

Coherence analysis of EEG during cataplexy attacks in narcoleptic adult patients

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Abstract

Objective: Cataplexy is defined as episodes of sudden, transient loss of voluntary muscle tone usually triggered by positive emotional stimuli. Due to the triggering factors, involvement of emotion-processing structures such as the amygdala and limbic system was suggested. Although electrophysiologically hypersynchronous paroxysmal slow wave activities were reported during cataplexy attacks, the involved area was not clear. In this study we examined functional couplings by using coherence analysis to investigate electrophysiological data among the involved brain regions during cataplexy attacks in adult patients.

Methods: Thirteen of our 31 patients with polysomnography recordings had type I narcolepsy. Seven emotionally triggered cataplectic attacks were recorded during monitoring in three patients. Spectral electroencephalography changes were analyzed and compared during whole attacks and interictal awakening periods with similar duration. The imaginary part of coherence for every electrode with other electrodes was also calculated respectively.

Results: The coupling of slow waves increased in temporal regions during the attacks. Coherence between the right side of temporal regions and frontal areas increased in slower waves (<4 Hz). The coherence of other slow waves (4-7 Hz) was pronounced in the left temporal region with almost all over the cortex.

Conclusion: Our electrophysiological findings related to the involvement of temporal and frontal lobes during cataplexy attacks supported previous neuroimaging and physiological reports. Further investigations to clarify the neural circuits involved in their manifestation should be considered in future.

Keywords: Hypersomnias, narcolepsy, cataplexy, spectral analysis, electroencephalography, slow waves

INTRODUCTION

Narcolepsy is characterized by an inability to maintain sustained periods of wakefulness. This leads to abrupt, irresistible episodes of sleep attacks during the day. According to the third edition of the International Classification of Sleep Disorders (ICSD-3), narcolepsy associated with cataplectic attacks is a disorder primarily characterized by excessive daytime sleepiness (EDS) and signs of REM-sleep dissociation, the most specific of which is cataplexy (1). Cataplexy is a symptom characterized by sudden and brief (5–30 s) losses of muscle tone (partial or total) triggered by emotions such as laughter and surprise (1, 2). Because of those triggering factors involvement of an emotion-processing structure, such as the amygdala and limbic system, was suggested (3-5).

Recently, according to electrophysiological and neuroimaging studies, there has been debate about the brain areas involved during cataplexy attacks to clarify the mechanisms of brain dysfunction in cataplexy. Frequently the role of the frontal lobe was impressed upon besides the amygdala in animal models and patients (6-9). Vassalli et al. reported electrophysiologically hypersynchronous paroxysmal slow wave activities during cataplexy and these activities were independent of hippocampal waves and involved the frontal cortex (8). They also reported that these hypersynchronous slow waves (2.5-5 Hz) were dominant in left-sided central regions of children having cataplexy attacks.

In this study we examined functional couplings using coherence analysis to investigate electrophysiological data among the brain regions involved during cataplexy attacks in adult patients (10). Due to only findings related to the presence of theta and delta waves abnormality during cataplexy attacks and the possible generation sides of

those slow waves (limbic system and thalamus region) we examined slow waves (8, 11, 12). To the best of our knowledge this is the first study including coherence analysis of expanded electroencephalography (EEG) recordings in adult patients with cataplexy attacks.

METHODS

In our center we have a polysomnography (PSG) recording device with video-EEG in two rooms of the video-EEG monitoring unit. For this study all reports were retrospectively examined and patients who had undergone video-EEG-PSG monitoring from 2010 to 2015 and had narcolepsy type I according to ICSD-3 were included (1). There were 31 adults with narcolepsy and 13 had narcolepsy type I. They had primarily EDS and cataplexy. All 13 patients reported cataplexy attacks. In three patients cataplexy attacks were recorded during the monitoring. At the time of the study, none of these three patients was taking any medication. The study was approved by the ethical committee of our university, and written informed consents were obtained from all subjects to use their PSG-EEG recordings for any investigations when they hospitalized.

