BRAIN COMMUNICATIONS

Hyperperfusion in the thalamus on arterial spin labelling indicates non-convulsive status epilepticus

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Non-convulsive status epilepticus describes the syndrome of unexplained impaired consciousness in critically ill patients. Non-convulsive status epilepticus is very likely to lead to delayed diagnosis and poor outcomes because of the absence of convulsive symptoms. EEG is essential for the diagnosis of non-convulsive status epilepticus to establish the association between periodic discharges and rhythmic delta activity in addition to ictal epileptiform discharges according to the Salzburg criteria. Arterial spin labelling, a type of perfusion MRI, has been applied for rapid and non-invasive evaluation of the ictal state. Ictal cerebral cortical hyperperfusion is the most common finding to demonstrate focal onset seizures. Hyperperfusion of the thalamus on single photon emission computed tomography was found in patients with impaired awareness seizures. We hypothesized that thalamocortical hyperperfusion on arterial spin labelling identifies non-convulsive status epilepticus and such thalamic hyperperfusion specifically associates with periodic/rhythmic discharges producing impaired consciousness without convulsion. We identified 27 patients (17 females; age, 39–91 years) who underwent both arterial spin labelling and EEG within 24 h of suspected non-convulsive status epilepticus. We analysed 28 episodes of suspected non-convulsive status epilepticus and compared hyperperfusion on arterial spin labelling with periodic/rhythmic discharges. We evaluated 21 episodes as a positive diagnosis of non-convulsive status epilepticus according to the Salzburg criteria. We identified periodic discharges in 15 (12 lateralized and 3 bilateral independent) episodes and rhythmic delta activity in 13 (10 lateralized, 1 bilateral independent and 2 generalized) episodes. Arterial spin labelling showed thalamic hyperperfusion in 16 (11 unilateral and 5 bilateral) episodes and cerebral cortical hyperperfusion in 24 (20 unilateral and 4 bilateral) episodes. Thalamic hyperperfusion was significantly associated with non-convulsive status epilepticus ($P = 0.0007$; sensitivity, 76.2%; specificity, 100%), periodic discharges ($P < 0.0001$; 93.3%; 84.6%), and rhythmic delta activity ($P = 0.0006$; 92.3%; 73.3%). Cerebral cortical hyperperfusion was significantly associated with non-convulsive status epilepticus ($P = 0.0017$; 100%; 57.1%) and periodic discharges ($P = 0.0349$; 100%; 30.8%), but not with rhythmic delta activity. Thalamocortical hyperperfusion could be a new biomarker of non-convulsive status epilepticus according to the Salzburg criteria in critically ill patients. Specific thalamic hyperexcitability might modulate the periodic discharges and rhythmic delta activity associated with non-convulsive status epilepticus. Impaired consciousness without convulsions could be caused by predominant thalamic hyperperfusion together with cortical hyperperfusion but without ictal epileptiform discharges.

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Graphical Abstract
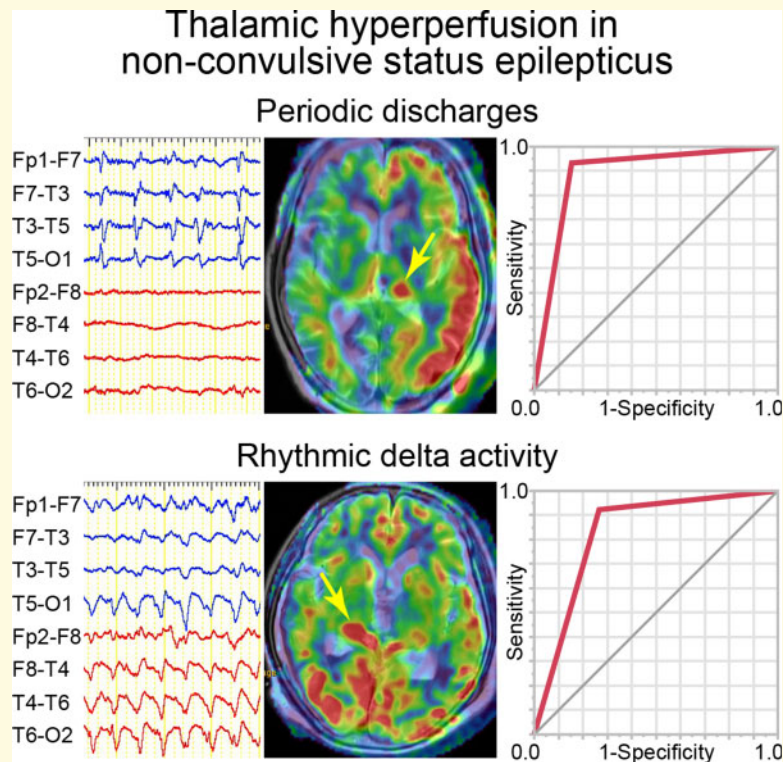
Introduction

