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Original Publication:

Helena Gauffin, Helene van Ettinger-Veenstra, Anne-Marie Landtblom, Daniel Ulrici, Anita McAllister, Thomas Karlsson and Maria Engström, Impaired language function in generalized epilepsy: Inadequate suppression of the default mode network, 2013, Epilepsy & Behavior, (28), 1, 26-35.
http://dx.doi.org/10.1016/j.yebeh.2013.04.001

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

Helena Gauffin[*a,b], Helene van Ettinger-Veenstra[*b,c], Anne-Marie Landtblom[a,b], Daniel Ulrici[a], Anita McAllister[d], Thomas Karlsson[b,e], and Maria Engström[b,c]

∗ Both authors contributed equally to the preparation of this article.

a Department of Clinical and Experimental Medicine (IKE), Division of Neurology, Linköping University, UHL, LiM, Linköping, Sweden
b Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden
c Department of Medical and Health Sciences (IMH), Division of Radiology, Linköping University, Linköping, Sweden
d Department of Clinical and Experimental Medicine (IKE), Division of Logopedics, Linköping University, Sweden
e Department of Behavioral Science and Learning, Division of Disability Research and Linnaeus Centre HEAD, Linköping University, Linköping, Sweden

Correspondence

Maria Engström, CMIV, Linköping University/US, 581 85 Linköping, Sweden. **e-mail**: maria.engstrom@liu.se. **telephone**: +46-101038901.

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 could demonstrate 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.

Keywords

generalized epilepsy, functional Magnetic Resonance Imaging (fMRI), language performance, sentence reading, verbal fluency, default mode network, hippocampus, temporal lobe, posterior cingulate cortex

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 sence of coherence (SOC) decrease over time [1] and that cognitive impairment places a heavy burden on the patient's daily life [2]. Cognitive problems are often rated highest on the list of problems associated with epilepsy [3]. Recurrent seizures, side effects of anti-epileptic drugs, or the underlying disease can affect vital cognitive domains such as memory, visuospatial functions, and, addressed in the current study, language [4, 5, 6, 7, 8]. Due to 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 GE patients 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 to 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 negative BOLD response during performance of various cognitive tasks as well as during rest [16, 17, 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 anti-correlated BOLD responses. It is hypothesized that a high degree of temporal correlation within executive networks facilitates cognitive processing [19] and likewise that the presence of anti-correlated networks are equally important [20].

Brain regions with negative BOLD response during cognitive processing are referred to as the default mode network (DMN) or the resting state network [21]. This 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 and 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 epilepsy patients with generalized myoclonic, tonic-clonic and/or absence seizures [22, 23, 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 anti-correlation 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, 28, 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]. Later interpretations of the N400 peak encompasses 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 response 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 previously have been shown 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 that were fluent in Swedish, without reported language dysfunction, and that had completed at least the required nineyears of elementary schooling. The diagnoses were set after examination of anamnesis, 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 use of a vagus nerve stimulator or other electrical or metal implant that could inter-

fere with the fMRI investigation, 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 GE participants are presented in Table 1.

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

All participants gave both verbal and written informed consent to participate in the study according to the Declaration of Helsinki. In a clinical interview before inclusion we ensured that none of the participants had cognitive deficits or other health issues that prevented them from giving an informed consent. Approval for the study was obtained from the Regional Ethical Review Board in Linköping (2010/157-31 and M152-07 T22-09).

2.2 Procedure

This study was part of a larger project aiming at investigating language and memory function in epilepsy of different origin and in healthy controls with varying language abilities. In a separate session before fMRI, all participants were tested with a neuropsychological test battery, including the language assessment tasks also used in the present study. During the fMRI session,

the participants were investigated with a sentence reading task.

2.3 Cognitive Language Tasks

Word fluency and higher language abilities were assessed using two tests (FAS and BeSS) taken from the Test of Language Competence translated into Swedish [36]. FAS is a version of the verbal fluency Controlled Oral Word Association Test (COWAT) and uses the phonemic cues F, A, and S [37]. The participants were asked to generate as many words as possible within one minute, excluding proper names and places. The BeSS test ("Bedömning av Subtila Språkstörningar" - Assessment of Subtle Language Deficits) consists of seven sub-tasks developed to provide an in-depth assessment of patients with milder but still significant language problems. This language assessment battery was used since people with epilepsy typically perform at normal or near-normal levels on traditional aphasia examinations, which aim at patients with more pronounced deficits. BeSS includes the following subtests: REP = sentence repetition, CON = sentence construction, INF = inference (text understanding), COM = understanding complex embedded sentences, GAR = understanding garden-path sentences, MET = understanding metaphors, and VOC = vocabulary. Each subtest of 10 questions can result in a maximum of 30 points and a total of 210 points for the entire test.

2.4 fMRI data acquisition

The functional images were obtained using a gradient echo planar imaging sequence, sensitive to the blood oxygen level dependent (BOLD) response. Repetition time (TR) = 3 s, time to echo (TE) = 40 ms, flip angle (FA) = 90°,

voxel size = 3×3×3 mm^3, slice gap = 0.5 mm, 35 slices, field of view (FOV) = 228×204×122 mm^3. The slices were aligned between the floor of the sella turcica and the posterior angle of the fourth ventricle. The MR-scanner was a Philips Achieva 1.5T. In addition, an anatomical 3D T_1-weighted image of each participants whole brain was acquired to use in the normalization process: TR = 25 ms, TE = 4.6 ms, FA = 30°, voxel size = 1×1×1 mm^3, 175 slices, FOV = 240×240×175 mm^3.