Each patient was monitored for 2 days by using a 32-channel EEG system (Grass-Telefactor, Xltek). T1 and T2 scalp electrodes were placed according to the standard 10–20 system. The other parameters recorded included electrooculogram (EOG), submental electromyogram and electrocardiogram (ECG), respiratory effort and airflow, oxyhemoglobin saturation, and anterior tibialis EMG. Digital EEG-PSG systems allow for monitoring of 32 inputs, to provide EEG coverage sufficient to define EEG changes during cataplectic attacks. The studies were manually scored for sleep stages in 30-s epochs with an expanded EEG montage by an experienced neurophysiologist. Sleep was scored according to the revised AASM criteria (13).

Multiple sleep latency tests (MSLT) were recorded from all patients. They were encouraged every 2 hours to fall asleep for 20 minutes; the test usually begins at 9 a.m. and ends at 5 p.m. All the involved narcoleptic patients felt asleep in less than 8 minutes and had REM sleep during at least two of these daytime naps (known as sleep-onset REM sleep periods, SOREMP). After each MSLT period and brief sleep attack, EEG-PSG recordings were continued for at least 30 min. During these periods patients watched humorous movies or listened to a joke or chatted with their friends/family to trigger cataplexy attacks. Patients were asked to take a brief nap before video recordings to reduce sleepiness and asked again whether they felt sleepy at the end of the cataplectic attack; this was done to avoid confounding effects of sleepiness on the observation of cataplexy. Cataplexy was identified by both minimal submental and tibialis EMG activities and confirmed by video imaging (14). Visually, the jaw sagged, the facial muscles suddenly became weak, the eyelids dropped, the head fell forward, speech became slurred, the arms dropped to the sides, and the knees buckled when cataplectic attacks involved the cranial and upper or lower limb muscles. For EEG analysis, the first visually confirmed clinical signs with minimal submental or tibialis EMG activities were noted in EEG recordings. Complete recovery from the attacks was noted when the patient was reported with appearance of obvious EMG activities.

Spectral EEG changes were analyzed during whole attacks and interictal-resting periods with similar duration (Figure 1). During the interictal periods, these patients were totally awake. Signals were sampled at 200 Hz and stored in European data format (EDF).

Patient 1

A 41-year-old female presented with EDS for the previous 10 years. She had also had cataplexy attacks over the previous

Figure 1. A sample of analyzed EEG epochs with 21 electrodes that included the onset of a cataplexy attack of patient 1. The arrow showed the beginning of the attack

