions enter the cell. Positively charged ions create an excitatory potential, while negatively charged ions create an inhibitory potential. Pyramidal cells in the cortex are arranged

perpendicular to the surface, with their dendrites extending outward. Therefore, the influx of ions creates an electrical dipole. Charges that are separated by a distance generate an electrical field that can be measured by EEG electrodes placed on the scalp. It is important to note that EEG can measure mostly the electrical activity of cortical neurons and not of subcortical structures (13).

Genetic generalized epilepsies are associated with abnormalities in the EEG, because they have an electrophysiological basis (17). Thus, the technique can be used for the diagnosis of GGE (18). Because the treatment can vary depending on the type of epilepsy, a correct diagnosis is essential (19). Generalized spike-wave complexes, occurring at a frequency of 3 Hz, are the main diagnostic features (20). The morphology of spike-wave complexes can vary, but these differences alone cannot distinguish the subtypes of generalized genetic epilepsy from each other (17). Specific characteristics are helpful in differentiating subtypes of the disorder. However, electroencephalography alone is not sufficient to make a definitive diagnosis and must be used in conjunction with the clinical picture. Juvenile myoclonic epilepsy is characterized by abnormal activity on electroencephalography with spike-wave discharges at 3.5 to 6 Hz (21). Approximately 83% of juvenile myoclonic epilepsy cases exhibit photoparoxysmal responses (22), while around 30% – 50% have focal abnormalities (23,24). Epilepsy with generalized tonic-clonic seizures alone is characterized by spike-wave discharges of 3.5 Hz (17), usually during sleep-wake transitions (25,26). Electroencephalographic abnormalities in patients with childhood absence epilepsy are characterized by spike-wave discharges of 3 Hz, which occur in 97% of cases while sleeping (27). Patients with childhood absence epilepsy may show occipital intermittent rhythmic delta activity, which can help to distinguish it from juvenile absence epilepsy (28). Around 52% show focal abnormalities (29). In juvenile absence epilepsy, spike-waves of 3.5 to 4 Hz are observed (30). However, there is no occipital intermittent rhythmic delta activity present. In juvenile absence epilepsy, epileptiform discharges are more common than in childhood absence epilepsy (17). There are a variety of techniques that can be used to improve the yield of EEGs. Among them are photic stimulation, hyperventilation, and sleep deprivation (19).

Functional Magnetic Resonance Imaging

While a structural MRI is performed to detect structural abnormalities, fMRI can detect abnormalities in brain function. Oxygenated and deoxygenated hemoglobin molecules have different magnetic properties. Based on this fact, fMRI can differentiate between areas that are rich in oxygen and areas that are poor in oxygen. It detects the blood oxygen level dependent

(BOLD) signal (31). When a neuron is active, it consumes oxygen. This causes a very short period of an increased concentration of deoxygenated hemoglobin, which is then followed by an increase in oxygenated hemoglobin because the blood flow to that specific area is increased. This increase in oxygenated hemoglobin can be measured and has its peak roughly 6 seconds after the neuronal activity. Therefore, fMRI can measure the precise area of the brain that is active (32,33). While fMRI has high spatial resolution, its temporal resolution is poor because changes in oxygenation occur several seconds after neuronal activity. This limitation can be overcome by combining fMRI with EEG (34).

The functional connectivity magnetic resonance imaging (fcMRI) technique is used to examine active brain regions over time. The results of this analysis can be used to identify functional networks. They are composed of groups of brain regions that exhibit correlated activity when performing particular tasks or during resting states. Functional networks are not necessarily anatomically connected but reflect the functional organization of the brain (35). Several networks have been identified in the human brain. The default mode network (DMN) and attention network (AN) are thought to play a significant role in genetic generalized epilepsy (36). They correspond to anatomical areas that are active under specific circumstances. The DMN, or task-negative network, is the area of the brain that is active when no active task is performed. Therefore, it belongs to the resting networks (37). It consists of the ventral medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), inferior parietal lobule, lateral temporal cortex, dorsal medial prefrontal cortex, and the hippocampal formation (37). The AN, or task-positive network, is the area of the brain that is active when performing active tasks (36).

