Neuropsychiatric Disease and Treatment

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REVIEW

Understanding of Consciousness in Absence Seizures: A Literature Review

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Abstract: Absence seizures are classically associated with behavioral arrest and transient deficits in consciousness, yet substantial variability exists in the severity of the impairment. Despite several decades of research on the topic, the pathophysiology of absence seizures and the mechanisms underlying behavioral impairment remain unclear. Several rationales have been proposed including widespread cortical deactivation, reduced perception of external stimuli, and transient suspension of the default mode network, among others. This review aims to summarize the current knowledge on the neural correlates of impaired consciousness in absence seizures. We review evidence from studies using animal models of absence epilepsy, electroencephalography, functional magnetic resonance imaging, magnetoencephalography, positron emission tomography, and single photon emission computed tomography.

Keywords: awareness, electroencephalography, functional magnetic resonance imaging, positron emission tomography, single photon emission computed tomography, magnetoencephalography, fMRI, MEG, PET

Introduction

Understanding human consciousness has proven challenging, both philosophically and scientifically. Research on disorders of consciousness has provided valuable insights into the neuronal mechanisms underlying consciousness and facilitated the development of practical definitions. Despite ongoing debates over the meaning of consciousness, it is typically defined as a state of arousal and awareness in the clinical setting.[1] Both cortical and subcortical structures have been implicated in consciousness. These include, but are not limited to, the brainstem's ascending reticular activating system as well as various reticulothalamocortical and extrathalamic pathways.[1] Connectivity within the default mode network (DMN), which comprises the medial frontal cortex, precuneus, posterior cingulate cortex (PCC), medial temporal and lateral parietal lobes, also appears to play a key role in maintaining consciousness.[2,3]

Typical absence seizures consist of brief episodes of staring and unresponsiveness associated with generalized 3–4 Hz spike-wave discharges on electroencephalogram (EEG). They typically last 2–10 seconds, are often accompanied by eyelid fluttering and automatisms, and may be provoked by hyperventilation.[4,5] Absence seizures can occur in various epilepsy syndromes (e.g., childhood absence epilepsy, juvenile absence epilepsy), each characterized by different ages of onset, seizure frequencies, other seizure types, and expected outcomes.[6] Although similar, atypical absence seizures are less common than typical absences, and involve less clear clinical onset and offset, slower and more irregular spike-wave discharges on EEG, and usually occur in association with more severe developmental impairment.[5,7]

While absence seizures are generally thought to involve transient deficits in consciousness, the degree of impairment can vary substantially between individuals as well as from one episode to the next in the same individual.[5,8] Over the past few decades, researchers have attempted to better understand the pathophysiology of absence seizures through various modalities ranging from animal models to EEG and functional magnetic resonance imaging (fMRI). However, several outstanding questions around the neural underpinning of impaired consciousness in absence seizures remain. A deeper grasp of neurobiological mechanisms may pave the way for new therapeutic approaches to reduce the impact of absence

Received: 24 February 2024
Accepted: 14 June 2024
Published: 24 June 2024

seizures on patients' attentive and cognitive functions, particularly among non-responders to current anti-seizure medications. This review therefore aims to describe our current understanding of the neural correlates of altered consciousness in absence seizures, drawing from behavioral, electrophysiological, and neuroimaging studies.

Methods

We performed a narrative review of the literature. The PubMed database was searched for available journal articles up to October 2023. Only articles published in English were reviewed. A variety of search terms relevant to the topic were used, such as "absence", "epilepsy", "consciousness", "awareness", "EEG", "fMRI", "MEG", and "emission tomography", among others. Additional relevant articles were also identified by reviewing the reference list of retrieved papers. Studies that described neural activity associated with absence seizures but did not specifically mention concurrent impairment in responsiveness were excluded. A summary of findings from different studies is provided in Table 1.

Table 1 Studies Supporting Key Findings of Altered Consciousness in Absence Epilepsy, Classified by Modality