2.5 fMRI paradigm

The fMRI examination consisted of a block designed sentence reading task, which was visually presented to the participants through high-resolution video goggles (Resonance Technology Inc., Northridge, CA, USA). During fMRI the participants read sets of semantically congruent and incongruent sentences, of which the latter was regarded as a more complex task. An example of a congruent sentence is: *The reindeer has very large antlers* ("Renen har mycket stora horn"), and an example of an incongruent sentence is: *We took a shower in the taxi* ("Vi tog en dusch i taxin"). After reading each sentence, the participants were asked to indicate by button presses on a response box (LUMItouch, Photon Control Inc., Burnaby, BC, Canada) if the sentence described an event or action indoors or outdoors, aiming to check if the participants had read all sentences. During the baseline task, the participants were presented alternating %-signs and arrows, together resembling the visual appearance of a sentence, and they were asked to indicate the direction of the arrows (left or right). Reaction times were used as performance measures for this task.

Each task block (congruent respectively incongruent sentence reading as

well as the baseline task) lasted 12 seconds and contained four trials, which were presented sequentially. The task blocks were presented in randomized order and repeated 10 times. The total time for the fMRI examination was approximately 6.5 minutes. Superlab Pro 4 (Cedrus Corp., San Pedro, CA, USA) software was used for task presentation and recording of behavioral responses.

2.6 Image analysis

Preprocessing and analysis of fMRI data were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8). In the preprocessing stage, the fMRI images were realigned to the first image to correct for movement during scanning, co-registered to the participants structural MRI, normalized to a $2\times2\times2$ mm^3 Montreal Neurological Institute (MNI) template using the parameters obtained from a segmentation of the structural MRI, and finally smoothed with an 8 mm full width half maximum (FWHM) Gaussian kernel.

All participants' images were analyzed for positive and negative BOLD response during reading the congruent and incongruent sentences. The covariates representing sentence reading were contrasted against baseline: sentence reading>baseline and sentence reading<baseline, respectively. The contrast images for each participant were entered into the second level analyses. Positive and negative BOLD responses to sentence reading were analyzed with a one-sample t-test of random effects for each group, GE and controls, separately. Differences in BOLD responses between people with GE and healthy controls were analyzed with two-sample t-tests.

Negative BOLD responses were estimated in Regions of Interest (ROIs) representing the default mode network (DMN). All ROIs were constructed us-

ing the Automated Anatomical Labeling atlas in the WFU PickAtlas tool [38] with guidance from [18]. The ROIs were bilateral regions in the medial prefrontal and anterior cingulate cortices, posterior cingulate cortex and precuneus, inferior parietal lobe, lateral temporal lobe (middle and superior temporal gyrus), and the hippocampal formation (hippocampus proper and parahippocampal gyrus). Since both positive and negative BOLD responses were observed in the temporal lobe, but in different regions, adapted DMN-related ROIs in the temporal lobe were used in the statistical comparison between individuals with GE and controls. Image masks in the temporal lobe were created from from clusters with negative BOLD response in healthy controls during reading of congruent sentences When creating the temporal lobe ROIs we used a significance threshold of p=0.01 and a spatial threshold of 10 voxels. The resulting temporal lobe ROIs were located in the anterior superior temporal gyrus and the posterior middle temporal gyrus in both hemispheres. Adapted ROIs in the temporal lobe were created using the MarsBar toolbox [39].

Statistical significance in the ROIs was calculated from unthresholded images (t=1). Results were reported as significant if the peak p-value was less than 0.05, corrected for multiple comparisons using the Family Wise Error (FWE) method.

2.7 Statistical analysis

Statistical analysis including t-tests of the behavioral results on FAS and reaction times and a multivariate analysis of variance of the BeSS subtests were performed using the SPSS statistics software, version 20.0. (IBM, Armonk, NY, USA)

3 Results

3.1 Behavioral results

People with GE performed worse than healthy controls according to the assessment of subtle language deficits (BeSS), see Table 2 for the statistical results. GE participants performed significantly worse than controls in all BeSS subtests except in the INF subtest, which measures inference or text understanding. The Levene's test indicated unequal variance between groups in INF. When correcting for the non equal variance, the difference between GE participants and controls did not reach significance. As can be seen in Table 2, some participants in both the GE group and the controls achieved maximum points (= 30) in some BeSS subtests, however, the range between minimum and maximum points was quite wide in all tests. The difference in performance on the standard vocabulary task (FAS) was not significant.

People with GE had longer reaction times during reading of both congruent and incongruent sentences, as well as during the baseline task. When comparing performance between the two conditions of the sentence reading task, it was found that the healthy controls had longer reaction times during the incongruent task, $p < 0.048$, indicating that this task might be more difficult to perform. There was no evidence of difference in reaction time between the congruent and the incongruent tasks for people with GE, $p = 0.350$, indicating that they might have perceived both tasks to be equally difficult. However, given the rather large standard deviation and the small number of participants in the GE group, the power of the test was limited.

3.2 Positive BOLD response

Reading both congruent and incongruent sentences elicited task-positive BOLD response in a mainly left-lateralized fronto-temporal network in all participants, although right lateralized activation was also observed in the frontal cortex (Figs. 1A, 1C). In addition, positive BOLD responses were observed in the anterior cingulate cortex, continuing to the supplementary motor area, and in the occipital cortex. Images of task-positive brain activation during the incongruent condition can be found in supplementary Figure S1. As seen in Figure 1A and 1C, healthy controls and people with GE had similar activation patterns. Note that for the visualization of the results different significance thresholds were used for controls and GE. A previous study, showed no statistical differences in task-positive BOLD response between healthy participants and people with GE [40].

