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Impaired language function in generalized epilepsy: Inadequate suppression of the default mode network

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ABSTRACT

We aimed to study the effect of a potential default mode network (DMN) dysfunction on language performance in epilepsy. Language dysfunction in focal epilepsy has previously been connected to brain damage in language-associated cortical areas. In this work, we studied generalized epilepsy (GE) without focal brain damage to see if the language function was impaired. We used functional magnetic resonance imaging (fMRI) to investigate if the DMN was involved. Eleven persons with GE and 28 healthy controls were examined with fMRI during a sentence-reading task. We demonstrated impaired language function, reduced suppression of DMN, and, specifically, an inadequate suppression of activation in the left anterior temporal lobe and the posterior cingulate cortex, as well as an aberrant activation in the right hippocampal formation. Our results highlight the presence of language decline in people with epilepsy of not only focal but also generalized origin.

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1. Introduction

Epilepsy is a complex condition that is often associated with cognitive impairment. Our work on young people with epilepsy has shown that self-esteem and sense of coherence (SOC) decrease over time [1] and that cognitive impairment places a heavy burden on the patients' daily life [2]. Cognitive problems are often rated highest on the list of problems associated with epilepsy [3]. Recurrent seizures, side effects of antiepileptic drugs, or the underlying disease can affect vital cognitive domains such as memory, visuospatial functions, and, addressed in the current study, language [4–8]. Because of the dominant role of the left temporal lobe in language processing, language function in epilepsy has been most extensively studied in patients with focal seizures originating in the left temporal lobe, although language impairment has also been demonstrated in right temporal lobe epilepsy [9].

Generalized epilepsy (GE) comprises a heterogeneous group of epilepsies of genetic origin with a widespread rather than focal atypical cortical activity [10,11]. Previous findings suggest subtle frontal executive impairments in patients with GE having normal IQ [12]. Language decline has been found in children with GE [13,14]. However, language function in adults with GE has not been studied as thoroughly as in individuals with epilepsy of focal origin.

By means of functional magnetic resonance imaging (fMRI), the functional networks of the brain that are involved in cognitive processing can be identified. Brain regions that are active during specific cognitive tasks show increased (i.e., positive) blood oxygen level dependent (BOLD) response during task performance compared with baseline. It has been shown that brain networks that are involved in several aspects of human brain function also display coherent low frequency BOLD fluctuations during rest [15]. In addition, it has repeatedly been shown that certain brain networks consistently show a negative BOLD response during performance of various cognitive tasks as well as during rest [16–18]. This means that during cognitive processing, some regions are activated, which is expressed as positive and correlated BOLD responses in fMRI, whereas other regions express negative and anticorrelated BOLD responses. It is hypothesized

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that a high degree of temporal correlation within executive networks facilitates cognitive processing [19] and likewise that the presence of anticorrelated networks is equally important [20].

Brain regions with negative BOLD responses during cognitive processing are referred to as the default mode network (DMN) or the resting-state network [21]. This is because DMN regions are functionally connected to each other during rest when spontaneous fluctuations of the BOLD time course occur. Commonly, the anterior and posterior cortical midline structures, the bilateral structures in the parietal and temporal cortices, and the hippocampal formation are regarded as DMN regions [18].

A number of studies have found decreased resting-state connectivity within DMN in patients with epilepsy with generalized myoclonic, tonic–clonic, and/or absence seizures [22–24]. McGill and coworkers [22] provided evidence of abnormal functional integration and segregation of DMN in GE. They observed decreased temporal correlation within DMN and decreased anticorrelation between DMN and other networks in the brain during rest. It has been shown that DMN is involved in loss of consciousness in epilepsy [25,26]. Thus, findings of decreased DMN connectivity in GE have been interpreted to be related to ictal unconsciousness [23,24]. Luo et al. [24] also posed the additional hypothesis of disrupted language networks in absence epilepsy based on their findings of decreased functional connectivity between language regions in the frontoparietal cortex and the temporal cortex during rest. Although a few studies have found aberrations within DMN in GE during resting-state fMRI, we are not aware of any study addressing the DMN in GE during language processing.