	Evidence From:				
Key Findings:	**EEG**	**fMRI**	**MEG**	**PET**	**SPECT**
1. Evidence of increased thalamic activity and/or decreased cortical activity during absence seizures.	Kumar, 2023.[9]	Bai, 2010,[10] Benuzzi, 2015,[11] Berman, 2010,[12] Carney, 2010,[13] Gotman, 2005,[14] Guo, 2016,[8] Laufs, 2006,[15] Li, 2009,[16] Moeller, 2008,[17] Moeller, 2010.[18]		Bilo, 2010,[19] Shimogori, 2017.[20]	Nehlig, 2004.[21]
2. Frontal lobe predominance in absence seizures.	Bai, 2010,[10] Berman, 2010,[12] Guo, 2016,[8] Kumar, 2021,[22] Kumar, 2023.[9]	Benuzzi, 2015,[11] Berman, 2010,[12] Laufs, 2006,[15] Li, 2009,[16] Moeller, 2010.[18]	Jiang, 2019,[23] Shi, 2019,[24] Sun, 2021,[25] Sun, 2021,[26] Sun, 2023,[27] Sun, 2023,[28] Tenney, 2013.[29]	Bilo, 2010,[19] Shimogori, 2017.[20]	Ianneti, 2001.[30]
3. Transient deactivation of DMN regions during absence seizures.	Kumar, 2021,[22] Kumar, 2023.[9]	Bai, 2010,[10] Benuzzi, 2015,[11] Berman, 2010,[12] Carney, 2010,[13] Gotman, 2005,[14] Guo, 2016,[8] Laufs, 2006,[15] Li, 2009,[16] Moeller, 2008,[17] Moeller, 2010.[18]	Shi, 2019,[24] Sun, 2021,[26] Sun, 2023,[28] Wang, 2023.[31]	Bilo, 2010,[19] Shimogori, 2017.[20]	
4. Spike-wave discharges with impaired consciousness are more physiologically intense (e.g., greater EEG/fMRI amplitude) than those with retained consciousness.	Guo, 2016,[8] Kumar, 2021,[22] Kumar, 2023.[9]	Berman, 2010,[12] Carney, 2010,[13] Guo, 2016,[8] Li, 2009.[16]			

(*Continued*)

Table 1 (Continued).

	Evidence From:				
Key Findings:	**EEG**	**fMRI**	**MEG**	**PET**	**SPECT**
5. Prolonged spike-wave discharges are more likely to be associated with impaired consciousness than brief seizures.	Guo, 2016,[8] Kumar, 2021,[22] Li, 2009.[16]	Carney, 2010,[13]			
6. Cortical and subcortical changes precede the initiation of absence seizures.	Aarabi, 2008.[32]	Bai, 2010,[10] Carney, 2010,[13] Guo, 2016.[8]	Sun, 2023,[27] Sun, 2023,[28] Tenney, 2013.[29]		

Measures of Consciousness in Absence Seizures

Awareness is a subjective experience that is inherently difficult to measure and evaluate. Therefore, numerous test paradigms have used recall and behavioral responsiveness as surrogates for consciousness.

Behavior during absence seizures can vary from complete unresponsiveness to no detectable deficits.[8] In absences, there is evidence that consciousness is more likely to be retained during tasks that are less behaviorally demanding.[8,33] This had initially been observed in older studies where performance was less severely affected during simple repetitive motor tasks (e.g., finger tapping) than during more complex tasks (e.g., counting aloud).[5,34,35] Recent studies have used the Continuous Performance Task (CPT), which consists of pressing a button each time the letter "X" appears in a sequence of letters, and the Repetitive Tapping Task (RTT), which consists of pressing a button each time any letter appears on the screen. Multiple groups have demonstrated greater and longer behavioral impairment during CPT, a more attentionally demanding task, compared to RTT.[8,10,12]

The assessment of behavioral responsiveness or task performance during absence seizures is a common approach for classifying episodes into those with either preserved or impaired consciousness. However, direct response testing can be challenging given the abrupt and brief nature of absence seizures as well as the limited collaboration of young pediatric patients.[22] Additionally, within the existing literature, there is a notable lack of consensus regarding what constitutes preserved awareness. Different studies use arbitrary performance thresholds on the CPT task, with one study using a threshold of correct responses above 75% to define spared awareness[8] compared to 100% in another study.[12] Others simply classified events into absences and subclinical spike-wave discharges based on clinical signs (e.g., the participant's response to direct questioning, behavioral arrest).[9,16,22] Lastly, the use of maneuvers such as hyperventilation to induce absence seizures was inconsistent between studies,[8,12,21,26] which may introduce additional confounders given differences in attentional demands and cerebral vasoconstriction.[10] This lack of standardization makes drawing definitive conclusions challenging.

Neural Correlates of Impaired Consciousness in Absence Seizures

Several rationales have been proposed to account for the variable severity of impaired awareness observed in absence seizures. One possible explanation is that seizures affecting or sparing consciousness may involve distinct focal brain regions.[5,36,37] Alternatively, some studies have suggested that all absence seizures engage generalized brain networks, but that consciousness-impairing seizures impact these networks more profoundly than consciousness-sparing seizures.[8,14,16] The next section reviews evidence from studies using different modalities to delve into the brain regions implicated in absence seizures and contrast them with those classically involved in consciousness.

