

# Non-Epileptiform EEG Patterns in Non-Convulsive Status Epilepticus: Can Quantified SPECT Imaging be Useful?

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#### Original research

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## **Abstract**

**Background:** The diagnosis of non-convulsive status epilepticus (NCSE) in patients with non-epileptiform EEG patterns remains a challenge.

**Objective:** To prove the usefulness of single photon emission computerized tomography (SPECT) and its quantification (QtSPECT) in co-localizing the abnormal focus in the EEG with an area of hyperperfusion, thus helping in the diagnosis of NCSE.

**Methods:** We retrospectively reviewed patients admitted with clinical suspicion of NCSE who underwent an HMPAO-SPECT controlled by scalp-EEG showing non-epileptiform patterns, in a 5-year period. We divided our patients in confirmed NCSE (n=11) and non-NCSE (n=8), and compared the EEG and SPECT results in both groups.

**Results:** Lateralized rhythmic delta activity (LRDA) was predominant in the NCSE group (45'4%, p=0'045), while lateralized irregular slowing was observed equally in both groups. Patients with NCSE showed significant hyperperfusion compared to non-NCSE patients (p=0.026). QtSPECT correctly classified 91% of patients in NCSE and 75% patients with non-NCSE (p=0.006).

**Conclusions:** Regional cerebral blood flow measured with SPECT could be useful in the diagnosis of NCSE in cases of an EEG pattern with lateralized slow activity and high clinical suspicion.

# **Highlights**

- When suspecting non-convulsive status epilepticus, a perfusion neuroimaging together with the scalp-EEG can help in the diagnosis.
- Lateralized rhythmic delta activity with a co-localized hyperperfusion focus on SPECT is highly suggestive of status epilepticus.
- Quantified SPECT can be useful to identify an abnormal area of hyperperfusion on functional neuroimaging.

# 1. Background

The diagnosis of non-convulsive status epilepticus (NCSE) has been a challenge for neurologists and neurophysiologists for decades [1], and requires the use of EEG to reach the diagnosis [2]. In recent years, the Salzburg criteria, a diagnostic EEG algorithm for patients with clinical suspicion of NCSE, has been proposed, with a reported high accuracy [3]. However, there are still a number of patients in which EEG does not allow a definite diagnosis, falling into the category of possible status epilepticus [3]. In these cases, non-epileptiform abnormalities as rhythmic delta activity can represent a high proportion of

patients [4], and pose a challenge to the diagnosis and treatment. Some of these EEG patterns are not definitely neither ictal nor interictal, and the term ictal-interictal continuum (IIC) is used to refer to them [5].

Single photon emission computerized tomography (SPECT) can serve as a useful tool in co-localizing the abnormal focus in the EEG with an area of hyperperfusion [6], thus helping into the diagnosis of NCSE [7]. SPECT imaging has shown hyperperfusion related to seizures [8–11] and to periodic lateralized discharges [12,13]. However, the use and interpretation of SPECT in the non-epileptiform patterns of the IIC spectrum remains elusive.

Our aim is to evaluate the role of SPECT in patients with clinical suspicion of NCSE and non-epileptiform patterns on EEG.

## 2. Methods

We retrospectively reviewed patients with clinical suspicion of NCSE who were admitted in Bellvitge University Hospital between 2014 and 2019. Among them, we selected those patients who underwent HMPAO-SPECT controlled by scalp-EEG as part of their diagnostic work-up realized during the ictal period. All patients were admitted into the neurology ward and underwent a complete work up including blood sampling, serial EEGs and brain MRI. Like Leitinger et al., 2016, we classified patients as NCSE or non-NCSE following a consensus decision between different raters inferred from all clinical and paraclinical data, including EEG readings, laboratory data, therapeutic response, follow-up and final outcome. For all patients and recordings, two authors evaluated these data independently, blinded to HMPAO-SPECT results. When consensus was not achieved in the diagnosis, a third author evaluated the patients. We then divided the patients into those who were diagnosed with NCSE (NCSE) and those who were not (non-NCSE). HMPAO-SPECT studies were then compared between the two groups (NCSE and non-NCSE).

For all patients, a suspected etiology was assigned based on the clinical history, physical exam and the results of all complementary tests. They were classified in acute, remote, progressive or unknown. The study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge with PR177/16. All patients or their relatives signed an informed consent form in accordance with the Helsinki declaration. The confidential information of the patients was handled in accordance with Spanish regulations.