3.3 Negative BOLD response in healthy controls

In healthy controls, negative BOLD response to the congruent condition of the sentence reading task was found in large parts of the DMN (Fig. 1B, S1). In Table 3, the p-values and Z statistics for the voxels with most negative BOLD in each ROI are shown together with the MNI co-ordinates for those voxels. For the incongruent condition, negative BOLD was observed in all bilateral DMN ROIs; however in the right parahippocampal gyrus the result showed only a trend. Inspecting the results in Table 3, it appears that the incongruent condition resulted in more negative BOLD responses compared to the congruent condition. A statistical analysis of the difference between the two conditions of the task revealed that lower BOLD responses, *i.e.* more

negative BOLD, were found during the incongruent condition in the anterior cingulate cortex, p=0.017 (left hemisphere), p=0.025 (right hemisphere); and the medial frontal cortex, p=0.012 (left hemisphere), p=0.023 (right hemisphere). The voxels that showed significant difference between the two conditions were located close to the midline and close the border between the anterior cingulate and medial frontal cortex ROIs, MNI co-ordinates = [-2, 54, -2]; [2, 52, 14]; [-2, 54, -4]; [2; 54, -4]. This area is commonly denoted as the pregenual part of the anterior cingulate cortex. Comparing the locations of those significantly different voxels, it was found that they were located within the areas of negative BOLD during the incongruent condition, but mostly inferior to the negative BOLD cluster during the congruent condition. This means that the more complex task induced a further reduction of the BOLD response in adjacent regions. Note that negative BOLD in the anterior cingulate/medial frontal cortex formed one connected cluster (Figs. 1B, S1B). There were no ROIs that showed more negative BOLD during the congruent condition as compared to the incongruent condition.

3.4 Negative BOLD response in generalized epilepsy

Viewing the images in Figure 1D, people with GE had seemingly insufficient suppression of DMN as compared to healthy controls. A statistical ROI analysis confirmed this result. In Table 4, the p-values and Z statistics for the voxels with most negative BOLD in each ROI are shown together with the MNI co-ordinates for those voxels. During reading of congruent sentences, people with GE had statistically significant negative BOLD response only in the bilateral anterior cingulate cortex and the left inferior parietal cortex.

During the incongruent version of the task, GE participants showed neg-

ative BOLD in the bilateral anterior and posterior cingulate cortex, bilateral medial frontal cortex, the right superior and middle temporal cortex (Table 4). A statistical comparison between conditions revealed that GE participants had significantly lower BOLD responses during the incongruent condition compared to the congruent condition in the right hippocampus, p=0.031, MNI co-ordinates = [28 -38 -2]; and the left superior temporal cortex, p=0.008, MNI co-ordinates = [-54 -16 2]. However, when inspecting the locations of those significantly different voxels it was found that they were not located within areas of negative BOLD, but rather in between areas displaying positive and negative BOLD, respectively.

As shown in Table 5, significant differences in negative BOLD between people with GE and healthy controls during the congruent version of the task were found in the left anterior temporal cortex (Fig. 2) and in the right posterior cingulate cortex (Fig. 3). There were also tendencies to different activation in the left posterior cingulate cortex (Fig. 3). For the congruent condition, GE participants had also significantly increased BOLD response in the right parahippocampal gyrus, and marginally significant increased BOLD response in the right hippocampus proper as compared to the controls (Fig. 4). Inspection of these results revealed that GE participants had *positive* BOLD response in the right-sided parahippocampal gyrus whereas the controls lacked task-related BOLD response, neither positive nor negative, in this region. There were no significant differences between GE and controls for the incongruent condition.

4 Discussion

In this study we investigated language ability and the negative BOLD response in DMN during language processing in adults with GE and healthy controls. Although abnormal function in DMN in people with GE has been pointed out by previous investigators, to our knowledge, this is the first time that DMN has been investigated in individuals with GE during language processing. As hypothesized, we found impaired language function in people with GE as well as inadequate suppression of the DMN during sentence reading.

4.1 Language dysfunction in generalized epilepsy

Language function in people with epilepsy is presently not focused in the clinical setting, probably because these patients seldom display any obvious speech problems, like in aphasia. It is well known that cognitive problems in epilepsy exist, as a consequence of the brain damage that caused the epileptic disorder, or as a side effect of anti-epileptic pharmaco-therapy. Language as a specific cognitive function is, however, seldom examined in the clinic. In research, language in epilepsy of focal origin, especially regarding the corresponding temporal and frontal cerebral areas, has frequently been investigated. In contrast, language function in persons with GE has hardly been focused at all. Our study shows that language difficulties clearly are present in generalized epilepsy. Interestingly, the examinations performed using the standard verbal fluency task (FAS) did not reveal any obvious pathology, but the instrument BeSS, determined to identify subtle language disturbance, turned out to be sensitive and displayed a great difference regarding language

performance in persons with GE compared with healthy controls. Language deficits in GE apparently involve several aspects of semantic language processing, since GE participants performed worse than controls in all BeSS subtests; however, the test for inference was not significant after a correction for nonequal variance.

These results showing language dysfunction in GE should be taken into consideration when dealing with persons with epilepsy, as adequately addressing language problems would help to minimize negative consequences of the impairment. Academic underachievement adds to the burden of epilepsy and the consequences of difficulties in reading and writing can have a big impact on both education and future employment possibilities. Among children with idiopatic epilepsy underachievement in school have been seen in 61% [41]. Learning disabilities have been mostly studied among children with epilepsy but the greatest consequences affect the adult. Young adults with epilepsy express that they believe their whole life would have been much better and easier if they could have achieved better results in school [2]. They feel they can not use their whole potential.

4.2 Inadequate negative BOLD response

It is well established that the human brain is organized into correlated and anti-correlated functional networks in the absence of external tasks [20, 42]. Cognitive processing is facilitated if the neuronal fluctuations within executive networks are correlated in time [19]. However, it is not only the presence of correlated, task-positive brain networks that governs performance. Increasing evidence supports the hypothesis that anti-correlated networks are as important for human brain function as correlated networks [20, 43, 44].

Research on working memory performance indicates that that DMN regions with decreased BOLD response is not simply disengaged during the task [45]. Rather, these DMN regions promote cognitive performance. Thus, for every cognitive task there is a balance between activated and deactivated neural networks, and if suppression is inhibited, a disturbance of cognitive functions may arise [46].