Evidence from Animal Studies

Animal models of absence epilepsy have markedly advanced our understanding of how spike-wave discharges are generated at the cellular level. Different genetic models in rodents (e.g., WAG/*Rij*, Stargazer, and genetic absence epilepsy rat from Strasbourg [GAERS]) have provided evidence that spike-wave discharges are initiated by a cortical focus, most commonly the primary somatosensory cortex, with subsequent propagation to the thalamus and motor

cortices.[36] Correspondingly, the localized administration of lidocaine or tetrodotoxin within the primary somatosensory cortex, but not in other thalamocortical areas, was observed to inhibit spike-wave discharges.[37,38] More precisely, in vivo intracellular electrophysiological recordings have identified deep-layer pyramidal neurons within the primary somatosensory cortex as the ictogenic neurons in absence seizures.[36]

Although rodent absence epilepsy models have face validity with respect to co-morbidities, developmental characteristics, and response to anti-seizure medications, their external validity has been questioned because of contradictory fMRI findings with human studies.[39] Indeed, human patients with absence seizures consistently exhibit decreased cortical blood-oxygen-level-dependent (BOLD) signal during seizures,[8,10,13,39] whereas rodents were found to have increased cortical BOLD signal.[36,40,41] However, McCafferty et al hypothesized that this discrepancy was secondary to the anesthetic agents given to rodents prior to the fMRI scan which altered their BOLD responses.[33] Through a habituation paradigm, they were able to obtain fMRI measurements in unanesthetized GAERS rats and found decreased cortical BOLD activity, consistent with findings in human studies. Subsequent invasive recording revealed a decrease in overall neuronal activity in the cortex during behavior-impairing absence seizures along with enhanced rhythmicity of all neuronal types.[33]

Through the years, various mechanisms for impaired consciousness in absence seizures have been proposed. For instance, in a study using two-photon calcium imaging in a genetic mouse model, Meyer et al suggested that asynchronous suppression of the visual cortex may mediate cortical network dysfunction and loss of awareness during absence seizures.[42] However, no direct comparison of neuronal activity in the primary visual cortex in absence seizures with impaired versus spared behavior was made.

Evidence from EEG

The high temporal resolution of EEG has been used in numerous studies to demonstrate the involvement of highly synchronized cortico-subcortical networks in absence seizures.[5,9,11,16] The bilateral synchronous 3–4 Hz spike-wave discharges characteristic of typical absence seizures tend to be broadly distributed, although a frontal amplitude predominance has been documented.[6,8,12] Interestingly, the overall distribution pattern for absences with preserved versus impaired task performance was similar.[8] However, in both animal and human studies, spike-wave discharges associated with behavioral impairment were found to have significantly greater mean fractional EEG power than those with preserved behavioral responses.[8,22,33] Prolonged absence seizures were also more likely to affect consciousness than brief seizures.[8,22,33]

The exact low-resolution electromagnetic tomography (eLORETA) algorithm has been applied to routine EEG data to compare the neuronal networks implicated in ictal and interictal spike-wave discharges in patients with childhood absence epilepsy.[9] Although electrographically indistinguishable, ictal spike-wave discharges during absence seizures are associated with behavioral impairments while interictal spike-wave discharges have no apparent clinical correlate. For delta band, the connectivity between the thalamus and the PCC, precuneus, angular gyrus, supramarginal gyrus as well as superior parietal and occipital regions was stronger in absence seizures compared to subclinical spike-wave discharges.[9] This increased connectivity between the thalamus and areas of the DMN was suggested to account for the impairment of consciousness observed in absence seizures.

Springer et al developed a machine-learning algorithm able to predict behavioral impairment during spike-wave discharges with 100% positive predictive value.[43] The model relied purely on a combination of preictal and ictal EEG features including spatial distribution, EEG time, and frequency domain. Although the model would benefit from further refinement and validation in a larger cohort, EEG-based machine learning systems represent a promising new approach for identifying more subtle predictors of behavioral impairment in absence seizures.

Evidence from fMRI

The high spatial resolution of MRI has proven instrumental in exploring which brain regions are involved in absence seizures and their relative contribution to the associated impairment in consciousness. Numerous groups have shown spike-wave discharges during absence seizures with transiently impaired consciousness to coincide with bilateral increases in BOLD signal in the thalamus and decreases in the frontal lobe, occipital cortex, caudate nucleus, and areas of the DMN.[8,10,12,13,17,18] Other subcortical structures such as the cerebellum and brainstem reticular formation

have also been implicated, although less consistently.[10,11,13] These findings suggest that abnormal thalamocortical synchronization during absence seizures results in momentary suspension of the DMN and widespread cortical deactivation, leading to a state of altered consciousness.[14–16] One study specifically focusing on the neural mechanisms underpinning the termination of absence seizure with impaired responsiveness found that spike-wave discharge offset was associated with increased BOLD signal in the PCC.[11] Evidence of suppressed PCC activity during absence seizure followed by BOLD signal recovery in this area at the time of seizure termination supports the role of the PCC in alterations of consciousness.[11]

Studies using the simultaneous acquisition of EEG and fMRI directly compared the neuronal networks underlying ictal and interictal spike-wave discharges in patients with absence epilepsy. The functional connectivity within the corticothalamic network was weaker and less widespread in interictal compared to ictal discharges, possibly accounting for the preserved consciousness observed during subclinical interictal events.[12,16] Similarly, Guo et al found that absence seizures with spared behavioral responses showed lower fMRI amplitude in the default-mode, task-positive, and primary sensorimotor-thalamic networks relative to absence seizures with greater behavioral impairments.[8] Although each individual study included only a small number of participants, the direct comparison of spike-wave discharges associated with and without behavioral alterations helps elucidate the brain network dynamics responsible for cognitive impairment during absence seizures.[12,16] Overall, the magnitude of BOLD signal changes in the thalamus and cortex have been consistently associated with the degree of impaired consciousness in absence seizures.