There are several methods of fMRI used to evaluate brain abnormalities in GGE. A few of them will be discussed in the following. The two main approaches to identifying functional networks are functional segregation and functional integration. Functional segregation describes the separation of different functional networks. In other words, segregation refers to the negative connectivity between different networks (38). It is measured by analyzing the resting-state fMRI activity of specific brain regions. Functional integration, on the other hand, describes the connectivity of brain regions that belong to a functional network. It is measured by resting-state fMRI connectivity. Segregation methods include both the amplitude of low-frequency fluctuations (ALFF) and the regional homogeneity (ReHo) analysis. The BOLD signal can oscillate at different frequencies. The ALFF method measures the BOLD signal at low frequencies of 0.01 to 0.1 Hz (39). Low-frequency oscillations are believed to be the result of spontaneous fluctuations in neural activity, even without a specific task or stimulus.

Therefore, it may reveal abnormalities in the DMN (40). A variation is the fractional-ALFF (fALFF), which measures the BOLD signal at low frequencies divided by the BOLD signal at all frequencies. In other words, it represents how low-frequency oscillations contribute to the overall power of the BOLD signal. Researchers have found that brain regions associated with the DMN have increased fALFF (41). As a result, the analysis of low frequencies can be a useful tool for detecting abnormalities within the DMN (40). Regional homogeneity measures the degree of similarity between the time series of the BOLD signal of neighboring voxels. A high ReHo value suggests high functional connectivity (39). Note that functional segregation methods are not directly measuring functional connectivity.

Functional integration methods, on the other hand, measure functional connectivity directly. There are several main analytical approaches: functional connectivity density, seed-based correlation analysis, independent component analysis, and graph theory analysis (39).

Functional connectivity density (FCD) is one of the most basic measures of functional connectivity. It shows how much a voxel is connected by evaluating the time series of the BOLD signal between a voxel and other voxels of the brain. It is possible to evaluate either the short-range connectivity or the long-range connectivity. As the name suggests, short-range connectivity refers to the connectivity between a voxel and its surrounding voxels. Conversely, long-range connectivity represents the connectivity between a voxel and all other voxels, except those surrounding it. FCD does not identify the specific regions that a voxel is connected to (39).

Seed-based correlation analysis requires a previous definition of a region of interest (ROI) or seed region (39). A variety of methods can be used to define regions of interest, including functional segregation methods, previous results, or anatomical structures (42). The time series of the BOLD signal within the ROI is then compared to the time series of all other voxels within the brain. In this way, functional connectivity between the ROI and other brain regions is measured (39).

Independent component analysis (ICA) analyzes the BOLD signal and separates the brain into functional networks in the form of spatial maps. The functional networks represent independent networks of neurons with synchronized BOLD activity (39).

In graph theory, the brain's functional architecture can be depicted as a graph, which is dependent on nodes and their functional connections. A node is defined as a collection of brain tissue (43). There are several parameters that can be used to analyze graph theory data. During this review, they will be discussed in more detail.

It is important to note that fMRI has certain limitations when it comes to detecting brain activity. They can lead to misinterpretation and make it difficult to compare studies. The data collected by fMRI often contains artifacts. They can be caused by several factors, including motion, respiration, cerebrospinal fluid, cardiac pulsation, and accelerated fMRI sequences. Data from functional connectivity retrieved by fMRI may differ depending on the artifact reduction method, which complicates validating and comparing results (44). Furthermore, the effect of draining veins may alter the BOLD signal. Draining veins are carrying blood low in deoxyhemoglobin away from activated regions to surrounding tissues, which may be misinterpreted as functional connectivity (45). The type of sequence used for analysis may also affect the interpretation of the results. Safi-Harb et al. find a difference in statistical values when comparing the echo-planar imaging (EPI) sequence with the magnetic resonance encephalography (MREG) sequence in patients with epilepsy (46).

Results

The body of research regarding functional neuroimaging in genetic generalized epilepsy has grown considerably over the past few years. Research that is not connected to a specific GGE subtype will be reviewed prior to findings specific to each subtype.