In the present study, we found less suppression in DMN in GE participants, when investigating the negative BOLD response during sentence processing. By inspection of Figure 1, we tentatively suggest that GE participants had a global deficiency to suppress DMN. Thus, a possible explanation of the result is that there is a reduced functional segregation of DMN in GE, as proposed by McGill *et al.* [22]. This reasoning is supported by the observed significant difference between GE participants and controls in the posterior cingulate cortex, as this region is suggested to be a central node in DMN with strong interactions to other nodes of the network [47]. In the present study, we also found significant differences in negative BOLD between GE participants and controls in the left anterior temporal cortex. This finding could have a direct implication for the language dysfunction in GE.

In accordance with previous work on the relation between cognitive capacity and the negative BOLD response in DMN, for example studies on normal aging [43, 44], we suggest that insufficient suppression of DMN is related to the language impairment that was observed in GE participants in the present study.

4.3 Hippocampal activation

According to the literature, the hippocampal formation is part of DMN [18]. In our study, the hippocampus proper and parahippocampal gyrus exhibited negative BOLD response during sentence reading in healthy participants. When comparing the BOLD response between the two groups, we found a difference between healthy controls and GE participants in the right parahippocampal gyrus during the congruent condition of the sentence reading task. A closer look into the images of positive and negative BOLD response revealed that GE participants had a positive BOLD response in the right parahippocampal gyrus and not an anticipated negative response in this region. Moreover, the healthy controls did not show negative BOLD response in this particular subregion of the parahippocampal gyrus, which is clearly visualized in Figure 4. Thus, the difference between people with GE and controls could not be interpreted as a difference in negative BOLD response, but rather as an additional activation in right-sided hippocampal areas for people with GE during performance of the sentence reading task. Although the hippocampus and the parahippocampal cortex are parts of the DMN, these areas have distinct functional properties. The hippocampus and the parahippocampal cortex has been thought to be exclusively involved in episodic memory, however, recent neuroimaging research has shown the importance of these regions in semantic processing [48, 49]. The role of the hippocampal formation in semantic tasks is also supported by the findings of reduced language production capacity in patients with hippocampal damage [50].

4.4 Task-complexity modulations

A third aim of the present study was to investigate if task complexity would modulate the negative BOLD response in the DMN. We approached this aim by designing the sentence reading task with two conditions: reading of congruent and incongruent sentences, respectively. We anticipated that reading of incongruent sentences would be more cognitive demanding, which also was supported by the longer reaction times for the incongruent condition in healthy participants. We also hypothesized that the more demanding version of the task would induce a further reduction of the BOLD response, according to previous findings in the literature [29]. Indeed, the healthy controls, reduced their BOLD response in the pregenual anterior cingulate cortex and adjacent regions in the medial frontal cortex during the incongruent condition of the sentence reading task. These results indicate that modulation of the BOLD response in the anterior cingulate/medial frontal cortex is especially important when switching between different task demands. This conclusion is supported by the common interpretation that the anterior cingulate cortex has a pivotal role in decision-making, task-switching, and integration of cognitive and emotional stimuli [51, 52, 53].

Brain responses to added complexity in sentence reading in GE participants were somewhat harder to interpret. Results indicate that GE participants did not further reduce the BOLD response in task-negative areas as was observed in the controls. The differences of the BOLD responses between the congruent and incongruent condition of the task were instead located in between task-positive and task-negative areas of the brain. This result could possibly be another expression of the reduced segregation between executive networks and DMN in GE [22]

4.5 Seizure-mediated structural changes

In the current study we observed abnormal function in DMN in people with GE. Is this abnormal function related to the pathophysiology of GE or secondary to GE? In other words: was the DMN dysfunction present already at onset of GE or did it evolve during the disease course? In GE, white and grey matter abnormalities have been demonstrated in several studies [54, 55, 56], which might be related to impaired neural pathways or to impaired functioning of affected regions due to structural changes. Impaired white matter connectivity has also been suggested as an explanation for cognitive decline in patients with focal onset seizures [57]. One possible explanation for these findings is that structural changes in epilepsy are secondary to repeated seizures [58]. Liu and colleagues [59] recently showed white matter changes in juvenile myoclonic epilepsy but not in generalized epilepsy with generalized tonic clonic seizures only. In contrary to previous findings they found no correlation between white matter changes and the number of experienced seizures, and stated that these two entities may be associated with distinctly different anatomic substrates.

4.6 Limitations and future directions

Although this study is limited by the small number of GE participants, the results are nevertheless in keeping with the current literature on the function of DMN in general, and also in keeping with previously reported studies on resting-state dysfunction of DMN in people with GE. More in depth testing of language functioning in people with GE is, however, needed to properly map their language deficits and thus enable more specific studies visualizing the

related neural correlates. Future studies on episodic and semantic memory in GE might also contribute to further knowledge regarding cognitive problems in people with GE.

4.7 Conclusion

In people with GE, the functional language network showed an imbalance of brain activation in the form of inadequate suppression of activation in the DMN during a sentence reading task. These results might explain our findings of impaired language performance exhibited in GE participants. Language difficulties clearly are present both in epilepsy with focal seizures and in GE. These results should be taken into consideration when dealing with persons with GE in order to adequately assess and address language problems and thereby minimize negative consequences of the impairment.

Acknowledgement

Linköping University and the County Council of Östergötland are acknowledged for financial support. We thank Ingmari Ruuth Knutsson for organizing logistics and booking of patients.

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5 Figure legends

Figure 1

Congruent sentences: Positive and negative Blood Oxygen Level Dependent (BOLD) response in healthy controls (A, B) and in people with generalized epilepsy (C, D). For the visualization, images of the controls were thresholded at p=0.001, uncorrected, and images of epilepsy patients were thresholded at p=0.01 to compensate for the smaller group size. L = left hemisphere.

Figure 2

A) Negative BOLD response in the left anterior superior temporal cortex in healthy controls. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the anterior superior temporal gyrus. The image is masked within the region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.

