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# Physiologic and cortical response to acute psychosocial stress in left temporal lobe epilepsy — A pilot cross-sectional fMRI study

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ABSTRACT

Stress is commonly reported as a seizure precipitant in individuals with poorly controlled seizures including temporal lobe epilepsy. The aim of the study was to assess the neural and physiologic correlates of psychosocial stress response during functional magnetic resonance imaging (fMRI) and their relationship with seizure occurrence in patients with left temporal lobe epilepsy (LTLE). We enrolled 23 patients with LTLE and 23 age- and sex-matched healthy controls (HCs); all underwent fMRI with control math task (CMT) and stress math task (SMT) and pre-/post-fMRI salivary cortisol analysis (acute stress reactivity calculated as % reduction from post-stress to recovery baseline; dCORT). The Beck Depression Inventory-II (BDI-II) and Perceived Stress Scale (PSS-10) were administered. T-tests of performance and cortisol variables were performed. Processing and single-subject modeling of fMRI response to CMT positive feedback and SMT negative feedback, group comparisons, and whole-brain correlation of seizure occurrence and fMRI response in patients with poorly controlled LTLE were performed. Patients with LTLE and healthy controls were similar in demographics, math performance, heart rate, and PSS-10 scores (all $p > 0.05$). Patients with LTLE exhibited greater dCORT ($p = 0.048$) and lower BDI-II scores ($p = 0.016$) compared with HCs. Patients with poorly controlled LTLE showed a positive association between seizure frequency and dCORT ($r = 0.73$, $p = 0.016$). Functional MRI activation to feedback was similar between groups, including midfrontal, temporal, parietal, and occipital regions. Regression analyses revealed no group differences to positive feedback, but, compared with HCs, patients with LTLE showed decreased activation to negative feedback in the left cerebellum/middle occipital/fusiform gyri, left hippocampus/parahippocampus, bilateral medial frontal/cingulate/superior frontal gyri, right postcentral gyrus/inferior parietal lobule, and right insula/postcentral gyrus ($p < 0.05$, corrected). Patients with poorly controlled LTLE showed negative association between seizure frequency and activation in the bilateral subgenual anterior cingulate ($p < 0.05$, corrected). This study is the first to characterize the cortical and physiologic responses to acute psychosocial stress and to show a significant relationship between seizure control in LTLE and both the hypothalamic–pituitary–adrenal axis and fMRI signal reactivity to acute psychosocial stress. These findings extend our understanding of the complex interplay between stress, physiologic stress markers, and seizures/epilepsy.



## 1. Introduction

Epilepsy affects approximately 2.2 million people in the United States, about one-third of whom have poorly controlled seizures [1–3]. Persons with epilepsy (PWEs) report stress to be a major precipitant of their seizures [4,5]; animal models of epilepsy provide further supporting evidence [6–8]. There is neural regulation of the hypothalamic–pituitary–adrenal (HPA) axis with its structural and functional connections to the temporal lobe as well as a number of other brain regions [9]. Hypothalamic–pituitary–adrenal axis activation is marked by hypothalamic secretion of corticotropin-releasing hormone, consequent pituitary release of adrenocorticotropic hormone, and resulting adrenal cortex release of corticosteroids (i.e., corticosterone in rodents and cortisol in humans) [9]. Studies have shown that administration of corticosterone results in increased susceptibility to convulsions [10] and increased rate of seizures [11,12] in an animal model of epilepsy. These and other studies suggest that the response to and management of stressful events may influence seizure control in PWEs. However, the neural underpinnings of the stress response

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and the physiologic correlates of such response have not been studied in detail in patients with left temporal lobe epilepsy (LTLE), particularly those with poorly controlled seizures. The knowledge of these responses is important for designing successful treatment paradigms for patients who perceive stress as a major precipitant of their seizures and for developing nonpharmacological (i.e., behavioral) interventions [13].

The objective of our study was to assess the neural and physiologic (cortisol level, heart rate (HR)) correlates of the stress response to acute psychosocial stress during fMRI (stress math task) and their relationship with seizure occurrence in patients with LTLE. Seizures are physiologically and psychologically stressful events, because they are unpredictable in nature, and PWEs, particularly those with uncontrolled seizures, may experience chronic stress as a result [6]. Temporal lobe epilepsy (TLE) is the most common form of intractable epilepsy in adults [14]. Seizure activity in TLE affects the structure, function, and neurochemical composition of the temporal lobe [6,8,15–17], and its interactions with the HPA axis may alter the neural response to stress [18]. The hippocampus and limbic system are particularly sensitive to HPA axis activation because of the high concentration of glucocorticoid and mineralocorticoid receptors that bind corticosterone/cortisol [6,9,19–21]. During chronic stress, limbic system neurons are more excitable both at rest (i.e., non-stressed state) and during HPA axis activation (i.e., stressed state) [22]. Further, patients with LTLE have been found to exhibit greater fMRI activation compared with healthy controls (HCs) when processing emotional facial expressions [23]. Therefore, we hypothesized that when exposed to acute psychosocial stress, patients with LTLE compared with HCs would exhibit increases in both HPA axis response and fMRI activation.