By analyzing the functional connectivity using a seed-based analysis, McGill et al. found an aberrant functional network organization. Their research revealed a reduced functional connectivity within nodes of the DMN and an abnormal segregation between the frontal lobe and areas that belong to the task-positive networks (38). In a later study, McGill et al. used the fALFF analysis to investigate brain activity in several brain areas. In contrast to their previous study, they failed to find a significant reduction in the anteromedial PFC, which belongs to the DMN. However, there was a reduction in neuronal activity in the prefrontal cortex (PFC) subregion that is structurally connected to the thalamus (47). The two studies use different analysis methods, which makes a direct comparison. Using a combination of EEG and fMRI techniques, Kay et al. were able to exclude the periods of generalized spike-wave discharges (GSWD) from their analysis. To assess the connectivity of the DMN, they used independent component analysis. According to their findings, DMN connectivity was significantly reduced among patients with treatment resistance when compared with both treatment-responsive patients and healthy individuals. Furthermore, the duration of the disease and DMN connectivity were negatively correlated. This indicates that the longer the disease persists, the greater the disruption of the DMN (48). A second study by Kay et al. examined the impact of GSWD frequency on resting-state functional connectivity. As GSWD frequency

increased, functional connectivity within the DMN, AN, and executive function brain regions increased (49). In contrast to previous study results, Moeller et al. found no altered resting-state functional connectivity in patients with GGE compared to controls (50).

Several studies have investigated brain activity during seizures or generalized spike-wave discharges. BOLD signal changes before and after GSWD were identified by Benuzzi et al. by combining EEG and fMRI. They were increased in brain areas related to the DMN around GSWD (51). Moeller et al. also investigated changes in brain activity during GSWD in patients with absence seizures. In contrast to Benuzzi et al. they found decreased activations in the DMN in 88% of patients. Deactivations were also found in the caudate nucleus. Like previous studies, they found activations in thalamic and several cortical areas (52). These findings indicate an involvement of the thalamus, cortical areas, the default mode network, and the caudate nucleus in the generation of generalized spike-wave discharges.

Functional Magnetic Resonance Imaging: epilepsy with tonic-clonic seizures alone

Several studies have examined abnormalities in the brain of patients suffering from epilepsy with tonic-clonic seizures alone.

In 2011, Song et al. investigated both the morphology and the functional connectivity in resting-state networks. They find no morphologic abnormality in comparison with the control group. Functional connectivity was analyzed using graph theory analysis. They found a reduced node degree in the anterior medial prefrontal cortex, the posterior cingulate cortex, and the bilateral superior frontal cortex. These areas are part of the DMN (53). Node degree refers to the number of connections that a node has. Thus, highly connected nodes can be identified within a network (39). Furthermore, the researchers found a decreased functional connectivity between these nodes, suggesting that the disruption of the DMN plays an important role in the pathogenesis of epilepsy with tonic-clonic seizures alone (53). A study from Zhu et al. supports previous findings. They discovered a reduction in resting-state functional connectivity within the DMN. Furthermore, they observed an increase in functional connectivity density in the cerebellum as well as in the pre- and postcentral gyrus. These areas are related to motor function (54). Gotman et al. suggest that the increased activity of the cerebellum may be associated with the complex motor manifestations of GTCSA (55).

Several studies have presented contradictory results regarding the functional connectivity of the DMN. Wang et al. found a reduction in functional connectivity among the medial prefrontal cortex, the precuneus, and the right angular gyrus, which are all part of the DMN. An interesting finding was the increased connectivity observed in the PCC, which is an

integral part of the DMN. Moreover, they observed both an increase and a decrease in connectivity within regions of the dorsal attention network (56). Wei et al. discovered increased intra-network connectivity of the anterior DMN. In contrast to healthy controls, the functional connectivity between the anterior DMN and the ventral attention network was positive in patients with GTCSA (57). A recent study by Liu et al. supports the previous findings. They observed increased connectivity within the anterior DMN by analyzing a relatively large sample of 50 patients with GTCSA. However, functional connectivity was decreased in the posterior DMN (58).

A later study by Wei et al. investigated the connectivity of key nodes of the main networks, including the DMN, the SN, and the central executive network (CEN). They used Granger-causality, which determines if there is a causal relationship between different time-series BOLD signals from different brain regions. Thus, it can show if there is a connection between different brain regions. They identified several alterations in inter-network connections, including a decreased causal connection in the right fronto-insular cortex (rFIC) and the PCC. The rFIC belongs to the salience network, which is part of the attention network, whereas the PCC is part of the default mode network (59).