In previous studies, it has been shown that the more difficult the task, the greater the negative BOLD response in DMN [27–29]. Task difficulty can be modulated parametrically by, e.g., changing stimulus presentation rate, working memory load, or number of presented objects. Language, on the other hand, is a complex cognitive process [30]. It is, therefore, not straightforward to parametrically vary the level of difficulty during language processing. Addressing this issue, manipulations of complexity have been used. This can be done by varying the structural complexity [31] or the semantic complexity, for example, by using congruent vs. incongruent sentences [32]. Brain responses to incongruent words measured by the N400 event-related potential (ERP) are commonly interpreted to signify mismatch of what is expected in a given context [33]. More recent interpretations of the N400 peak encompass a broader definition, and the prevalent interpretation of the N400 peak is that it denotes 'contextual integration' and reflects the capacity to integrate complex, anomalous information [34]. Thus, congruent sentences are easier and less complex to process, whereas incongruent sentences are more difficult and require more complex language processing [32,34].

In the present study, we investigated language performance with a test battery for subtle language deficits in adults and the negative BOLD response during a sentence-reading task. The aims were to assess language function in GE and to identify DMN regions with negative BOLD responses during language processing in people with GE and in healthy controls. A third aim was to investigate if adding complexity to the language task by using incongruent sentences would modulate the negative BOLD response. We hypothesized that adult people with GE would have language deficits as have been shown previously in children with GE [13,14]. We also hypothesized that people with GE would have inadequate suppression of DMN during language processing expressed by abnormal task-related functional DMN segregation, in line with the recent resting-state findings by McGill et al. [22]. Finally, we also hypothesized that adding complexity to the sentence-reading task would induce a further reduction of the BOLD response in DMN according to previous findings in the literature [29].

2. Methods

2.1. Participants

Eleven participants with GE were recruited from the Department of Neurology at Linköping University Hospital or from the outpatient clinic at Motala General Hospital. Inclusion criteria were people with GE in ages between 18 and 35 years who were fluent in Swedish, without reported language dysfunction, and had completed at least the required nine years of elementary schooling. The diagnoses were set after examination of anamnesis, seizure semiology, MRI, electroencephalogram (EEG), and – when applicable – ictal EEG registration. The International League Against Epilepsy revised terminology of seizures and epilepsies was applied [35]. Exclusion criteria were the use of a vagus nerve stimulator or other electrical or metal implants that could interfere with the fMRI investigation and other concomitant medical, neurological, or psychiatric illnesses and the use of psychoactive drugs (apart from epilepsy treatment) that could interfere with performance. Demographic data for all participants with GE are presented in Table 1.

The study population included 11 participants with GE: five were male, and six were female. The mean age of the patients with epilepsy was 26.5 years (range = 20–35 years, sd = 5.0). One participant with GE was left-handed. The participants with GE had a mean of 13.2 years of education (range = 12–16 years, sd = 1.4). In addition, data from 27 healthy controls are reported; 13 controls were male, and 14 controls were female. The mean age of the controls was 25.5 years (range = 18–35 years, sd = 4.21). One control was left-handed. The controls had a mean of 14.6 years of education (range = 12–20 years, sd = 2.25).

Table 1
The table shows clinical information on patients with generalized epilepsy. F = female, M = male; y = years, Educ. = education. SFP = length of seizure free period, where 1 is less than one month, 2 is less than a year, and 3 is more than one year ago. AED = antiepileptic drugs. Seizure frequency is approximated.

Sex	Age (y)	Educ. (y)	Onset (y)	Classification	Etiology	Seizure (frequency)	SFP	AED[a]
F	20	12	6	Tonic–clonic seizures only	Unknown	Convulsive annually	1	LTG, LEV
F	27	14	17	Tonic–clonic seizures only	Unknown	Convulsive weekly	1	LTG, LEV
M	22	12	15	Tonic–clonic seizures only	Unknown	Convulsive annually	3	VAL, LTG
M	32	15	18	Tonic–clonic seizures only	Unknown	No seizures	3	VAL, LTG
M	32	14	22	Tonic–clonic seizures only	Unknown	Convulsive annually	2	VAL, LEV
M	27	12	19	Tonic–clonic seizures only	Unknown	No seizure	3	VAL
M	29	16	9	Tonic–clonic seizures only	Unknown	No seizure	3	CBZ, VAL
F	22	12	0	Febrile seizures plus	Genetic	No seizures	3	CLO, ACE
F	35	12	15	Juvenile myoclonic epilepsy	Genetic	Convulsive monthly Some myoclonies and absences	1	LTG, TOP, LAC
F	23	13	17	Juvenile myoclonic epilepsy	Genetic	No seizure	3	LEV
F	22	13	17	Juvenile absence epilepsy	Unknown	Convulsive annually	2	LTG, LEV

[a] LTG = lamotrigine, LEV = levetiracetam, VAL = valproate, CBZ = carbamazepine, CLO = clonazepam, ACE = acetazolamide, TOP = topiramate, LAC = lacosamide.

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