Non-convulsive status epilepticus

Non-convulsive status epilepticus (NCSE) is the term used to describe unexplained impaired consciousness or altered mental status from the baseline in critically ill patients (Sutter *et al.*, 2016). NCSE presents a complex problem in neurocritical care because of the absence of the convulsive symptoms found in convulsive status epilepticus. EEG is essential for the correct diagnosis of NCSE since the clinical signs are very subtle and non-specific (Claassen *et al.*, 2004). Several EEG diagnostic criteria for NCSE have been proposed (Chong and Hirsch, 2005; Kaplan, 2007; Sutter and Kaplan, 2012), and renewed diagnostic criteria for NCSE were proposed by a panel of experts at the fourth London-Innsbruck Colloquium on Status Epilepticus in Salzburg (Beniczky *et al.*, 2013).

This Salzburg criteria integrate the standardized critical care EEG terminology of the American Clinical Neurophysiology Society (Hirsch *et al.*, 2013) to reduce the false-positive diagnosis of NCSE (Leitinger *et al.*, 2015b), as well as apply to comatose patients (Trinka and Leitinger, 2015). The Salzburg criteria achieve high diagnostic accuracy and excellent inter-rater agreement for the diagnosis of NCSE in various clinical settings (Leitinger *et al.*, 2016). The interpretation of periodic discharges (PDs) and rhythmic delta activity (RDA) in addition to EEG seizures has established the defining landmark for NCSE in the field of intensive care (Trinka and Leitinger, 2015; Leitinger *et al.*, 2015b, 2016).

Arterial spin labelling

Arterial spin labelling (ASL) is one of the methods used in perfusion MRI studies. ASL can provide non-invasive

evaluation of cerebral perfusion without the requirement of exogenous tracer administration (Detre et al., 1992; Williams et al., 1992). ASL has demonstrated cerebral cortical hyperperfusion in acute seizures (Yoo et al., 2017), during the ictal and peri-ictal periods of focal onset seizures (Pizzini et al., 2013; Kim et al., 2016; Schertz et al., 2020), during status epilepticus (Oishi et al., 2012; Matsuura et al., 2015) and in NCSE (Shimogawa et al., 2017). ASL findings of cortical hyperperfusion are more sensitive for status epilepticus seizure than hyperintensity on diffusion-weighted imaging (DWI) (Matsuura et al., 2015; Shimogawa et al., 2017; Schertz et al., 2020). However, any association between thalamic hyperperfusion on ASL and EEG findings, indicating suspected NCSE based on the Salzburg criteria, has not been established.

Thalamus and periodic discharges

The thalamus is the most important component of the arousal system in humans (Steriade et al., 1993). Consciousness is maintained by the ascending reticular activating system consisting of the thalamus, thalamocortical connections and temporolimbic systems. Single photon emission computed tomography (SPECT) study revealed that thalamic hyperperfusion was associated with impaired consciousness during seizures (Lee et al., 2002). Perfusion MRI study demonstrated that thalamic hyperperfusion was associated with prolonged epileptic activities in patients with focal impaired awareness seizure status (Szabo et al., 2005). Therefore, thalamic hyperperfusion could be associated with impaired consciousness in addition to specific EEG findings during NCSE.