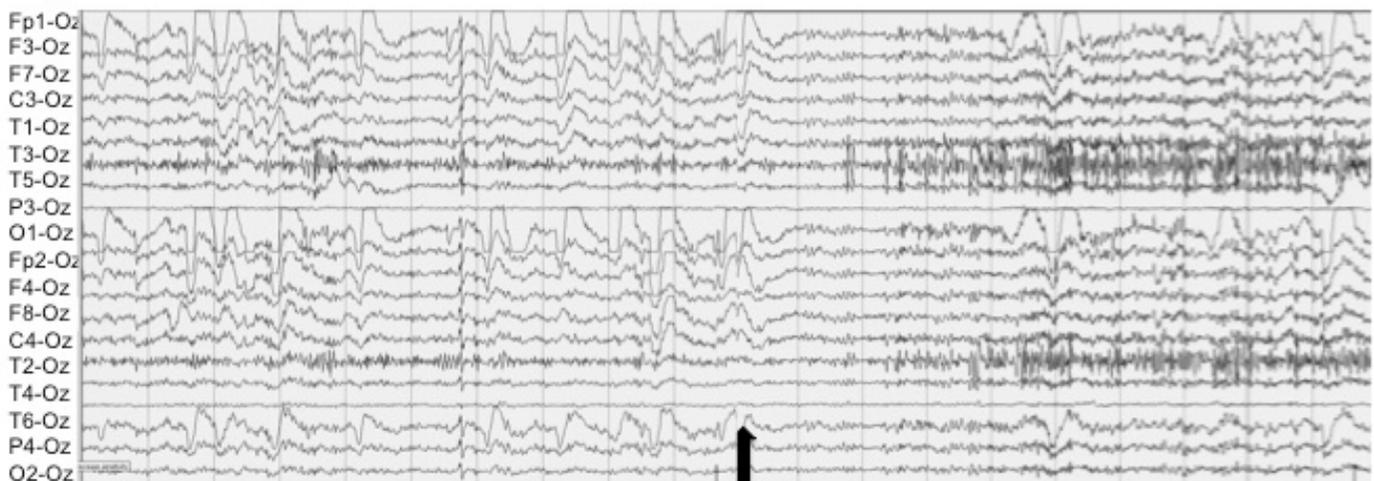
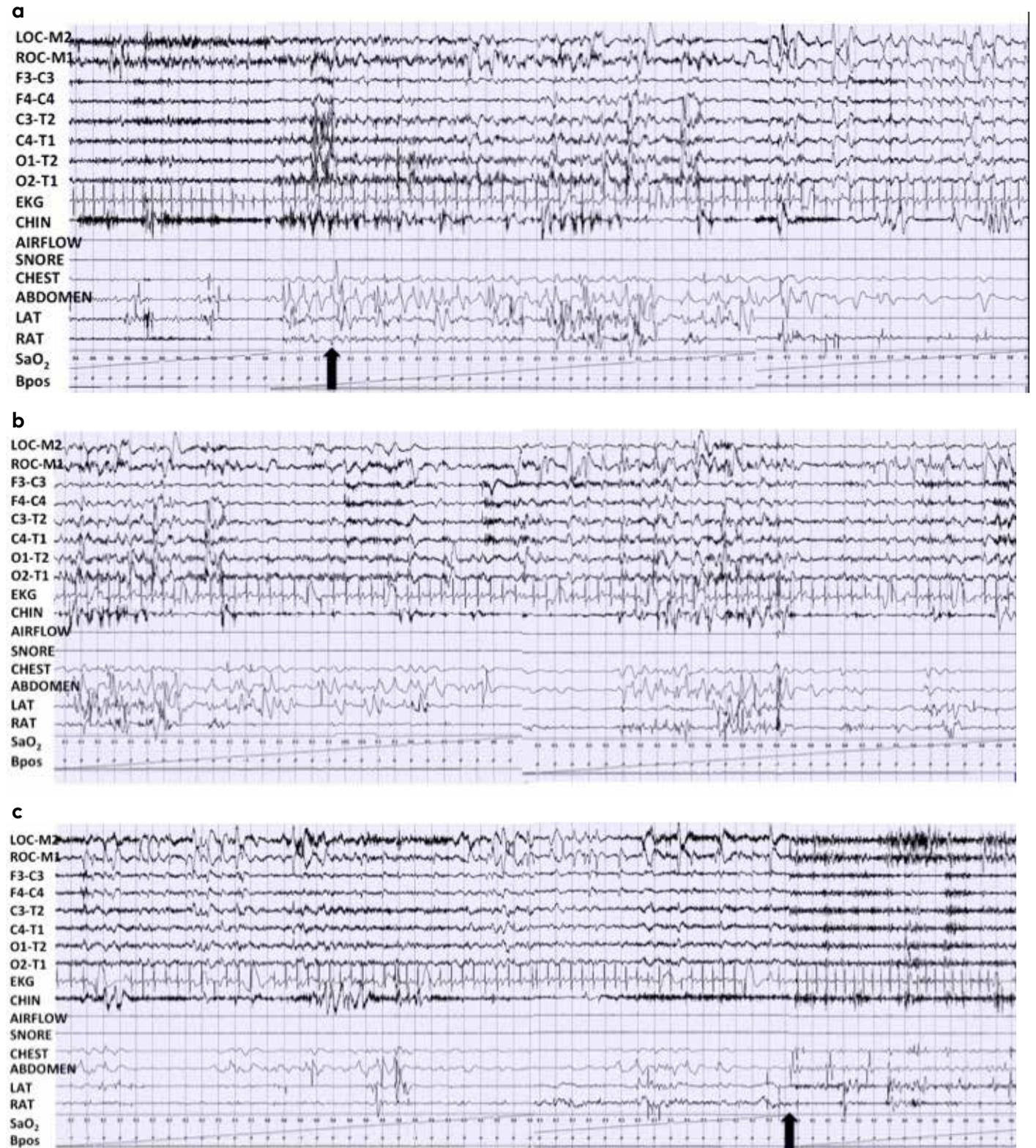


Figure 2. a-c. Polysomnography recording of patient 1 during a cataplexy attack triggered by laughing. Total duration of this clinical cataplexy attack was 117 s (a-c). The first arrow was showed the beginning of the attack by drooping of her head (a). The second arrow was showed end of the clinical attack with full recovery (c)

LOC: left electro-oculogram; ROC: right electro-oculogram; LAT: left tibialis anterior muscle; RAT: right tibialis anterior muscle; EKG: electrocardiogram; Bpos; body position



3-4 years. The frequency of cataplexy episodes ranged between 5/day to more than 4 in 5 min. These episodes were triggered by anger or sharing jokes. They lasted for 5-6 s on average, with a maximum duration of around 20 s. During such episodes her face, neck, and shoulders drooped, she could not speak.