## 2.1. SPECT data acquisition and processing

The SPECT scans and their quantification were performed using the same protocol described by Jaraba et al., 2019, in our same center. All scans were performed within 120 min from the administration of 740 Mbq (20 mCi) of 99mTc-HMPAO (Amersham Inter- national, Arlington Heights, IL). The patients were scanned in a Philips Skylight two-head gammacamera equipped with an LEGP collimator. The acquisition protocol was a 180° rotation in step-by-step mode. Reconstruction was done using filtered back-projection, and transaxial, coronal, and sagittal slices were obtained. The injections were done during the clinical episode suspected of being NCSE, while patients were monitored with video-EEG. To do the quantified SPECT (QtSPECT), all data were normalized to the SPM SPECT template, which is a

software package for analysis and processing of neuroimaging data sequences. We used an external healthy normal database [14] to obtain a Z-score map for each individual's ictal SPECT scan versus that normal database. The Z-score maximum (Zmax) was extracted from each region using the Automated Anatomical Labeling (AAL) atlas, as well as the percentage of voxels with a Z-score higher than 2.5 (N). Only the voxels inside a mask of the brain (excluding the sublobar areas) were considered, and all clusters of fewer than 100 pixels were also excluded. From the resulting map the maximum value (Zmax), the number of significant voxels with Z-score > 2.5 (N) and the anatomical region with the maximum value were recorded. The latter was obtained using the AAL, which is a software and a digital human brain atlas with a labeled volume. Labels indicate macroscopic brain structures. The results of the QtSPECT were considered positive based on a logistic regression trained with a different patient database [7]; regression considered the Zmax, the N, the anatomical region with more voxels and the age of the patient. If the EEG showed a lateralized pattern, we considered the SPECT positive only if the hyperperfusion was located concordantly to the EEG findings.

#### 2.2 EEG data acquisition and processing

EEG was done during the SPECT injection in all cases. All scalp EEG recordings were placed according to the standard international 10-20 system for at least 30 minutes with standard procedure (eyes closed, impedances <5 k $\Omega$ , band-pass = 0.5–70 Hz, notch filter ON, sampling rate = 256 Hz). The EEG findings were described according to the glossary of the International Federation of Clinical Neurophysiology [15], the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology (SCCET) [16] and the Salzburg Consensus Criteria for NCSE [3]. All EEG recordings were made and evaluated by neurophysiologists and neurologists specialized in epilepsy. Continuous video-EEG or prolonged video-EEG were done whenever was possible.

#### 2.3. Statistics

Statistical analyses were performed in SPSS v.22 (SPSS Inc, Chicago, USA) and R (R Core Team, 2020). Mann–Whitney U test and Fisher's exact test of independence were used to describe clinical and sociodemographic differences between groups.

## 3. Results

During the above-mentioned period, 62 patients with clinical suspicion of NCSE were admitted into our ward and underwent SPECT concomitantly with VEEG. In 43 cases of this initial cohort, epileptiform discharges of any kind were found, being discarded from the analysis (see the flowchart of the study in Figure 1).

Finally, 19 patients showed non-epileptiform EEG patterns and were included. The median age was 76 years old (range 28-87), and 12 of them were women (63.2%). Final diagnosis of NCSE was done in 11 out of these 19 patients (57.9%), 8 of them women (72'7%) (Table 1). The most frequent etiologies for

NCSE were acute vascular event (n=3, 27'3%), remote vascular event (n=2, 18'2%), neoplastic (n=1, 9'1%), genetic (n=1, 9'1%), mesial temporal sclerosis (n=1, 9'1%), or unknown (n=3, 27'3%).

Initially, most of the patients presented with bilateral tonic-clonic seizures (n=4, 21%) or impaired consciousness (n=6, 31'6%) at the debut, while others presented with focal cortical signs: language disturbance (n=7, 36'8%), focal myoclonus with preserved consciousness (n=1, 5'3%), and hemiplegia (n=1, 5'3%). However, the following suspicion of NCSE after this initial symptoms was based on persistent impaired consciousness (n=6, 31'6%) or language disturbance (n=13, 68'4%), so the EEG and QtSPECT were performed at this moment.

The initial EEG showed non-epileptiform, theta or delta range slowing in all cases, in most of them lateralized (15 out of 19 patients). LRDA was predominant in the NCSE group (n=5, 45'4%) versus the non-NCSE group (p=0'045), while a lateralized irregular slowing was observed equally in both groups (n=5, 45'4% for NCSE; n=5, 62'5% for non-NCSE).