Hypothesis

We proposed that the PDs and RDA indispensable to diagnose NCSE are associated with thalamic hyperperfusion on ASL. This study investigated the association of ASL with EEG findings in critically ill patients with suspected NCSE using the Salzburg criteria. We hypothesized that thalamic hyperperfusion on ASL is a surrogate biomarker of NCSE, and represents thalamic hyperexcitability, modulating the PDs and RDA associated with NCSE in critically ill patients.

Materials and methods

Subjects

A total of 1038 adult patients were admitted to our emergency room in the Department of Neurosurgery of South Miyagi Medical Center between November 2013 and December 2018. We retrospectively identified 31 patients with clinically suspected NCSE, manifesting as symptoms consisting of unexplained impaired consciousness or decreasing levels of cognitive performance from the baseline for at least 10 min (Leitinger et al., 2015b).

Patients with prior seizure episodes of epileptic disorders were excluded in this study to exclude the long-term effects of anti-epileptic drugs on EEG findings. We excluded four patients in whom ASL and EEG were not performed within 24 h of the onset of suspected NCSE. The study was approved by the local Ethical Committee of South Miyagi Medical Center. The caregivers of all patients provided written informed consent.

MRI and ASL data collection

MRI was performed with a 3T system (Signa HDxt 3.0T; GE Healthcare, Milwaukee, WI, USA) with a 12-channel phased array head receiving coil for conventional non-contrast sequences and ASL. The conventional sequences included axial echo-planar DWI [b value $= 1000$ s/mm^2; repetition time (TR)/echo time (TE) $= 6500/80$ ms]; T2 fluid-attenuated inversion recovery (TR/TE/inversion time $= 10\,000/140/2500$ ms); T2-star-weighted imaging (TR/TE $= 500/15.0$ ms); and three-dimensional time-of-flight magnetic resonance angiography from the carotid bifurcation to all brain arteries (TR/TE $= 25/3.4$ ms).

ASL was performed using a three-dimensional fast-spin-echo pulsed continuous ASL with background suppression and superimposed T2-weighted imaging. The pulsed continuous ASL sequences consisted of interleaved stack spiral readout with the following parameters: TR, 4600 ms; TE, 9.8 ms; 512 sampling points on 8 spiral arms; field-of-view, 240 mm; section thickness, 4 mm; reconstructed matrix, 512×512; reconstructed slice thickness, 5 mm; post-labelling delay, 1525 ms; number of excitations, 2 and total scan time, 3:14 min. T2-weighted imaging used the following parameters: TR, 4700 ms; TE, 100 ms; field-of-view, 240 mm and slice thickness, 4 mm. Quantitative cerebral blood flow (CBF) (ml/100 g/min) was automatically calculated from the pulsed continuous ASL images using the following formula:

$$CBF = 6000$$
$$\times \frac{\lambda\left(1 - \exp\left(-\frac{ST}{T_{1t}}\right)\right)\exp\left(\frac{PLD}{T_{1b}}\right)}{2T_{1b}\left(1 - \exp\left(-\frac{LT}{T_{1b}}\right)\right)\varepsilon \times NEX}\left(\frac{PW}{SF \times RPD}\right)$$

where λ is the brain-blood partition coefficient set to 0.9, ST is the saturation time set to 2000 ms, T_{1t} is the grey-matter T1 value set to 1200 ms, T_{1b} is the blood T1 value set to 1600 ms, LT is the labelling duration set to 1500 ms, ε is the labelling efficiency set to 0.80×0.75, PW is the difference between labelling and control images, SF is a scaling factor, RPD is the reference proton density images, PLD is the post-labelling delay and NEX is the number of excitations.