She also reported having sleep paralysis. Her past medical history was unremarkable. However, her brother and grandmother had also complained of EDS.

Epworth Sleepiness Scale (ESS) was used to identify the degree of EDS. ESS is a self-administered eight-item questionnaire. The users rate their chances of sleeping in eight situations on a 4-point scale with a minimum score of 4 and maximum of 24. Normal score range between 0 and 10. Score above 10 require an investigation for EDS. There are several translations including Turkish and the reliability - validity of the ESS in the Turkish language was reported (15).

Patient 1 scored 22/24 on the ESS, indicating very severe EDS. The overnight PSG showed a REM sleep latency of 5.5 min. The MSLT revealed SOREMPs in all 5 naps. Between the periods of MSLT laughing triggered her three cataplexy attacks. She was sitting on her bed and while laughing her head and neck drooped, and she could not speak for 15-130 s (Figure 2). An autoimmune work-up including HLA typing was not done. Her cranial MRI was normal.

She was initially put on modafinil 200 mg daily and venlafaxine 75 mg daily. Along with the medications, scheduled napping was also recommended. She had a remarkable improvement in EDS and cataplexy episodes.

Patient 2

A 57-year-old female presented with EDS and very frequent attacks with drooping of the neck and immobilization with a sense of weakness in her legs. These complaints were obvious two months prior to her visiting the sleep clinic. However, her history revealed a moderate degree of EDS with no cataplexy attacks.

She started having cataplexy attacks in the previous 3-4 weeks. The frequency of cataplexy episodes ranged from 10/day to more than 2 in 10 min. These episodes commonly occurred while crying and laughing. They lasted 15-90 s on average. During these episodes her face, neck, and shoulders drooped and she sometimes fell. She did not have any history of head injury nor did she report flu-like illness or immunization.

She scored 24/24 on the ESS. The overnight PSG showed a REM sleep latency of 4 min. The MSLT revealed SOREM in all 5. Due to a short history of cataplexy and increased EDS with no family history, we performed a CSF investigation including paraneoplastic findings. Her CSF examination was normal.

Her cranial MRI was also normal. During recording, she had two attacks of cataplexy for 60-140 s while she was crying and laughing. She could not speak and her neck drooped in both attacks. During one of them she was walking and she slumped down. Deep tendon reflexes were decreased. The diagnosis of idiopathic narcolepsy with cataplexy was obvious from clinical findings, MSLT, and neuroimaging.

She was initially put on modafinil 200 mg daily and venlafaxine 150 mg daily. The EDS reduced with the addition of a brief scheduled nap at noon.

Patient 3

A 25-year-old male presented with a 2-year history of EDS. He was not aware of the cataplexy attacks. He also reported visual hallucinations involving seeing snakes while awakening from sleep and he had sleep paralysis. His past medical history and family history were unremarkable. However, he had a grandfather with a history of EDS.

He scored 20/24 on ESS. The MSLT revealed SOREM periods in all 4 naps and his mean sleep onset was 3 min. The overnight PSG did not show any other primary sleep disorders. He had two cataplexy attacks while laughing and talking with his friends with dropping of the head and he could not speak. His cranial MRI was normal.

He was put on modafinil 100 mg daily and venlafaxine 37.5 mg daily. He made a full recovery.