Evidence from MEG

Magnetoencephalography (MEG) is an attractive modality to study neural networks implicated in absence seizures because of its superior spatiotemporal resolution and robustness to signal distortions from the skin and skull. MEG studies of patients with childhood absence epilepsy have shown early ictal activity to be predominantly localized to the frontal and parietal cortices.[23,25,26,29] Some groups have also demonstrated altered activity of the precuneus and other regions of the DMN during absence seizures, although the exact nature of these changes was inconsistent between studies.[26,31]

Similar to fMRI and EEG, MEG has been used to contrast ictal and subclinical interictal generalized spike-wave discharges in an attempt to uncover the mechanism behind altered consciousness in absence seizures. In the alpha frequency band, the magnetic source of ictal spike-wave discharges localized to the frontal lobes, whereas the magnetic source of interictal spike-wave discharges primarily localized to the PCC and precuneus.[24,28] Compared to the interictal group, the ictal group was found to have enhanced theta-band oscillations in the lateral occipital cortex, suggesting decreased neuronal activity in the occipital region and thus impaired visual processing.[27] Additionally, while alpha-frequency activity was dominant in the frontal lobes of both ictal and interictal discharges, ictal discharges exhibited enhanced power.[27] Excessive alpha oscillations within the frontal areas are thought to dampen the influence of irrelevant information and block the reception of meaningful external stimuli. As a result, patients gradually transition into a deeply introspective state.[28] These results have led the authors to propose that impaired responsiveness in absence seizures stems not from loss of consciousness, but rather from insensitivity to incoming visual signals and transition into an introspective state.[27]

Evidence from PET

Numerous studies using ictal positron emission tomography (PET) identified global and focal changes in brain metabolism during absence seizures. However, discrepancies exist between findings from older and newer studies, which have primarily been attributed to the superior resolution of modern PET scanners.[20] In the 1980s to early 2000s, some studies using 18F-fluorodeoxyglucose (FDG)-PET in patients with absence seizures found evidence of diffuse hypermetabolism,[44] while others found no consistent change in brain metabolism in the ictal and interictal periods.[45] More recent studies revealed consistent findings of increased metabolism of the thalamus and cerebellum along with reduced metabolism of the frontal, parietal, and posterior cingulate cortices.[19,20] This pattern of activation and deactivation is strikingly similar to that observed in fMRI studies. It also supports the hypothesis that relative deactivation of the DMN may be responsible for the alterations in consciousness observed during absence seizures.[19]

It has been suggested that cortical hypometabolism may result from glucose depletion or glycogen underutilization.[45] Accordingly, prolonged absence seizures would be associated with more severe neuronal compromise due to substrate depletion, thereby explaining why longer absences are associated more pronounced alterations in consciousness.

Evidence from SPECT

Single photon emission computed tomography (SPECT), a tool used in preoperative assessment of drug-resistant epilepsy, non-invasively measures changes in cerebral blood flow and helps identify epileptogenic foci. However, SPECT has seldom been used to study generalized epilepsy, particularly typical absence seizures. In 2000, a Turkish group used concomitant SPECT and EEG recordings to investigate the pathophysiology of childhood absence epilepsy.[46] They found evidence of diffusely increased cerebral blood flow, which was more pronounced in patients with clinical absence seizures than those with spike-wave discharges without clinical correlate. Ianneti et al also demonstrated cortical, basal ganglia, and thalamic hyperperfusion during ictal SPECT.[30] Conversely, a study using superimposed MRI and SPECT images reported diffusely reduced cerebral perfusion during typical absence seizures, in accordance with human fMRI and animal studies.[21] Overall, SPECT studies have yielded controversial results, which likely reflect a combination of technical limitations and confounders such as the effects of hyperventilation and anti-seizure medications on cerebral blood flow.