Figure 3

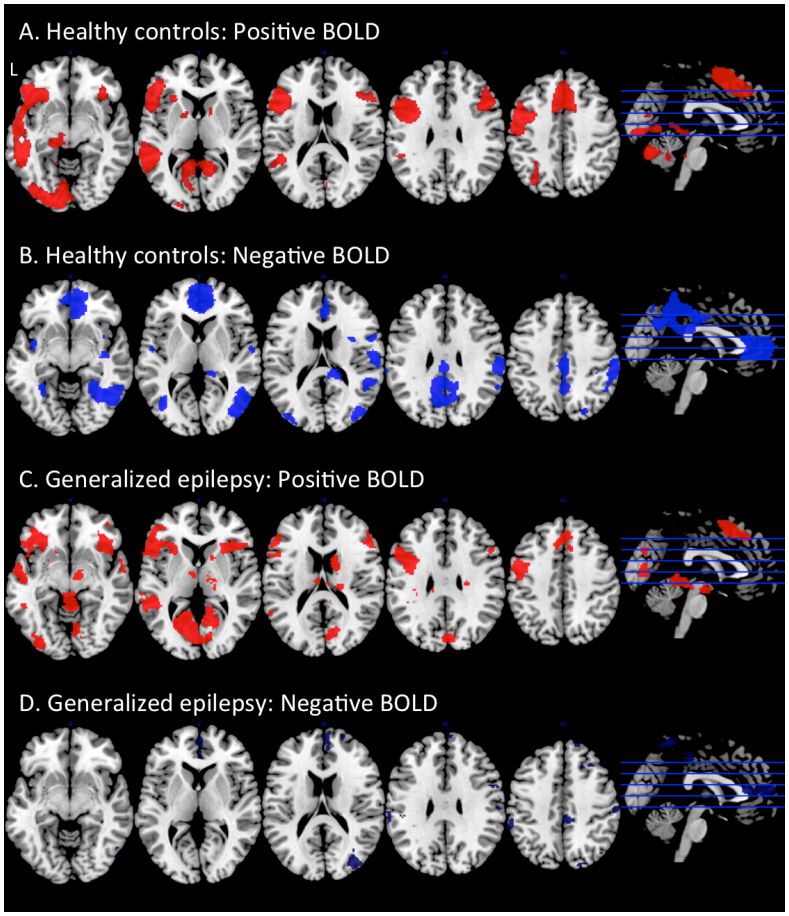
A) Negative BOLD response in the posterior cingulate cortex in healthy controls. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the posterior cingulate cortex. The image is masked within the region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.

Figure 4

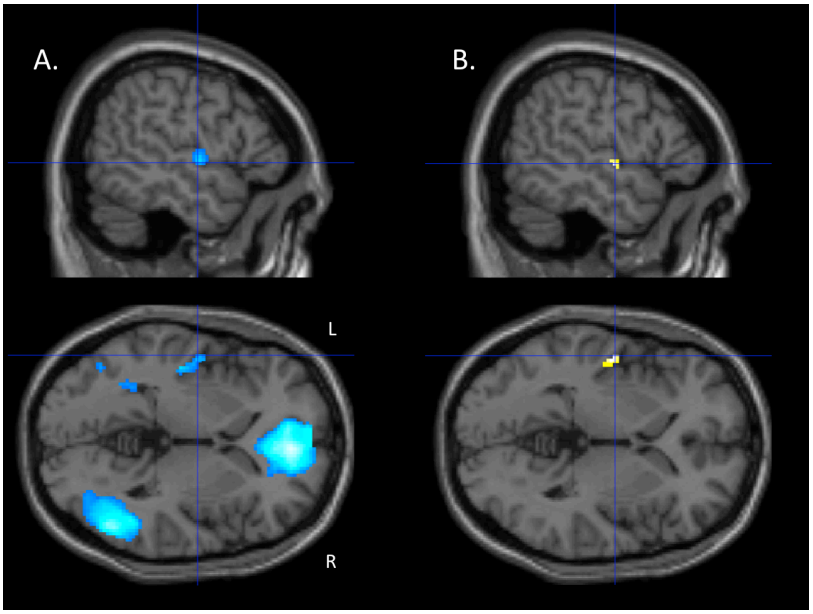
A) Negative BOLD response in healthy controls. The crosshair is located at the peak of the BOLD response in the right parahippocampal gyrus of generalized epilepsy participants. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the right parahippocampal gyrus. The image is masked within the hippocampus and parahippocampal region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.

Supplemantary figure

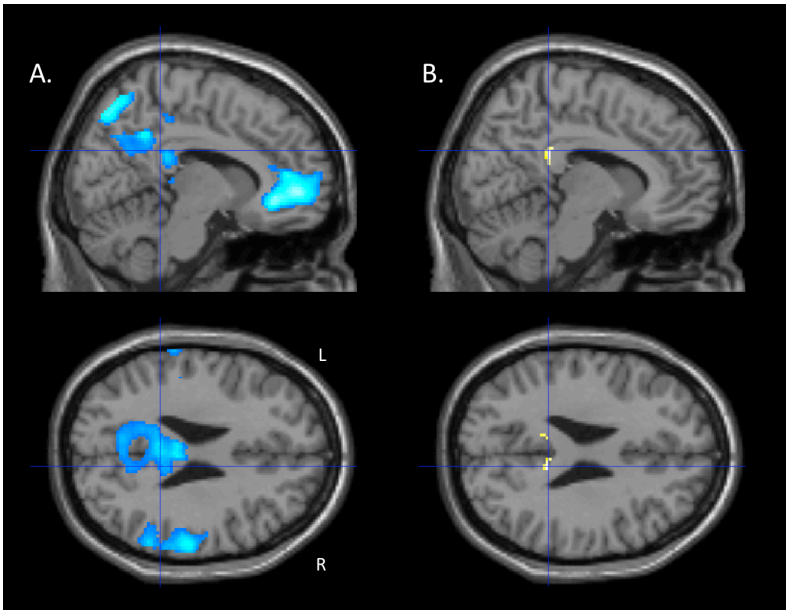
Incongruent sentences: Positive and negative BOLD response in healthy controls (A, B) and in people with generalized epilepsy (C, D). Images of the controls were thresholded at p=0.001, uncorrected, and images of epilepsy patients were thresholded at p=0.01 to compensate for the smaller group size of epilepsy patients. L = left hemisphere.