Electroencephalography Analysis

Calculation of Coherence Values

Coherence measures the linear relationship between two sources by measuring phases of the corresponding sources and yields a normalized value. The basic definitions are as follows (16):

Let $a_x(f)$ and $a_y(f)$ be the Fourier transform of two time series a_x and a_y ; the corresponding cross- (a) and auto-spectrum (b, c) are defined as

$$S_{xy}(f) = \langle a_x(f) a_y^*(f) \rangle \quad (a)$$

$$S_{xx}(f) = \langle a_x(f) a_x^*(f) \rangle \quad (b)$$

$$S_{yy}(f) = \langle a_y(f) a_y^*(f) \rangle \quad (c)$$

Coherence is defined as the normalization of cross-spectrum with respect to auto-spectra (d) and the absolute value of coherence (e), respectively.

$$C_{xy}(\lambda) = \frac{S_{xy}(\lambda)}{[S_{xx}(\lambda) \cdot S_{yy}(\lambda)]^{1/2}} \quad (d)$$

$$Coh_{xy}(\lambda) = |C_{xy}(\lambda)| \quad (e)$$

Coherence is a complex value and its imaginary part represents phase lag between the sources. Coherence as a real number reflects both magnitude and phase relations together and is affected by common reference and volume conduction effects observed in EEG. Since these artefacts are zero-time lag effects and the imaginary part of coherence is only sensitive to phase lags, using the imaginary part of coherence was recommended as a solution (10). The imaginary part of coherence is calculated as follows.

Procedure

The epochs were obtained with respect to the narcoleptic event: the attack itself and 2 min of interictal-resting period. Each epoch was divided into 2 s non-overlapping segments. All segments from all patients were collected together for further analysis to eliminate subject-specific changes and to obtain 'event'-related changes. Coherency was calculated for each segment and for all electrode pairs by applying a Fourier transform to Hanning windowed data.

For the statistics of the coherence between each pair of electrodes, we used arctanh transformation as described by Rosenberg et al. and Amjad et al. and calculated corresponding 95% confidence intervals of the imaginary part of coherence as described by Nolte et al. (17, 18, 10). After the normalization of (complex) coherence values (Equation f), variance of the imaginary part of it was calculated (Equation g). The procedure was completed by inverse transformation of averaged/differenced values of coherence (Equation h).

$$C_{xy} \rightarrow \frac{C_{xy}}{|C_{xy}|} \arctanh(|C_{xy}|) \equiv \tilde{C}_{xy} \quad (f)$$

$$\text{var}(\text{Im}(C_{xy})) = \frac{(1 - |C_{xy}|^2) \arctanh^2(|C_{xy}|)}{2N} \quad (g)$$

$$C_{xy} \rightarrow \frac{\tilde{C}_{xy}}{|\tilde{C}_{xy}|} \tanh(|\tilde{C}_{xy}|) \quad (h)$$

In order to compare different conditions by suppressing ongoing common activity, we used a subtraction method. In order to obtain connectivity changes during the attack and interictal-resting period ("after") we calculated the following quantity:

$$\Delta \text{Im}(C_{xy}) = \langle \text{Im}(C_{xy}(f))_{\text{event}} \rangle - \langle \text{Im}(C_{xy}(f))_{\text{after}} \rangle \quad (i)$$

A decrease or an increase in coherence is assumed to be significant if both confidence limits are smaller (coded as blue) or higher (coded as red) than zero (white), respectively.

Visualization

We calculated the imaginary part of coherence for every electrode with other electrodes respectively. In order to see all of the changes in the couplings (differences in the imaginary part of coherence), a small circle is placed at the position of the corresponding electrode, and all significant increases (red) or decreases (blue) are plotted using the EEGLAB topographic plot routine (19). White is used for changes in the imaginary part of coherence that are not significant.

RESULTS

Seven emotionally triggered cataplectic attacks were recorded in three subjects, all of them classified on the basis of their behavioral aspects. All cataplexy recordings were preceded by segmental cataplexy with waxing and waning EMG tonus and in one (patient 2) of them ended in blunting of all EMG activity, indicating complete postural collapse, as confirmed by video recording.

Electroencephalography Analysis

We analyzed changes in coherence (couplings) with respect to attacks and showed statistically significant changes in topological view ($p < .05$). If coherency was lower after the attack it was coded as blue. In contrast, an increase in coherence after the attack was coded as red. An increase or decrease in coherence during the attack was coded as red or blue, respectively.

Delta Waves (0.1-3 Hz)

The couplings were more pronounced on the bilateral parietooccipital parts and right side of the brain with increased coherence on bilateral frontal and temporal electrodes. If we consider only bilateral occipital electrodes the coherence was increased with right-sided temporal electrodes (Figure 3a).