All patients underwent follow-up EEGs in the consecutive days, and 3 of them were monitored with continuous EEG for 24h. Among them, the theta or delta slowing usually persisted for more than 24 hours, improving in frequency and rhythmicity in most of the patients (n=14) and getting worse in a minority of them (n=2), without significant changes in the rest. No epileptiform discharges were observed after subsequent EEGs except for one patient, in which PLDs were detected on routine EEG 3 days after the SPECT.

EEG + QtSPECT were done in a median period of 2 days (range 12h – 18 days) after the clinical presentation and always while the patient was still symptomatic (considered ictal). Final diagnosis and EEG findings for each patient are presented in Table 2.

In all patients QtSPECT was done using a normal database. Patients with NCSE showed significant increased and larger hyperperfusion than non-NCSE patients (p=0.026, Figure 2). QtSPECT correctly classified 91% of patients in NCSE and 75% patients with non-NCSE (p=0.006). Figure 3 presents an example of one of our patients.

## 4. Discussion

In our study we presented a group of patients with clinical suspicion of NCSE and EEG patterns showing non-epileptiform abnormalities. In our series, the use of QtSPECT concomitantly with the EEG allowed the diagnosis of NCSE in a majority of patients, with good sensibility and high specificity. Quantification allows a rapid interpretation and avoids the necessity of an interictal SPECT study.

Foremost, in the diagnosis of NCSE a clinical suspicion is needed. However, patients in NCSE can present with unspecific clinics, showing mild neurological symptoms like eye deviation or aphasia, which could mimic other diseases such as a stroke, or even go unnoticed. These symptoms may occur from onset or, in other occasions, appear after more evident seizure activity resolves, frequently delaying the diagnosis

[1]. Being this the case, the EEG is crucial in order to diagnose this condition; notwithstanding, it may not allow a definite diagnosis in some occasions, as there are patterns that do not allow for either confirm or discard NCSE [3]. Especially in those cases where clinical suspicion is high, even non-specific EEG findings cannot reliably discard ongoing seizures [11,17]. In this report, we provide a description of a set of patients with high clinical suspicion of NCSE and an indefinite EEG pattern, in which the aid of neuroimaging is of substantial relevance for the diagnosis and management of these cases.

To date, there is increasing information about the utility of neuroimaging techniques as a diagnostic tool for NCSE, but its use in non-epileptiform patterns remains scarce. Most of the published studies are case series [11,17–23] and no direct comparison of EEG and neuroimaging studies accuracy was carried out in most of them. Some of these studies confirm the relation between increased perfusion imaging and the presence of confirmed NCSE with an ictal EEG pattern [18,19,22,23]. Those cases with non-epileptiform EEG patterns are unclear; small case-series studies reported how these non-epileptiform patterns can relate to focal hyperperfusion on neuroimaging, even in cases of irregular slowing [11,17,18,20,21].

The non-epileptiform patterns within the IIC remain a challenge. In our study we have found that lateralized patterns are more frequently associated to NCSE than generalized ones. Other studies have observed that LRDA has been associated with non-convulsive seizures [24], with a higher risk of seizures at higher frequencies [25]. It has been found an association between LRDA and LPDs in up to 44% of the cases, suggesting that both LPDs and LRDA might have the same significance in relation with the presence of seizures [24]. Less evidence is available for GRDA, which hasn't been associated with seizures even at higher frequencies [25]. On the other hand, patterns of irregular, lateralized, slowing have been described in patients with ongoing seizures [17], as we have also found. In fact, in a series of patients, these irregular slowing patterns on the scalp EEG have been proven to reflex the presence of deeper electrical seizures, detected by intracranial electrodes [26].

Injection of SPECT tracer has been approximated to take 30 seconds to reach the brain, where its uptake is dependent on a pattern of ictal perfusion remaining present for between 1 – 2 minutes, and around 70% of the ligand is taken [27]. Consequently, SPECT imaging offers a good perfusion correlate of the EEG pattern at the time of the injection [8]. Studies comparing SPECT with EEG-fMRI have also found a high correlation between perfusion measured by SPECT and real time fMRI-EEG findings [28]. In this sense, SPECT is a good neuroimaging technique in order to relate the perfusion associated with different EEG patterns, and evaluate the presence of ongoing seizures, as it shows the real-time perfusion of the brain at the time of injection. In our series, patients with LRDA on the EEG at the time of injection showed hyperperfusion, together with other patients with more unspecific findings as irregular lateralized slowing (Table 2). This hyperperfusion was finally concordant with the diagnosis of NCSE, for all LRDA patterns and in some cases of more irregular lateralized slowing. Accordingly, we put forward the role of functional neuroimaging when these EEG patterns arose together with a high clinical suspicion.