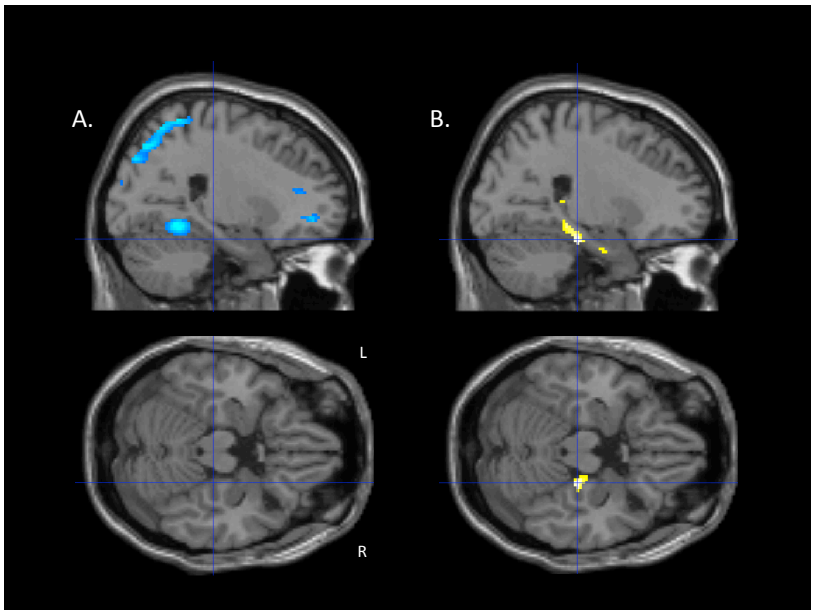
Figur 1: ***Congruent sentences****: Positive and negative Blood Oxygen Level Dependent (BOLD) response in healthy controls (A, B) and in people with generalized epilepsy (C, D). For the visualization, images of the controls were thresholded at p=0.001, uncorrected, and images of epilepsy patients were thresholded at p=0.01 to compensate for the smaller group size. L = left hemisphere.*



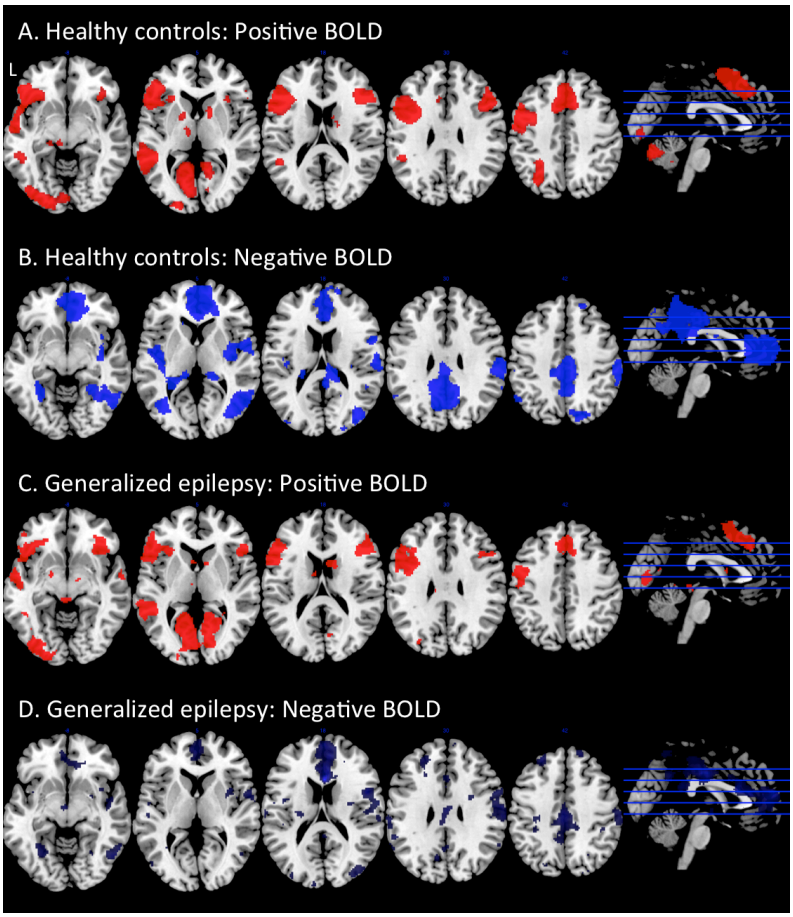
Figur 2: *A) Negative BOLD response in the left anterior superior temporal cortex in healthy controls. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the anterior superior temporal gyrus. The image is masked within the region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.*



Figur 3: *A) Negative BOLD response in the posterior cingulate cortex in healthy controls. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the posterior cingulate cortex. The image is masked within the region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.*



Figur 4: *A) Negative BOLD response in healthy controls. The crosshair is located at the peak of the BOLD response in the right parahippocampal gyrus of generalized epilepsy participants. The image is thresholded at p=0.001. B) Significant difference in negative BOLD response between people with generalized epilepsy and healthy controls in the right parahippocampal gyrus. The image is masked within the hippocampus and parahippocampal region of interest and thresholded at p=0.01, for visualization purpose. L = left hemisphere, R = right hemisphere.*



Figur 5: ***Incongruent sentences (SUPPLEMENTARY)****: Positive and negative BOLD response in healthy controls (A, B) and in people with generalized epilepsy (C, D). Images of the controls were thresholded at p=0.001, uncorrected, and images of epilepsy patients were thresholded at p=0.01 to compensate for the smaller group size of epilepsy patients. L = left hemisphere.*

Tables

Tabell 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 = Anti-Epileptic 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 seizure 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.