Seizure Time Course and Consciousness

Using a variety of different modalities, a number of groups have demonstrated that cortical and subcortical changes can precede the initiation of absence seizures.[8,27,32,42,47] For instance, rodent studies of absence seizures identified EEG alterations that began up to 60 seconds prior to the first spike-wave discharge, and that coincided with a reduction in neuronal firing and altered behavior.[33,39] Similarly, multiple human fMRI studies have demonstrated early BOLD signal changes beginning at least five to ten seconds before seizure onset.[6,10,13,18] Although these findings were corroborated by Guo et al, they observed that fMRI changes only preceded absence seizures that were associated with impaired, but not spared, behavior.[8]

In light of these findings, some authors have postulated on the emergence of a pre-ictal susceptible brain state, characterized by reduced DMN/cortical activity and decreased arousal.[6,33] This pre-ictal brain state may make brain networks particularly vulnerable to absence seizures, facilitating the occurrence of ictal spike-wave discharge.[48] Pre-ictal brain states engaging a larger number of neurons or more intense neuronal activity are thought to result in more severe behavioral impairments and longer lasting EEG changes.[8] This brings forth the intriguing possibility that impairment in consciousness is not caused by, but rather predisposes to, prolonged spike-wave discharges.[49] The suggested permissive role of the DMN in absence seizure occurrence aligns well with the observation that absences occur more frequently in periods of fatigue or rest, when the DMN is active.[6] Alternatively, abnormal fMRI signals prior to seizure onset could be explained by changes occurring in deeper brain structures, which are not captured by surface EEG electrodes.[49]

Genetic Factors

While genetic factors play a key role in absence seizures in most individuals, identifying specific genes and associated molecular mechanisms involved has been challenging. For patients with epilepsy syndromes involving only absence seizures, the two most common being childhood absence epilepsy and juvenile absence epilepsy, the underlying genetics appear to be complex, involving multiple genes and possibly influenced by epigenetic and environmental factors.[50] There are, however, several monogenic causes of absence epilepsy.

One associated gene is *SLC2A1* (OMIM 138140), which encodes glucose transporter 1 (GLUT1), responsible for transport of glucose into the cerebrospinal fluid.[51] Pathogenic variants in *SLC2A1* are associated with a range of absence epilepsy phenotypes, and are identified in 10% of early-onset absence epilepsy patients.[52–54] However, *SLC2A1* pathogenic variants are also associated with other phenotypes, with features including hypoglycorrhachia, intellectual disability, microcephaly, paroxysmal kinesigenic dyskinesia, hemiplegic migraine, and other seizure types such as myoclonic and generalized tonic-clonic, illustrating that impaired brain energy metabolism can result in a range of neurological sequelae.[55,56]

Genes encoding gamma-aminobutyric acid (GABA) receptor subunits such as *GABRA1* (OMIM 137160), *GABRB3* (OMIM 137192), and *GABRG2* (OMIM 137164) have also been associated with absence epilepsy, suggesting disruption of GABA-mediated pathways could play a role in absence seizure generation.[57–59] However, in all cases, the same genes have been implicated in other forms of epilepsy, indicating that the GABA receptor dysfunction is not specifically linked to absence seizures alone.[57,58,60–62]

Finally, disruption in cerebral calcium channel function has been suggested as a risk factor for absence epilepsy, largely based on variants identified in *CACNA1H* (OMIM 607904).[63,64] Evidence in this area is more limited, but the mechanism may be a gain of function.[64]

Conclusion

Overall, the specific physiological processes underpinning alterations in consciousness in absence seizures are not well established. While absence seizures engage widespread brain networks, studies across various modalities have shown regional variations with some brain areas, notably the frontal cortex, being more intensely involved than others. However, whether this regional heterogeneity is responsible for the variable impairment in consciousness observed in absences remains unclear. Interestingly, observed changes in EEG and fMRI signals prior to seizure onset has raised the question of what comes first: a vulnerable state which predisposes to impaired consciousness or the initiation of spike-wave discharges. Larger studies using concurrent recordings with different modalities and standardized definitions of altered versus preserved consciousness are needed. Gaining insights into the mechanism underlying impaired consciousness in absence seizures may inform the development of new therapies and ultimately mitigate the cognitive and psychiatric consequences of absence epilepsy on patients.