Theta Waves (4-7 Hz)

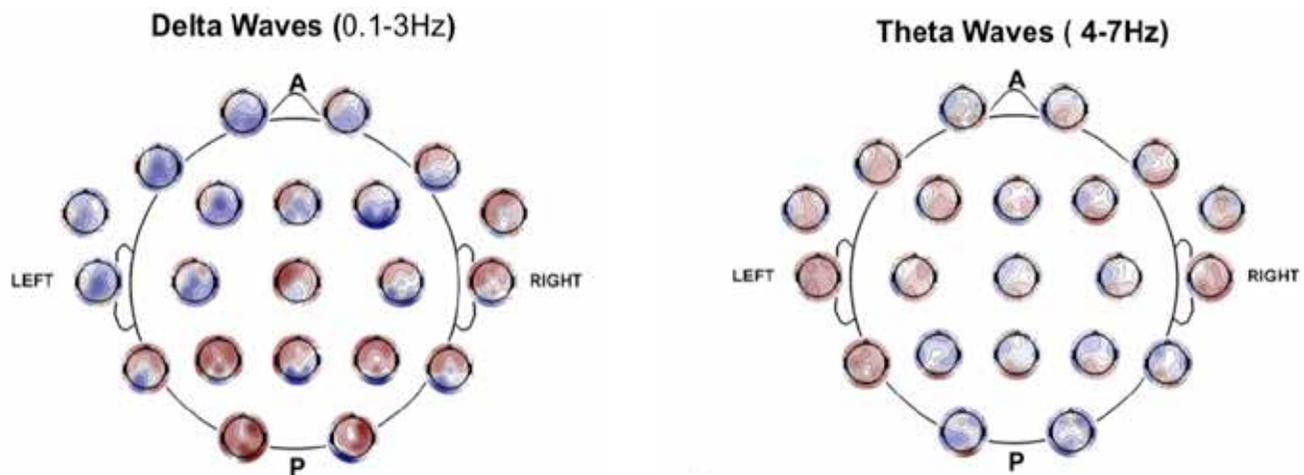
The couplings were more pronounced on temporal electrodes (T1-T2). The bilateral temporal and frontotemporal electrodes showed higher coherence with overall cortex during the attack compared to the period following it.

However, that was larger on the left side. The coherence was increased in all electrodes covering the entire scalp (Figure 3b).

DISCUSSION

In this novel study, we analyzed functional couplings among brain regions by using the imaginary part of coherence during cataplexy attacks. Coherence is a complex number showing linear relations between two sources, but its real part is affected by volume conduction and common reference effect in the case of EEG. Using the imaginary part of coherence makes it possible to focus on the time delay relations/interactions between the sources. In addition, by taking the difference between the coherence values during the attack and resting, we focused on functional coupling changes in relation to cata-

Figure 3. a, b. Comparison of the coherence values during the cataplexy attacks and the interictal-resting periods in delta (a) and theta (b) frequency bands. The high coherence values during the attacks compared the interictal periods were coded with red whereas the lower values were coded with blue



plexus attacks. Furthermore, movement artifacts on EEG yielded zero time lag signals and it can be assumed that imaginary part of coherence can be a solution to avoid these.

Cataplexy is thought to represent the abnormal expression of REM sleep, whereby muscular atonia typical of REM sleep occurs inappropriately when awake. During these cataplectic attacks desynchronization of EEG with waxing-waning of the theta-delta waves have been reported (20). According to our EEG analysis of cataplectic attacks, the results showed that the coupling of slow waves increased in temporal regions. Slower waves (<4 Hz) coherence increased on the right side of temporal regions and they showed increased coupling with frontal areas. The coherence for 4-7 Hz waves was more apparent in the left temporal region and coupling was found in all electrodes. Reports of EEG activity during cataplexy in animals and humans are relatively few and only two of them described special EEG changes like slow wave bursts during cataplexy attacks in mice and children (8, 11). Vassalli et al. reported electrophysiologically hypersynchronous paroxysmal slow wave activities during cataplexy and these activities involved the frontal cortex (8). Although their physiological meaning is still unknown, they also reported that these hypersynchronous slow waves (2.5-5 Hz) were dominant in left-sided central regions of children with cataplexy attacks. They suggested that those discharges were unlikely to represent hypnagogic hypersynchronies, but their patients were younger than 11 years old. In our study we examined 7 cataplexy attacks' recordings in 3 adults. In addition, compared to our study they did not use expanded EEG recordings (including 21 electrodes with T1 and T2 according to 10-20 system, Figure 1), and the functional activation or coupling was not obvious in these reports. Therefore, the findings related to involved brain areas (i.e. left-sided central regions) were not clear. In contrast to that, we found that the functional activity of temporal regions was obvious during cataplexy attacks.