## 2. Methods

### 2.1. Institutional Review Board (IRB) approval

This cross-sectional study was approved by the University of Cincinnati IRB per guidance on the use of deception in research involving human subjects (here exposure to stress and deception regarding the remuneration for study participation — see below) [24]. The board determined that the research protocol involved minimal risk, the deception would have no adverse effects on rights or welfare of the participants, and the stress experienced by the participants was similar to moderate levels of stress experienced by anyone on a daily basis. The informed consent document contained as much information about the study as possible without revealing the true nature of the study (e.g., that the subjects would receive $40 or $100 for participation, depending on performance, although everyone received $100). As per IRB requirement, all participants were debriefed at the end of the study to provide an explanation of the rationale for the study design and methods used.

### 2.2. Subjects

Twenty-three patients with LTLE, 21–59 years old, were consecutively recruited from the University of Cincinnati Epilepsy Center. Inclusion criteria for patients with TLE included normal MRI, and patients with cortical atrophy or lesions other than medial temporal lobe sclerosis (e.g., vascular lesions or malformations of cortical development) were excluded. Diagnosis of epilepsy was confirmed by clinical history and EEG findings (focal epileptiform discharges emanating from the left temporal lobe); in all patients who were not seizure-free, the diagnosis of LTLE was confirmed by video-EEG monitoring. Patients with epileptiform discharges originating independently from other than the left medial temporal head regions were included, provided that unifocal onset of their seizures was confirmed with video-EEG. Patients suspected of having extratemporal lobe or temporal neocortical epilepsy were also excluded. Thirteen patients with LTLE had been seizure-free for 3 months prior to study participation (LTLE − sz), and ten had uncontrolled epilepsy (LTLE + sz). Twenty-three age- and sex-matched HCs, 22–61 years old, were also recruited from the Greater Cincinnati, Ohio and Northern Kentucky communities. All subjects provided written informed consent according to established guidelines before study participation. Individuals with depression were permitted to participate as long as they had no suicidal ideation in the previous year. Subjects were physically healthy, had no premorbid history of psychiatric (one HC with euthymic bipolar disorder was excluded from further analyses) or neurological illness (except epilepsy), and had no contraindications to receiving an MRI. Prior to study participation, urine pregnancy tests were obtained for all female subjects, and the results were negative. Two-tailed t-tests and either chi-squared test or Fisher's exact test, when appropriate, were performed using SAS (Statistical Analysis System version 9.3, Cary, NC) to compare demographic and clinical variables between groups, with $p < 0.05$ considered significant.

### 2.3. Assessments

Subjects were administered the 10-item Perceived Stress Scale (PSS-10) and the Beck Depression Inventory-II (BDI-II) before the MRI. The PSS-10 asks about a person's feelings or thoughts during the last month and measures stress perception and the degree to which one finds situations or life experiences stressful [25]. The BDI-II is a standard measure of depression [26]. Two-tailed t-tests were performed to compare groups ($p < 0.05$ was considered significant). We also examined the relationship between seizure control (i.e., the number of seizures experienced in the last 3 months) and stress perception using Pearson's correlation analysis.

### 2.4. Stress tasks for fMRI

The fMRI tasks were programmed using E-prime, version 1.1 (Psychology Software Tools, Inc.). Subjects were given verbal instructions and performed a practice task prior to the scan. Practice items were unique to items in the actual tasks to eliminate practice effect. The stress tasks consisted of a control math task (CMT) designed to be non-stressful and a stress math task (SMT) intended to induce a moderate amount of psychosocial stress. The SMT is based on the Trier Social Stress Task [27] and the Montreal Imaging Stress Task [28], both of which were designed to activate the HPA axis and produce moderate increases in cortisol level. All subjects performed the CMT followed by the SMT; they were not aware that the SMT was more difficult. All instructions (during practice and fMRI) were scripted to assure uniformity of the experimental conditions (Appendix A).

The fMRI tasks are diagrammed in Fig. 1. The CMT included subtraction problems in which subjects had to select the correct answer from two choices by pushing the corresponding button on the response box. Throughout the task, subjects heard 8 different prerecorded messages that provided positive evaluative feedback regardless of actual performance. After completing the CMT and prior to SMT initiation, subjects were told that “researchers” would be evaluating their performance and would give them feedback during the task and that, for each question, they had a variable time of 1–5 s to respond in order for their answer to count, and that for their data to be used and to be reimbursed the full $100, they needed to achieve an unspecified number of correct answers based on the average score for people of their age and level of education (i.e., deception). Subjects performed more difficult subtraction problems during the SMT than during the CMT, and with three answers to choose from. Subjects also heard 8 different prerecorded messages, all of which provided negative evaluative feedback regardless of actual performance. Both tasks included 8 instances of a tone condition where subjects were instructed to press “1” or “2” on the response box while hearing a train of tones. The tone condition was designed to monitor attentiveness during the task regardless of actual performance. For both tasks, HR was recorded following each feedback message to assess physiologic response. Two-tailed t-tests were