Abbreviations

BOLD, blood-oxygen-level-dependent; CPT, Continuous Performance Task; DMN, default mode network; EEG, electroencephalogram; FDG, 18F-fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PCC, posterior cingulate cortex; PET, positron emission tomography; RTT, Repetitive Tapping Task; SPECT, single photon emission computed tomography.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Eapen BC, Georgekutty J, Subbarao B, Bavishi S, Cifu DX. Disorders of consciousness. *Phys Med Rehabil Clin N Am*. 2017;28(2):245–258. doi:10.1016/j.pmr.2016.12.003
2. Danielson NB, Guo JN, Blumenfeld H. The default mode network and altered consciousness in epilepsy. *Behav Neurol*. 2011;24(1):55–65. doi:10.3233/ben-2011-0310
3. Wang C, Vander Voort W, Haus BM, Carter CW. COVID-19 and youth sports: what are the risks of getting back on the field too quickly? *Pediatr Ann*. 2021;50(11):e465–e469. doi:10.3928/19382359-20211019-01
4. Sadleir LG, Scheffer IE, Smith S, Connolly MB, Farrell K. Automatisms in absence seizures in children with idiopathic generalized epilepsy. *Arch Neurol*. 2009;66(6):729–734. doi:10.1001/archneurol.2009.108
5. Blumenfeld H. Consciousness and epilepsy: why are patients with absence seizures absent? *Prog Brain Res*. 2005;150:271–286. doi:10.1016/s0079-6123(05)50020-7
6. Carney PW, Jackson GD. Insights into the mechanisms of absence seizure generation provided by EEG with functional MRI. *Front Neurol*. 2014;5:162. doi:10.3389/fneur.2014.00162
7. Velazquez JL, Huo JZ, Dominguez LG, Leshchenko Y, Snead OC. Typical versus atypical absence seizures: network mechanisms of the spread of paroxysms. *Epilepsia*. 2007;48(8):1585–1593. doi:10.1111/j.1528-1167.2007.01120.x
8. Guo JN, Kim R, Chen Y, et al. Impaired consciousness in patients with absence seizures investigated by functional MRI, EEG, and behavioural measures: a cross-sectional study. *Lancet Neurol*. 2016;15(13):1336–1345. doi:10.1016/s1474-4422(16)30295-2
9. Kumar A, Lyzhko E, Hamid L, Srivastav A, Stephani U, Japaridze N. Neuronal networks underlying ictal and subclinical discharges in childhood absence epilepsy. *J Neurol*. 2023;270(3):1402–1415. doi:10.1007/s00415-022-11462-8
10. Bai X, Vestal M, Berman R, et al. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. *J Neurosci*. 2010;30(17):5884–5893. doi:10.1523/jneurosci.5101-09.2010
11. Benuzzi F, Ballotta D, Mirandola L, et al. An EEG-fMRI study on the termination of generalized Spike-and-Wave discharges in absence epilepsy. *PLoS One*. 2015;10(7):e0130943. doi:10.1371/journal.pone.0130943