Definition of hyperperfusion

We recruited 28 age- and sex-matched subjects (11 males and 17 females; mean age, 75.6 years) as controls to

establish the reference values of regional CBF. The control subjects had undergone ASL during the same period for the investigation of primary brain disease. The control subjects were matched with the patients according to the brain disease, without seizures or impaired consciousness episodes. Regions of interest (ROIs) were drawn on the ASL images to measure regional CBF using the workstation of the MRI scanner (AW4.6; GE Healthcare). The area of ROIs was $461\,mm^2$ at the cerebral cortex and $210\,mm^2$ at the thalamus. The total number of ROIs was 48 including three in the thalamus, six in the frontal lobe and five in each of the temporal, parietal and occipital lobes, in the unilateral hemisphere (Supplementary Fig. 1). Based on the ROIs of the control subjects, the mean and standard deviation of regional CBF were calculated as references for both lesion and non-lesion sides in the thalamus and cerebral cortical regions (Supplementary Table 1).

The ROIs were placed by two co-authors (H.A., Y.S.) in the patients to include visually identified hyperperfusion areas in the thalamus (fixed location as in control subjects) and the frontal, temporal, parietal and occipital lobes. These authors independently reviewed ASL data, unaware of the patients' clinical data including the findings of EEG. The ROIs consisted of three in the thalamus, six in the frontal lobe and five in each of the temporal, parietal and occipital lobes, in the unilateral hemisphere. A total of 48 ROIs were selected in the bilateral hemispheres. The CBF value of each ROI in patients was compared to that of the control subjects in the corresponding region as summarized in Supplementary Table 1. If the CBF value of ROI was 2 standard deviations or more above the mean reference value of CBF in the control subjects, the ROI was considered to indicate hyperperfusion. If one or more hyperperfusion ROIs were identified among the three ROIs in the unilateral thalamus, we defined thalamic hyperperfusion. If two or more hyperperfusion ROIs were identified in each cerebral lobe in the unilateral hemisphere, we defined cortical hyperperfusion in the cerebral lobe.

EEG

Digital scalp EEG (Neurofax; Nihon-Kohden, Tokyo, Japan) was recorded with the international 10–20 system electrode placement and additional T1/T2 electrodes. The EEG recordings were performed for at least 1 h for all patients. Continuous EEG monitoring (more than 6 h) was performed in 15 patients. PDs and RDA were identified using standardized critical care EEG terminology of the American Clinical Neurophysiology Society (Hirsch et al., 2013). The PDs were subcategorized as lateralized, bilateral independent and generalized PDs. The RDA was subcategorized as lateralized, bilateral independent and generalized RDA. The EEG seizures were identified as frequency change and apparent spatiotemporal evolution pattern of epileptiform discharges with a frequency of >25 times per 10 s epoch. Brief rhythmic epileptiform discharges were identified as repetitive epileptiform discharges occurring two or three times per second, lasting only a few seconds. Single spike or sharp waves were not evaluated in this study. Two experienced, board-certified experts of EEG and clinical neurophysiology (S.O., H.O.) independently reviewed the recordings of EEG, unaware of the patients' clinical data including ASL.

Non-convulsive status epilepticus

NCSE was diagnosed using the Salzburg criteria (Beniczky et al., 2013; Leitinger et al., 2016). The minimal duration of the EEG epoch required to fulfil the Salzburg criteria was defined as 10 s with abnormal findings during the entire EEG recordings (Leitinger et al., 2016). We categorized the EEG findings associated with NCSE using the terminology proposed previously (Leitinger et al., 2015a, 2016) as follows:

(1) Epileptiform discharges with the frequency of >25 times per 10 s epoch (2.5 cycles per second).
(2) Epileptiform discharges with the frequency of ≤2.5 cycles per second or continuous (quasi-) RDA with the frequency of >0.5 cycles per second, and at least one of:
(2a) EEG and clinical improvement with intravenous antiepileptic drugs.
(2b) Subtle clinical ictal phenomena during the EEG.
(2c) Typical spatiotemporal evolution.
(2d) Only EEG improvement to intravenous antiepileptic drugs.
(2e) Fluctuation of EEG findings without definitive evolution.
(3) The absence of (1) or (2).