Functional Magnetic Resonance Imaging: juvenile myoclonic epilepsy

In 2011, Vollmar et al. conducted a study that significantly improved our understanding of the pathophysiology of JME. During cognitive tasks, the DMN should be deactivated. However, a reduced deactivation was observed in patients with JME compared to healthy controls. Furthermore, both the motor cortex and supplementary motor area exhibit coactivation in response to increased cognitive load. Additionally, there was an increase in functional connectivity between motor areas and cognitive networks. These findings may explain why cognitive effort can cause myoclonic jerks (60). A study conducted by Bartolini et al. in 2014 investigated the BOLD signal in response to intermittent photic stimulation. The frontoparietal and putamen showed reduced positive BOLD responses, while the primary sensorimotor cortex and DMN showed stronger negative responses (61). According to a systematic review published in 2022 by Moghaddam et al., patients with juvenile myoclonic epilepsy have abnormal brain function patterns. Several brain networks show functional changes during resting-state fMRI, including the cortex-thalamo-striato-cerebellar network, the DMN, and the salience network (SN). Additionally, these networks are thought to be involved in the propagation or regulation of seizures. Task-based fMRI studies suggest that abnormal function in these networks may contribute to cognitive and emotional impairments in JME, but further

studies are needed to confirm this. These abnormalities are also correlated with the severity of the clinical features of JME, such as the disease duration and age at onset (62).

Functional Magnetic Resonance Imaging: childhood absence epilepsy

Functional neuroimaging has gained increasing attention in the research of childhood absence epilepsy. Recent studies have found abnormalities in functional networks in patients with CAE.

According to Drenthen et al., children with CAE have impaired functional network organization. Moreover, they found a significant correlation between longer path lengths and the duration of the disease (63). Path length reflects the global connectivity of a network (39). These findings are supported by a recent study from Yang et al. They examined whole brain networks in drug-naive patients using graph analysis. The results are a decrease in global small-worldness as well as reduced and increased nodal centrality in several brain areas. In the prefrontal-thalamocortical circuit, nodal centrality decreased bilaterally, while it increased in the right middle temporal gyrus and left hippocampus (64). Nodal centrality indicates how much a node is connected within a network, whereas small-worldness indicates how efficiently a network is organized (39).

Killory et al. conducted a study to investigate functional connectivity in the attention network using EEG and fMRI. To evaluate the attentional or task-positive network, they applied the continuous performance task and the repetitive tapping task. They discovered a reduction in functional connectivity within the attention network. Moreover, the researchers observed a correlation between interictal inattention, which is common in patients with CAE, and reduced activation in the medial frontal cortex, a component of the attention network (65).

As reported by Li et al. (2015), there is an increased level of functional connectivity within the DMN. In addition, they found a decreased antagonism between the DMN, the dorsal attention network (DAN), and the SN. A task-positive network, such as the DAN and SN, is usually suppressed when a task-negative network is active. There is a disruption of this antagonism. Furthermore, individuals with CAE exhibited an atypical connection between the central executive network and the task-positive system. The discovery may explain the impairment of attention and executive functions observed in patients with CAE. In addition, they discovered decreased functional connectivity between the DAN and AN, as well as between the SN and the sensorimotor network (66).

Luo et al. found that functional connectivity had been altered in 21 patients with CAE. The functional integration of parts of the SN located in the right anterior insula, anterior temporoparietal junction, and bilateral dorsolateral frontal cortex was decreased. In contrast,

other parts of the SN, such as the anterior and middle cingulate gyrus and the caudate nucleus, showed increased connectivity (67).

Previous studies indicate that the thalamus is involved in the generation of GSW (68). However, Masterton et al. observed a reduction in functional connectivity in the thalamus in resting state fMRI between GSWD (69).