However, some limitations of SPECT use should be considered. In acute neurological patients, the blood brain barrier is disturbed, and different patterns of perfusion can arise; the quantification of the results

and the co-localization with the EEG could help to avoid overcalling unrelated perfusion changes. Different etiologies may produce hyperperfusion patterns, which may generate false positives; however, in our sample, no patient had a definite diagnosis of a pathology which could produce these findings (i.e. infectious encephalitis or high-grade glioma). On the other hand, compared to PET, SPECT does not measure metabolism, which could be more specific of ictal activity [17,20]. The main limitation of PET, however, is the prolonged uptake period of the tracer, which could yield results difficult to interpret [29], especially in patients with suspected NCSE, were admixed EEG patterns may be found. Also, as mentioned previously, the quantification of the SPECT allows a more robust interpretation of the hyperperfusion found, and helps eliminating sporous data.

Recently, a multimodal approach to evaluating the treatment options of patients in the IIC spectrum has been proposed [6]. According to our data, QtSPECT can provide a useful and reliable multimodal approach to the acute patient, helping decision making. As mentioned previously, clinical suspicion is the basis of NCSE diagnosis, together with the EEG findings. Notwithstanding, as some limitations of the EEG, mainly the non-epileptiform patterns, could not reliable discard the diagnosis, selected patients could benefit of undergoing functional neuroimaging.

Our work has several limitations. In the first place, the limited number of patients; however, the pathology and EEG patterns reported is rare, and as the number of previous reports in the literature is low, we consider our series of significance. As the patients in our series had a high suspicion of NCSE, the groups are not equally balanced, which provides less information on the sensibility of the SPECT. Further data is needed in order to confirm our findings.

## 5. Conclusions

Regional cerebral blood flow measured with HMPAO-SPECT could be useful in the diagnosis of NCSE in cases of non-epileptiform EEG patterns with high clinical suspicion.

## **Declarations**

#### **Author's contributions**

Albert Muñoz-Vendrell for the collection, analysis and interpretation of data and for the writing of the report; Jacint Sala-Padró for the analysis and interpretation of data and for the writing and correction of the report; Sonia Jaraba for the collection and analysis of the data; Gabriel Reynés-Llompart for the collection and analysis of the data; Misericòrdia Veciana for the correction of the report; Jaume Mora for the interpretation of data; and Mercè Falip for the correction of the report.

#### Competing interests

None of the authors have potential conflicts of interest to be disclosed.

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#### **Ethics approval**

The study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge with PR177/16. All patients or their relatives signed an informed consent form in accordance with the Helsinki declaration. The confidential information of the patients was handled in accordance with Spanish regulations.

## Consent for publication

Not applicable.

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# **Tables**

**Table 1**. Clinical, electrical and demographical characteristics of patients. BTCS = bilateral tonic clonic seizures; LRDA = lateralized rhythmic delta activity; GRDA = generalized rhythmic delta activity.

		Global (19)	NCSE (11)	Non- NCSE (8)	р
Age in years (Median (range)	76 (28- 87)	76 (57- 87)	73 (28- 83)	0.363	
Women (n (percentage))	12 (72'7%)	8 (72'7%)	4 (50%)	0.377	
Etiology	Acute	12 (63'2%)	4 (36'4%)	8 (100%)	Nil
	Remote	3 (15'79%)	3 (27'3%)	Nil	Nil
	Progressive	1 (5'26%)	1 (9'1%)	Nil	Nil
	Unknown 3 3 (15'79%) (27'3%		3 (27'3%)	Nil	Nil
Semiology at presentation	BTCS	4 (21%)	2 (18'2%)	2 (25%)	1
	Language disturbance	7 (36'8%)	5 (45'5%)	2 (25%)	0.633
	Impaired consciousness	6 (31'6%)	3 (27'3%)	3 (37'5%)	1
	Focal myoclonus	1 (5'3%)	1 (9'1%)	0	Nil
	Hemiplegia	1 (5'3%)	0	1 (12'5%)	Nil
Semiology while SPECT was injected	Language disturbance	13 (68'4%)	10 (90'9%)	3 (37'5%)	0.041
	Impaired consciousness	6 (31'6%)			0.041
EEG characteristics (during SPECT injection)	LRDA	5	5 (45.4%)	0	0.045
	GRDA	1	1 (9%)	0	Nil
	Irregular theta-delta slowing localized	10	5(45.4%)	5 (62.5%)	0.650
	Irregular theta-delta slowing generalized	3	0	3 (37.5%)	0.058