We classified episodes of Salzburg criteria (1), (2a), (2b) and (2c) as NCSE, (2d) and (2e) as possible NCSE, and (3) as no NCSE (Leitinger et al., 2016). Episodes classified as possible NCSE were considered as a positive diagnosis of NCSE in the previous proposal (Leitinger et al., 2016).

Statistical analysis

Fisher's exact test was used for significance testing between thalamic and cerebral cortical hyperperfusion on ASL, and the presence of NCSE and EEG findings. The sensitivity and specificity of thalamic and cerebral cortical hyperperfusion were calculated using standardized formulas for PDs, RDA, EEG seizures and brief rhythmic epileptiform discharges. Based on the sensitivities and specificities for NCSE, PDs and RDA, receiver operating characteristic curves were calculated, and the differences of the area under the curve (AUC) were compared between thalamic hyperperfusion and cerebral cortical hyperperfusion. For comparison of the AUCs, P-values and 95% confidence intervals (CIs) were calculated using

the concordance statistics. The Wilcoxon rank sum test was used to calculate the differences in patients' age, Glasgow Coma Scale (GCS) at suspected NCSE, times of ASL or EEG starting from suspected NCSE, time interval between ASL and EEG and EEG recording periods. Significance level of $\alpha = 0.05$ was used for all statistical analyses. The data were analysed using commercially available software (JMP Pro 13.2; SAS Institute Inc.) and the open-source statistical package R (version 3.3.3; The R Project for Statistical Computing).

Gwet's AC_1 (for categorical data) was calculated for the EEG findings to assess the inter-rater agreement (Gwet, 2008). Inter-rater agreement was interpreted according to the following groups: poor ($\kappa < 0$), slight ($\kappa = 0.01$–0.2), fair ($\kappa = 0.21$–0.4), moderate ($\kappa = 0.41$–0.6), substantial ($\kappa = 0.61$–0.8) and almost perfect agreement ($\kappa > 0.8$) (Landis and Koch, 1977).

Data availability

The data used in this study are available upon reasonable request.

Results

Patient profiles

The clinical profiles of the patients are listed in Table 1. ASL and EEG were studied within 24 h for 28 episodes of suspected NCSE in our 27 patients. One patient had two separate episodes (Episodes 16 and 17), both with ASL and EEG. The 27 patients consisted of 17 females and 10 males with a mean age of 77.7 years (range, 39–91 years). The primary diseases of patients were as follows: subarachnoid haemorrhage in nine patients, intracerebral haemorrhage in seven, acute subdural haematoma in seven, chronic subdural haematoma in two and hydrocephalus in one. Three patients had generalized convulsions, including one with acute subdural haematoma and one with hydrocephalus. The laterality of lesions was the left hemisphere in 13 patients, right in 10, bilateral in 2 and non-lesion in 2. Surgical treatments for the primary diseases were performed in 18 patients. GCS at the suspected NCSE ranged from 5 to 11 (median, 8). In addition to impaired consciousness, subtle clinical phenomena were seen in 13 episodes consisting of eye deviation in six, twitching of the mouth in five and eye movement and twitching of the extremities in one each. ASL or EEG started from 1 to 12 h (mean, 6.8) after the suspected NCSE except for three episodes of no recovery of consciousness after generalized convulsion with ASL or EEG 24 or 36 h after the generalized convulsion. The time differences between ASL and EEG ranged from 0.5 to 23 h (mean, 8.0). The recording periods of EEG ranged from 1 to 64 h (mean, 11.9).

Continuous EEG monitoring (more than 6 h) was performed in 15 episodes.

EEG

The EEG findings are described in Table 2. PDs were identified in 15 episodes including lateralized PDs in 12 and bilateral independent PDs in 3. Generalized PDs were not found in any episodes. The laterality of PDs was bilateral in six episodes, left in five and right in four. The locations of PDs consisted of multifocal in six episodes, hemispheric in five, regional in two and focal in two. The frequency of PDs ranged from 1 to 2.5 Hz.