12. Berman R, Negishi M, Vestal M, et al. Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. *Epilepsia*. 2010;51(10):2011–2022. doi:10.1111/j.1528-1167.2010.02652.x
13. Carney PW, Masterton RA, Harvey AS, Scheffer IE, Berkovic SF, Jackson GD. The core network in absence epilepsy. Differences in cortical and thalamic BOLD response. *Neurology*. 2010;75(10):904–911. doi:10.1212/WNL.0b013e3181f11c06
14. Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci U S A*. 2005;102(42):15236–15240. doi:10.1073/pnas.0504935102
15. Laufs H, Lengler U, Hamandi K, Kleinschmidt A, Krakow K. Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia*. 2006;47(2):444–448. doi:10.1111/j.1528-1167.2006.00443.x
16. Li Q, Luo C, Yang T, et al. EEG-fMRI study on the interictal and ictal generalized spike-wave discharges in patients with childhood absence epilepsy. *Epilepsy Res*. 2009;87(2–3):160–168. doi:10.1016/j.eplepsyres.2009.08.018
17. Moeller F, Siebner HR, Wolff S, et al. Simultaneous EEG-fMRI in drug-naive children with newly diagnosed absence epilepsy. *Epilepsia*. 2008;49(9):1510–1519. doi:10.1111/j.1528-1167.2008.01626.x
18. Moeller F, LeVan P, Muhle H, et al. Absence seizures: individual patterns revealed by EEG-fMRI. *Epilepsia*. 2010;51(10):2000–2010. doi:10.1111/j.1528-1167.2010.02698.x
19. Bilo L, Meo R, de Leva MF, Vicidomini C, Salvatore M, Pappatà S. Thalamic activation and cortical deactivation during typical absence status monitored using [18F]FDG-PET: a case report. *Seizure*. 2010;19(3):198–201. doi:10.1016/j.seizure.2010.01.009
20. Shimogori K, Doden T, Oguchi K, Hashimoto T. Thalamic and cerebellar hypermetabolism and cortical hypometabolism during absence status epilepticus. *BMJ Case Rep*. 2017;2017. doi:10.1136/bcr-2017-220139
21. Nehlig A, Valenti MP, Thiriaux A, Hirsch E, Marescaux C, Namer IJ. Ictal and interictal perfusion variations measured by SISCOM analysis in typical childhood absence seizures. *Epileptic Disord*. 2004;6(4):247–253.
22. Kumar A, Lyzhko E, Hamid L, Srivastav A, Stephani U, Japaridze N. Differentiating ictal/subclinical spikes and waves in childhood absence epilepsy by spectral and network analyses: a pilot study. *Clin Neurophysiol*. 2021;132(9):2222–2231. doi:10.1016/j.clinph.2021.06.011
23. Jiang W, Wu C, Xiang J, et al. Dynamic neuromagnetic network changes of seizure termination in absence epilepsy: a magnetoencephalography study. *Front Neurol*. 2019;10:703. doi:10.3389/fneur.2019.00703
24. Shi Q, Zhang T, Miao A, et al. Differences between interictal and ictal generalized spike-wave discharges in childhood absence epilepsy: a MEG study. *Front Neurol*. 2019;10:1359. doi:10.3389/fneur.2019.01359
25. Sun J, Li Y, Zhang K, et al. Frequency-dependent dynamics of functional connectivity networks during seizure termination in childhood absence epilepsy: a magnetoencephalography study. *Front Neurol*. 2021;12:744749. doi:10.3389/fneur.2021.744749
26. Sun Y, Li Y, Sun J, et al. Functional reorganization of brain regions into a network in childhood absence epilepsy: a magnetoencephalography study. *Epilepsy Behav*. 2021;122:108117. doi:10.1016/j.yebeh.2021.108117
27. Sun F, Wang S, Wang Y, et al. Differences in generation and maintenance between ictal and interictal generalized spike-and-wave discharges in childhood absence epilepsy: a magnetoencephalography study. *Epilepsy Behav*. 2023;148:109440. doi:10.1016/j.yebeh.2023.109440
28. Sun F, Wang Y, Li Y, et al. Variation in functional networks between clinical and subclinical discharges in childhood absence epilepsy: a multi-frequency MEG study. *Seizure*. 2023;111:109–121. doi:10.1016/j.seizure.2023.08.005
29. Tenney JR, Fujiwara H, Horn PS, Jacobson SE, Glauser TA, Rose DF. Focal corticothalamic sources during generalized absence seizures: a MEG study. *Epilepsy Res*. 2013;106(1–2):113–122. doi:10.1016/j.eplepsyres.2013.05.006
30. Iannetti P, Spalice A, De Luca PF, Boemi S, Festa A, Maini CL. Ictal single photon emission computed tomography in absence seizures: apparent implication of different neuronal mechanisms. *J Child Neurol*. 2001;16(5):339–344. doi:10.1177/088307380101600506
31. Wang Y, Li Y, Sun F, et al. Altered neuromagnetic activity in default mode network in childhood absence epilepsy. *Front Neurosci*. 2023;17:1133064. doi:10.3389/fnins.2023.1133064
32. Aarabi A, Wallois F, Grebe R. Does spatiotemporal synchronization of EEG change prior to absence seizures? *Brain Res*. 2008;1188:207–221. doi:10.1016/j.brainres.2007.10.048
33. McCafferty C, Gruenbaum BF, Tung R, et al. Decreased but diverse activity of cortical and thalamic neurons in consciousness-impairing rodent absence seizures. *Nat Commun*. 2023;14(1):117. doi:10.1038/s41467-022-35535-4
34. Shimazono Y, Hirai T, Okuma T, Fukuda T, Yamamasu E. Disturbance of Conciousness in Petit Mai Epilepsy. *Epilepsia*. 1937;B1(1):49–55. doi:10.1111/j.1528-1157.1937.tb05578.x
35. Mirsky AF, Vanburen JM. On the nature of the "absence" in centrencephalic epilepsy: a study of some behavioral, electroencephalographic and autonomic factors. *Electroencephalogr Clin Neurophysiol*. 1965;18:334–348. doi:10.1016/0013-4694(65)90053-2
36. Depaulis A, Charpier S. Pathophysiology of absence epilepsy: insights from genetic models. *Neurosci Lett*. 2018;667:53–65. doi:10.1016/j.neulet.2017.02.035
37. Polack PO, Mahon S, Chavez M, Charpier S. Inactivation of the somatosensory cortex prevents paroxysmal oscillations in cortical and related thalamic neurons in a genetic model of absence epilepsy. *Cereb Cortex*. 2009;19(9):2078–2091. doi:10.1093/cercor/bhn237
38. Sitnikova E, van Luijtelaar G. Cortical control of generalized absence seizures: effect of lidocaine applied to the somatosensory cortex in WAG/Rij rats. *Brain Res*. 2004;1012(1–2):127–137. doi:10.1016/j.brainres.2004.03.041
39. Gallagher MJ. Neuronal physiology of generalized seizures: the 4 horsemen of absence epilepsy. *Epilepsy Curr*. 2023;23(4):262–264. doi:10.1177/15357597231172322
40. Youngblood MW, Chen WC, Mishra AM, et al. Rhythmic 3–4Hz discharge is insufficient to produce cortical BOLD fMRI decreases in generalized seizures. *Neuroimage*. 2015;109:368–377. doi:10.1016/j.neuroimage.2014.12.066
41. Mishra AM, Ellens DJ, Schridde U, et al. Where fMRI and electrophysiology agree to disagree: corticothalamic and striatal activity patterns in the WAG/Rij rat. *J Neurosci*. 2011;31(42):15053–15064. doi:10.1523/jneurosci.0101-11.2011
42. Meyer J, Maheshwari A, Noebels J, Smirnakis S. Asynchronous suppression of visual cortex during absence seizures in stargazer mice. *Nat Commun*. 2018;9(1):1938. doi:10.1038/s41467-018-04349-8
43. Springer M, Khalaf A, Vincent P, et al. A machine-learning approach for predicting impaired consciousness in absence epilepsy. *Ann Clin Transl Neurol*. 2022;9(10):1538–1550. doi:10.1002/acn3.51647
44. Engel J, Kuhl DE, Phelps ME. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science*. 1982;218(4567):64–66. doi:10.1126/science.6981843