Previous neuroimaging studies have tried to identify involving brain areas during cataplexy attacks (9, 21-24). Furthermore histopathological studies showed that reduced number of hypocretin neurons in the anterior hypothalamus of narcoleptic patients with cataplexy (25). As an indirect finding for cataplexy attacks, volumetric changes in the hypothalamus and/or the frontal cortex were reported in patients with hypocretin-deficient narcolepsy (21, 22). Several studies have also reported amygdala dysfunction in narcolepsy/cataplexy (23, 24). By comparing the findings of patients with narcolepsy with/without cataplexy, the involvement of the inferior frontal gyrus in addition to the amygdala was emphasized (9, 26). In contrast to electrophysiological studies, these neuroimaging studies did not show real-time changes during cataplexy attacks. In an electrophysiological study by Oishi et al., they found that palatable foods markedly increased cataplexy and activated neurons in the medial prefrontal cortex of orexin knockout mice (7). We also found that delta waves coupling was increased with right-sided temporal regions and the frontal areas.

Clinically cataplexy is best triggered by emotions, and neuroimaging, neurophysiological, and clinical studies have shown that the amygdala is involved in emotional processing (3-5). Therefore, our finding related to involvement of the temporal region during cataplexy attacks is not surprising. The amygdala also has widespread reciprocal projections to many cortical areas, allowing for modulation of top-down processing of emotional content. Especially neurons in the medial prefrontal cortex innervated parts of the amygdala and lateral hypothalamus that contain neurons active during cataplexy and that innervate brainstem regions are known to regulate motor tone (7). Lateralization of the amygdala could also be important. While many neuroimaging studies observe bilateral responses during different types (happiness, fear, anxiety) of emotional studies, unilateral responses at the group sub-

ject level are also common. Functional MRI studies frequently show individual differences in the lateralization of responses, with some subjects demonstrating right amygdala foci while other subjects show left amygdala foci (27). Individual differences beyond sex, such as personality (28) or genotype (29), modulate amygdala activity. However, a difference in action was also reported, for example the action of the right amygdala is fast, short, and relatively automatic and the left amygdala is involved in more detailed-sustained response (27). In our study we could not examine the temporal relation of coupling in theta and delta waves. Therefore, we were unable to explain why delta waves coupling was increased in the right temporal region or theta waves coupling was more pronounced in the left temporal region. However, laterality differences might reflect rapid or late-sustained responses during cataplexy attacks.

We had no findings related to CSF orexin levels to categorize the patients. But updated diagnostic criteria of narcolepsy type 1 in ICSD-3 requires cataplexy and either positive multiple sleep latency testing (MSLT)/PSG findings or CSF hypocretin deficiency (1). All our patients had mean sleep latency ≤ 8 minutes on MSLT with ≥ 2 SOREM periods.

A limitation of our study was that we had only three patients. Because we could not study with a standardized protocol to elicit cataplexy and the cataplectic attacks of our patients were captured almost by chance. In future, the number of patients could be increased and they could be grouped as emotionally triggered and spontaneously occurring cataplexy attacks. Furthermore, features of triggering events (i.e. visual or auditory) can be investigated. For example, visual triggerings can lead to occipital region activation firstly. Therefore, sex-individual differences and emotional factors could be eliminated or compared.

Finally, in cataplectic attacks involvement of the temporal lobes and frontal lobes was shown electrophysiologically. Further investigations on those localized-lateralized slow waves are required in order to investigate their physiological meaning and to clarify the neural circuits involved in their manifestation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.İ.T.; Design – N.E.; Supervision – F.İ.T., N.E.; Data Collection and/or Processing – F.İ.T., N.E.; Analysis and/or Interpretation – F.İ.T., N.E.; Literature Search – F.İ.T., N.E.; Writing Manuscript – F.İ.T.; Critical Review – F.İ.T., N.E.

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