Conversely, Wang et al. found an increase in degree centrality in the thalamus (70). Degree centrality is a measure of functional connectivity. It determines how many direct connections there are between a node and the rest of the brain (39). A decrease in degree centrality has also been observed in the brain regions associated with the DMN (70). This is supported by the results of Yang et al. They report a reduction in regional homogeneity (ReHo) within the thalamus, caudate, and posterior cerebellum, as well as in DMN regions such as the precuneus, PCC, and bilateral inferior lateral parietal lobule. The bilateral insula and left occipital cortex, however, showed an increase in ReHo (71).

As opposed to previous studies, Berman et al. investigated abnormalities of the BOLD signal during absence seizures. By detecting GSWD with an EEG and evaluating continuous performance and repetitive tapping tasks, they were able to identify the absence seizures. During seizures, the fMRI results showed mainly increased activity in the thalamus and both elevated and reduced activity in the cortex (72). The results of this study are supported by Moeller et al. Their study investigated changes in the BOLD signal during GSWD that occur at a frequency of three per second and found an increase in the signal bilaterally in the medial thalamus. In the parietal areas, precuneus, and caudate nucleus, some of which are part of the DMN, the signal during GSWD is reduced (73).

Functional Magnetic Resonance Imaging: juvenile absence epilepsy

Only one study has investigated the resting-state networks of people with JAE. In 2021, Zhang et al. discovered that patients with JAE had a decrease in nodal centrality in the right caudate nucleus, left thalamus, and limbic system. In contrast, the study also found a rise in nodal centrality in various cortices, including the left superior parietal gyrus, the right superior temporal gyrus, the right orbital part of the middle frontal gyrus, and the bilateral supplementary motor area. Furthermore, an increase in degree centrality in the right caudate nucleus and right hippocampus correlated with the disease's duration. This may be explained by the recovery of brain regions following anti-epileptic treatment (74).

Conclusions and suggestions

In conclusion, functional neuroimaging methods are critical to the understanding of the pathophysiology of genetic generalized epilepsies. Electroencephalography remains the key diagnostic tool in these conditions and can be combined with functional magnetic resonance imaging to gain further insight into the underlying mechanisms.

Our understanding of genetic generalized epilepsies and their subtypes has greatly improved because of recent advances in functional magnetic resonance imaging and its combination with electroencephalography. Abnormal functional connectivity, particularly within the default mode network, has been observed across genetic generalized epilepsy subtypes. However, alterations in functional networks vary depending on the subtype of GGE. While some studies have shown reduced connectivity in the default mode network, others have demonstrated increased functional connectivity. Moreover, a negative correlation between default mode network connectivity and disease duration has been observed. Additionally, increased functional connectivity in the default mode network, attentional networks, and executive networks has been reported when the frequency of generalized spike-wave discharges increases. Thus, the default mode network could contribute to the generation of generalized spike-wave discharges. Epilepsy with generalized tonic-clonic seizures alone is characterized by altered functional connectivity within the default mode network and motor-related areas, such as the cerebellum and pre- and postcentral gyrus. These findings suggest a disruption of the default mode network and motor-related regions in the pathogenesis of epilepsy with tonic-clonic seizures alone. In juvenile myoclonic epilepsy, findings highlight the involvement of the cortex-thalamo-striato-cerebellar network, default mode network, and salience network in the regulation and propagation of seizures. A coactivation of the motor areas and supplemental motor areas, as well as increased functional connectivity between motor areas and cognitive areas, may explain the occurrence of seizures when the cognitive demand increases. For childhood absence epilepsy, studies reported both increased and decreased functional connectivity within the precuneus, posterior cingulate cortex, and bilateral inferior lateral parietal lobule. These regions are associated with the default mode network. Furthermore, research has revealed disrupted antagonism between the default mode network, dorsal attention network, and salience network. This might be related to the impairments in attention and executive function observed in childhood absence epilepsy patients. Additionally, alterations have been identified in the prefrontal-thalamocortical circuit and in the attention networks, suggesting that these brain regions and networks might play a role in the complex pathophysiology of childhood absence epilepsy. Based on the limited research that has been

done on the resting state networks of people with juvenile absence epilepsy, some functional network changes have been found.

Even though the research in the past years has been extensively growing, the exact pathophysiology is still unknown. Further research is needed to improve our understanding of genetic generalized epilepsy. As a result, better diagnosis and identification of possible therapeutic targets may be possible.

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