Tabell 2: *Results from the verbal fluency (FAS) and the assessment of subtle language deficits (BeSS) tasks, and reaction times (RT) during the baseline, congruent, and incongruent conditions in fMRI. The table shows mean values, standard deviation (sd), range (minimum–maximum value), and p-value for the statistical comparison between generalized epilepsy participants and controls.*

	GENERALIZED EPILEPSY			**HEALTHY CONTROLS**			
Task	**Mean**	**sd**	**Range**	**Mean**	**sd**	**Range**	p
FAS	34.7	12.7	11–57	43.3	11.5	22–62	0.052
BeSS (total)[a]	122.6	35.6	66–181	163.1	20.4	117–193	0.004
- REP	14.9	4.9	4–21	21.0	3.6	12–28	<0.001
- CON	20.4	5.0	12–26	25.4	4.1	14–30	0.002
- INF	20.5	6.9	9–30	24.9	3.5	19–30	0.011/0.062[b]
- COM	21.9	5.5	12–30	25.9	3.9	16–30	0.016
- GAR	18.5	7.3	3–30	26.8	4.5	15–30	<0.001
- MET	14.4	7.9	1–25	20.6	5.0	10–30	0.005
- VOC	11.9	7.7	4–28	18.5	6.6	3–26	0.011
RT Baseline	869	190.5	735–1400	694	81.5	550–825	<0.001
RT Congruent	2154	333.8	1529–2633	1848	264.1	1207–2444	0.005
RT Incongruent	2286	309.2	1690–2674	1989	249.2	1370–2569	0.004

[a]BeSS includes the following subtests: REP = sentence repetition, CON = sentence construction, INF = inference (text understanding), COM= understanding complex embedded sentences, GAR = understanding garden-path sentences, MET = understanding metaphors, and VOC = vocabulary.

[b]Levene's test indicated unequal variance. Assuming non equal variances resulted in the higher $p = 0.062$

Tabell 3: *Negative BOLD response in healthy controls during sentence reading. The p-value refers to the family wise error corrected p-value of the voxel with minimum negative BOLD in the respective predefined region of interest. Significant p-values (p <0.05) are marked in bold and trends (p <0.1) are marked in italics. Z is the statistic value, and x, y and z are the Montreal Neurological Institute co-ordinates of the voxel with minimum BOLD.*

CONGRUENT SENTENCES						
Region of Interest	**Hemisphere**	***p*-value**	*Z*	*x*	*y*	*z*
Anterior Cingulate	Left	**<0.001**	8.5	2	42	12
Anterior Cingulate	Right	**<0.001**	8.9	6	44	12
Posterior Cingulate	Left	**0.001**	5.2	-4	-40	26
Posterior Cingulate	Right	**0.002**	4.9	2	-42	26
Precuneus	Left	**0.002**	5.9	0	-48	50
Precuneus	Right	**<0.001**	8.4	18	-76	48
Medial Frontal	Left	**<0.001**	6.5	-6	50	-4
Medial Frontal	Right	**<0.001**	8.0	8	50	-2
Inferior Parietal	Left	0.207	3.4	-58	56	36
Inferior Parietal	Right	**0.002**	5.4	52	-32	50
Middle Temporal	Left	**0.044**	4.5	-40	-68	8
Middle Temporal	Right	**<0.001**	8.8	54	-60	-2
Superior Temporal	Left	**0.009**	5.0	-52	-6	2
Superior Temporal	Right	**0.021**	4.7	52	-44	18
Hippocampus	Left	0.239	3.0	-26	-40	6
Hippocampus	Right	**0.015**	4.4	16	-36	6
Parahippocampal	Left	**0.015**	4.4	-32	-46	-6
Parahippocampal	Right	*0.056*	3.8	26	-44	-6
INCONGRUENT SENTENCES						
Region of Interest	**Hemisphere**	***p*-value**	*Z*	*x*	*y*	*z*
Anterior Cingulate	Left	**<0.001**	10.4	-2	46	0
Anterior Cingulate	Right	**<0.001**	9.1	2	44	0
Posterior Cingulate	Left	**<0.001**	5.7	-6	-44	30
Posterior Cingulate	Right	**0.001**	5.1	2	-46	30
Precuneus	Left	**<0.001**	6.4	0	-48	48
Precuneus	Right	**<0.001**	7.4	14	-62	62
Medial Frontal	Left	**<0.001**	8.6	0	46	-6
Medial Frontal	Right	**<0.001**	9.4	2	48	-2
Inferior Parietal	Left	**0.012**	4.8	-50	-60	46
Inferior Parietal	Right	**0.004**	5.1	58	-36	46
Middle Temporal	Left	**0.014**	5.1	-42	-66	6
Middle Temporal	Right	**0.010**	5.2	56	-60	-2
Superior Temporal	Left	**0.003**	5.5	-50	-8	2
Superior Temporal	Right	**0.006**	5.2	54	0	2
Hippocampus	Left	**0.001**	5.5	-26	-40	6
Hippocampus	Right	**0.002**	5.4	18	-34	8
Parahippocampal	Left	**<0.001**	8.7	-32	-46	-4
Parahippocampal	Right	*0.079*	3.7	30	-44	-6

Tabell 4: *Negative BOLD response in patients with generalized epilepsy during sentence reading. The p-value refers to the family wise error corrected p-value of the voxel with minimum negative BOLD in the respective predefined region of interest. Significant p-values ($p < 0.05$) are marked in bold and trends ($p < 0.1$) are marked in italics. Z is the statistic value, and x, y and z are the Montreal Neurological Institute co-ordinates of the voxel with minimum BOLD.*