**Table 2.** Diagnosis, EEG patterns and SPECT results in our patients. Neg = negative; Pos = positive; LRDA = lateralized rhythmic delta activity; Rt = right; Lt= left; f-t = Fronto-temporal; NORSE = new-onset refractory status epilepticus; MTS = mesial temporal sclerosis; BZD = benzodiazepines; FIRES = febrile infection-related epilepsy syndrome.

Ν	Gender	Age	QtSPECT	NCSE	EEG pattern	Diagnosis	Etiology
1	Woman	82	Neg	Yes	Diffuse delta slowing	Vascular	Acute
2	Male	87	Pos	Yes	Irregular theta slowing, lt hemisphere	Vascular	Acute
3	Woman	67	Pos	Yes	Irregular theta slowing, rt temporal	MTS	Remote
4	Woman	76	Pos	Yes	Irregular theta-delta slowing, lt f-t	NORSE	Unknown
5	Male	67	Pos	Yes	Irregular theta-delta slowing, It temporal	Vascular	Remote
6	Woman	59	Pos	Yes	Irregular theta-delta slowing, rt frontal	MELAS	Acute
7	Woman	71	Pos	Yes	LRDA, It hemisphere	Vascular	Acute
8	Woman	77	Pos	Yes	LRDA, It hemisphere	Vascular	Remote
9	Male	85	Pos	Yes	LRDA, It hemisphere	NORSE	Unknown
10	Woman	79	Pos	Yes	LRDA, It hemisphere	FIRES	Unknown
11	Woman	57	Pos	Yes	LRDA, It hemisphere	Ganglioglioma	Progressive
12	Woman	78	Neg	No	Irregular delta slowing, bifrontal	Vascular	Acute
13	Woman	83	Neg	No	Irregular delta slowing, generalized	Vascular	Acute
14	Male	35	Neg	No	Irregular delta- slowing, generalized	Wernicke encephalopathy	Acute
15	Male	70	Pos	No	Irregular theta slowing, generalized	Vascular	Acute
16	Male	51	Neg	No	Irregular theta slowing, It centro- parietal	BZD Deprivation	Acute
17	Woman	28	Neg	No	Irregular theta-delta slowing, bitemporal	NMDA encephalitis	Acute
18	Woman	79	Pos	No	Irregular theta-delta slowing, lt f-t	Vascular	Acute
19	Male	76	Neg	No	Irregular theta-delta slowing, lt parietal	Vascular	Acute

# **Figures**

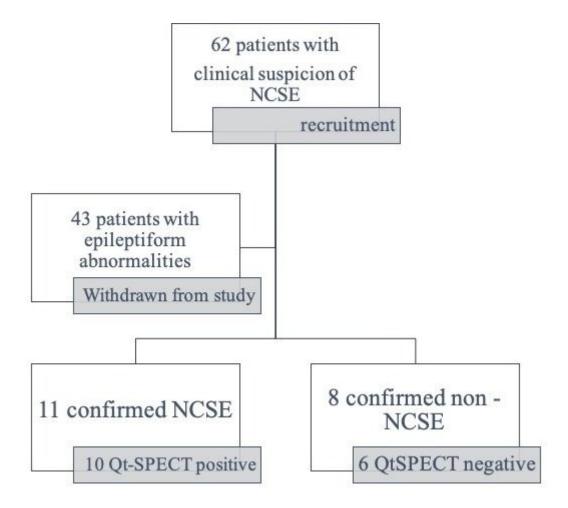


Figure 1

Flowchart showing the patients recruited for the study, and those finally included with concomitant SPECT and EEG showing non-epileptiform abnormalities. NCSE = Non-convulsive status epilepticus; QtSPECT = Quantified SPECT.