45. Theodore WH, Brooks R, Margolin R, et al. Positron emission tomography in generalized seizures. *Neurology*. 1985;35(5):684–690. doi:10.1212/wnl.35.5.684
46. Yeni SN, Kabasakal L, Yalçinkaya C, Nişli C, Dervent A. Ictal and interictal SPECT findings in childhood absence epilepsy. *Seizure*. 2000;9(4):265–269. doi:10.1053/seiz.2000.0400
47. Roche-Labarbe N, Zaaimi B, Berquin P, Nehlig A, Grebe R, Wallois F. NIRS-measured oxy- and deoxyhemoglobin changes associated with EEG spike-and-wave discharges in children. *Epilepsia*. 2008;49(11):1871–1880. doi:10.1111/j.1528-1167.2008.01711.x
48. Crunelli V, Lőrincz ML, McCafferty C, et al. Clinical and experimental insight into pathophysiology, comorbidity and therapy of absence seizures. *Brain*. 2020;143(8):2341–2368. doi:10.1093/brain/awaa072
49. Moshé SL, Galanopoulou AS. Searching for the mechanisms of consciousness in epilepsy. *Lancet Neurol*. 2016;15(13):1298–1299. doi:10.1016/s1474-4422(16)30278-2
50. Hirsch E, French J, Scheffer IE, et al. ILAE definition of the idiopathic generalized epilepsy syndromes: position statement by the ILAE task force on nosology and definitions. *Epilepsia*. 2022;63(6):1475–1499. doi:10.1111/epi.17236
51. Mueckler M, Caruso C, Baldwin SA, et al. Sequence and structure of a human glucose transporter. *Science*. 1985;229(4717):941–945. doi:10.1126/science.3839598
52. Arsov T, Mullen SA, Damiano JA, et al. Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency. *Epilepsia*. 2012;53(12):e204–e207. doi:10.1111/epi.12007
53. Mullen SA, Suls A, De Jonghe P, Berkovic SF, Scheffer IE. Absence epilepsies with widely variable onset are a key feature of familial GLUT1 deficiency. *Neurology*. 2010;75(5):432–440. doi:10.1212/WNL.0b013e3181eb58b4
54. Suls A, Mullen SA, Weber YG, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol*. 2009;66(3):415–419. doi:10.1002/ana.21724
55. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med*. 1991;325(10):703–709. doi:10.1056/NEJM199109053251006
56. Koch H, Weber YG. The glucose transporter type 1 (Glut1) syndromes. *Epilepsy Behav*. 2019;91:90–93. doi:10.1016/j.yebeh.2018.06.010
57. Wallace RH, Marini C, Petrou S, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. *Nat Genet*. 2001;28(1):49–52. doi:10.1038/ng0501-49
58. Tanaka M, Olsen RW, Medina MT, et al. Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy. *Am J Hum Genet*. 2008;82(6):1249–1261. doi:10.1016/j.ajhg.2008.04.020
59. Maljevic S, Krampfl K, Cobilanschi J, et al. A mutation in the GABA(A) receptor alpha(1)-subunit is associated with absence epilepsy. *Ann Neurol*. 2006;59(6):983–987. doi:10.1002/ana.20874
60. Shen D, Hernandez CC, Shen W, et al. De novo GABRG2 mutations associated with epileptic encephalopathies. *Brain*. 2017;140(1):49–67. doi:10.1093/brain/aww272
61. Epi4K Consortium and Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies. *Nature*. 2013;501(7466):217–221. doi:10.1038/nature12439
62. Cossette P, Liu L, Brisebois K, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat Genet*. 2002;31(2):184–189. doi:10.1038/ng885
63. Chen Y, Lu J, Pan H, et al. Association between genetic variation of CACNA1H and childhood absence epilepsy. *Ann Neurol*. 2003;54(2):239–243. doi:10.1002/ana.10607
64. Heron SE, Khosravani H, Varela D, et al. Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. *Ann Neurol*. 2007;62(6):560–568. doi:10.1002/ana.21169