CONGRUENT SENTENCES						
Region of Interest	**Hemisphere**	***p*-value**	Z	x	y	z
Anterior Cingulate	Left	**0.018**	6.5	2	34	12
Anterior Cingulate	Right	**0.021**	6.3	4	34	12
Posterior Cingulate	Left	0.732	1.6	0	-42	22
Posterior Cingulate	Right	0.744	1.5	2	-42	22
Precuneus	Left	0.290	4.4	0	-54	66
Precuneus	Right	0.181	4.9	2	-56	66
Medial Frontal	Left	0.553	2.2	-2	30	-12
Medial Frontal	Right	0.606	2.2	0	30	-12
Inferior Parietal	Left	**0.014**	7.4	-48	-28	36
Inferior Parietal	Right	0.669	2.1	42	-40	44
Middle Temporal	Left	0.687	3.5	-52	-58	-4
Middle Temporal	Right	0.650	3.5	48	4	-32
Superior Temporal	Left	0.270	4.1	-64	-28	22
Superior Temporal	Right	0.851	2.6	62	-54	20
Hippocampus	Left	0.972	0.7	-30	-18	-22
Hippocampus	Right	0.975	0.9	12	-34	8
Parahippocampal	Left	0.970	0.8	-30	-18	-24
Parahippocampal	Right	0.950	1.4	30	8	-30
INCONGRUENT SENTENCES						
Region of Interest	**Hemisphere**	***p*-value**	Z	x	y	z
Anterior Cingulate	Left	**0.002**	9.2	2	34	14
Anterior Cingulate	Right	**0.003**	8.8	4	24	18
Posterior Cingulate	Left	**0.027**	5.1	-6	-40	22
Posterior Cingulate	Right	**0.042**	4.5	2	-42	24
Precuneus	Left	0.261	4.5	0	-56	34
Precuneus	Right	0.284	4.4	8	-62	66
Medial Frontal	Left	**<0.001**	8.6	0	46	-6
Medial Frontal	Right	**<0.001**	9.4	2	48	-2
Inferior Parietal	Left	0.259	4.2	-58	-36	50
Inferior Parietal	Right	0.314	3.5	46	-34	46
Middle Temporal	Left	0.557	3.8	-52	-74	8
Middle Temporal	Right	**0.006**	9.1	48	-66	2
Superior Temporal	Left	*0.055*	5.8	-46	-2	0
Superior Temporal	Right	**0.008**	8.4	52	0	-2
Hippocampus	Left	0.956	1.0	-22	-40	0
Hippocampus	Right	0.798	2.0	30	-10	-20
Parahippocampal	Left	0.776	2.1	-20	-28	-24
Parahippocampal	Right	0.725	2.4	22	-40	-4

Tabell 5: *Difference in negative BOLD response between patients with generalized epilepsy (GE) and healthy controls during sentence reading. The p-value refers to the family wise error corrected p-value of the difference between GE and controls in the respective predefined region of interest. Significant p-values ($p < 0.05$) are marked in bold and trends ($p < 0.1$) are marked in italics. Z is the statistic value, and x, y and z are the Montreal Neurological Institute co-ordinates of the voxel with minimum BOLD.*

CONGRUENT CONDITION: GENERALIZED EPILEPSY > CONTROLS						
Region of Interest	**Hemisphere**	***p*-value**	Z	x	y	z
Anterior Cingulate	Left	0.316	2.9	0	26	-4
Anterior Cingulate	Right	0.342	2.7	2	40	-2
Posterior Cingulate	Left	*0.073*	3.2	-10	-42	28
Posterior Cingulate	Right	**0.043**	3.3	10	-40	26
Precuneus	Left	0.273	3.3	2	-68	30
Precuneus	Right	0.238	3.3	14	-62	28
Medial Frontal	Left	0.186	2.8	-10	48	-6
Medial Frontal	Right	0.257	2.7	16	52	-6
Inferior Parietal	Left	0.971	1.4	-50	-56	36
Inferior Parietal	Right	0.700	2.0	44	-52	40
Anterior Temporal	Left	**0.015**	3.7	-52	-8	0
Anterior Temporal	Right	0.274	2.7	62	-10	4
Posterior Temporal	Left	0.153	2.3	-40	-68	8
Posterior Temporal	Right	0.614	2.2	52	-68	10
Hippocampus	Left	0.502	2.3	-32	-40	-2
Hippocampus	Right	*0.061*	3.6	28	-28	-12
Parahippocampal	Left	0.345	2.6	-32	-42	-4
Parahippocampal	Right	**0.049**	3.7	24	-26	-20
INCONGRUENT CONDITION: GENERALIZED EPILEPSY > CONTROLS						
Region of Interest	**Hemisphere**	***p*-value**	Z	x	y	z
Anterior Cingulate	Left	*0.084*	3.5	-2	48	0
Anterior Cingulate	Right	0.335	2.7	2	40	-2
Posterior Cingulate	Left	0.330	2.3	-6	-44	30
Posterior Cingulate	Right	0.178	2.6	14	-40	12
Precuneus	Left	0.745	2.5	-14	-56	28
Precuneus	Right	0.818	2.3	26	-46	6
Medial Frontal	Left	0.126	3.0	-4	50	-4
Medial Frontal	Right	0.174	2.9	12	44	-14
Inferior Parietal	Left	0.978	1.3	-46	-28	48
Inferior Parietal	Right	0.941	1.1	50	-54	50
Anterior Temporal	Left	0.940	0.6	-40	-20	-2
Anterior Temporal	Right	0.880	1.4	50	-4	-2
Posterior Temporal	Left	0.797	0.2	-48	-70	6
Posterior Temporal	Right	0.929	1.2	50	-78	8
Hippocampus	Left	*0.078*	3.4	-36	-12	-18
Hippocampus	Right	*0.099*	3.3	18	-34	6
Parahippocampal	Left	0.153	3.1	-32	-46	-4
Parahippocampal	Right	0.431	2.6	26	-26	-18