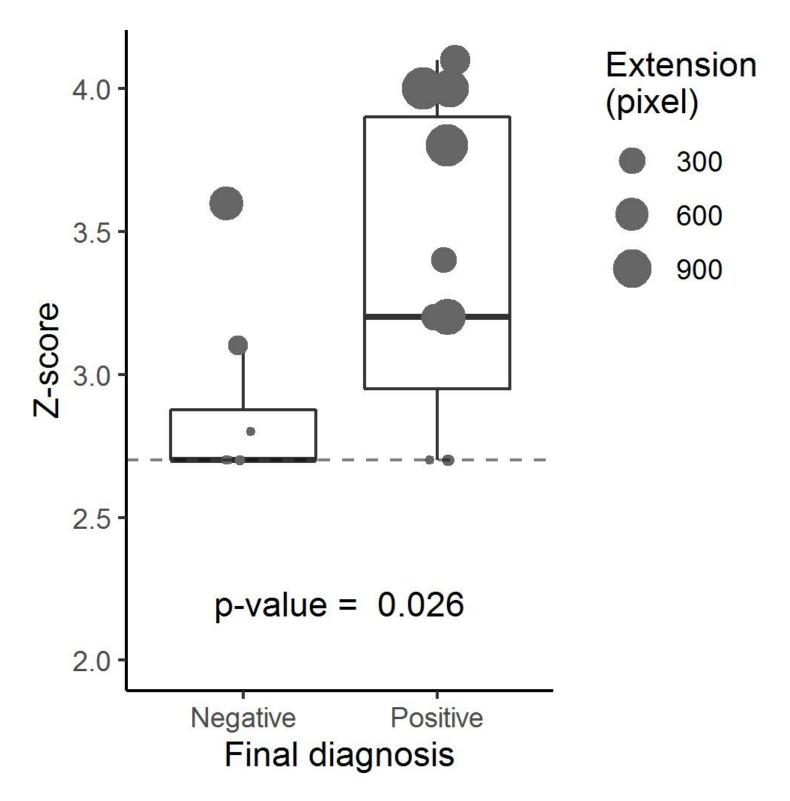


Figure 2

Relation between the Z-score and the focus extension. Dashed line represents a minimum z-score threshold of 2.7, all values bellow that where considered 2.7 in the graphic. Patients with NCSE (deemed "positive" on the X axis) showed increased perfusion (Z-score) on a larger area (pixel Extension)

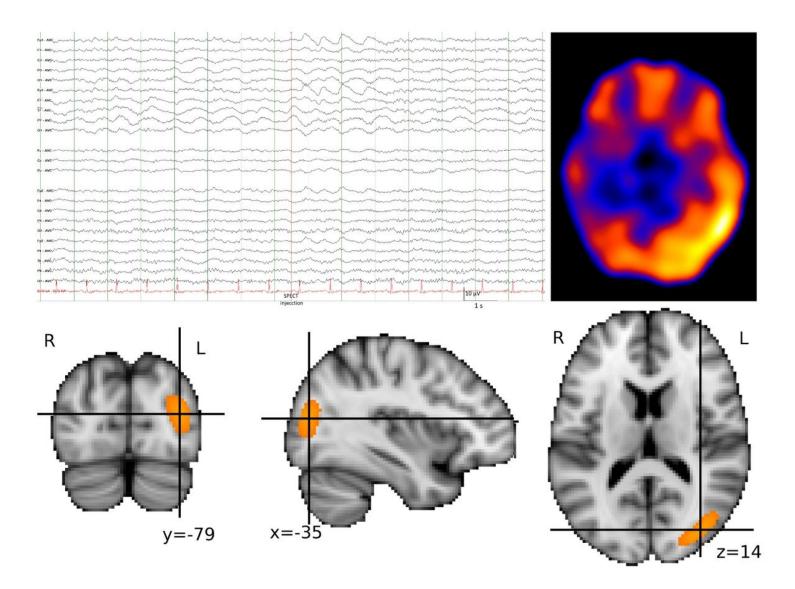


Figure 3

VEEG, SPECT and Qt SPECT of a patient in NCSE. On top left, the VEEG (longitudinal bipolar montage, High pass filter 0.3Hz, low pass filter 70Hz, amplitude 10mV) showed continuous rhythmic delta activity over the left hemisphere when the injection of HMPAO was performed. Top right, SPECT image showing increased perfusion of the left posterior quadrant area. Bottom, Qt SPECT (z-score filtered, yellow blob indicates Z>4) showing the area of hyperperfusion on the left posterior quadrant quantified against controls.