RDA was identified in 13 episodes including lateralized RDA in 10, bilateral independent RDA in one and generalized RDA in two. The laterality of RDA was bilateral in five episodes, left in four and right in four. The locations of RDA consisted of regional in five episodes, multifocal in three, hemispheric in three and focal and generalized in one each. The frequency of RDA ranged from 1 to 4 Hz.

EEG seizures were detected in nine episodes. Seven episodes showed spatiotemporal evolutions. The other two episodes showed no spatial evolution. Brief rhythmic epileptiform discharges were detected in 17 episodes. The laterality of brief rhythmic epileptiform discharges was right in eight episodes, left in seven and bilateral in two. The locations of brief rhythmic epileptiform discharges were focal in eight episodes, regional in seven and hemispheric in two. The inter-rater agreement was 1.0 for PDs, 0.93 for RDA, 1.0 for EEG seizures and 0.93 for brief rhythmic epileptiform discharges, indicating almost perfect agreement in all categories.

Non-convulsive status epilepticus

The diagnoses of NCSE are described in Table 2. Based on the EEG findings and subtle clinical phenomena under Salzburg criteria, we diagnosed NCSE in 19 episodes, possible NCSE in 2 and no NCSE in 7. Nine episodes showed epileptiform discharges with the frequency of >25 times per 10 s epoch (Salzburg criteria 1). Eight episodes showed subtle clinical ictal phenomena during the EEG (Salzburg criteria 2b). Two episodes showed typical spatiotemporal evolution of the epileptiform discharges with the frequency of ≤ 2.5 cycles per second (Salzburg criteria 2c). Two episodes showed fluctuation of PDs or RDA without definitive evolution (Salzburg criteria 2e). These 21 episodes were considered as a positive diagnosis of NCSE. The other seven episodes did not fulfil the criteria of NCSE (Salzburg criteria 3). No significant differences were found between the NCSE and the possible NCSE groups and no NCSE group in patients' age, GCS at suspected NCSE, times of ASL or EEG starting from suspected NCSE, time differences between ASL and EEG and EEG recording periods (Supplementary Table 2).

Table 1 Clinical profiles

Episode No.	Age (years)	Sex	Primary disease — Brain disease	Laterality of lesion	Surgery for primary disease	Subtle clinical phenomena	GCS at the suspected NCSE	Times of ASL/EEG starting from suspected NCSE (h)	Time differences between ASL and EEG (h)	Recording periods of EEG (h)
1	88	Male	ASDH	Right	No		9	12	3.5	—
2	72	Male	ASDH	Right	No	Twitching of mouth	9	1.5	1	—
3	87	Female	ASDH, GC	Right	No	Eye deviation	5	24[a]	1	—
4	87	Female	ASDH	Left	No		8	4.5	21	—
5	58	Male	ICH	Right	Yes	Eye deviation	5	4.5	22	—
6	81	Female	ASDH	Left	No		9	3.5	0.5	12
7	70	Female	SAH	Left	Yes	Twitching of mouth	8	5	7	—
8	83	Female	ASDH	Bilateral	No		8	6	5	—
9	75	Female	ICH, ASDH	Right	Yes		10	12	18	—
10	84	Female	ICH	Right	Yes	Eye deviation	7	12	4.5	19
11	80	Male	CSH	Bilateral	Yes	Eye movement	9	2.5	2	16
12	75	Female	SAH	Right	Yes		8	8.5	16	—
13	78	Female	SAH	Left	Yes	Twitching of extremities	9	8.5	15	—
14	86	Female	SAH	Left	Yes	Eye deviation	8	4.5	7.5	16
15	91	Male	CSH	Left	Yes	Twitching of mouth	9	12	2	15
16[b]	80	Female	SAH	Left	Yes	Eye deviation	5	5	6	17
17[b]	80	Female	SAH	Left	Yes	Eye deviation	7	4	4	18
18	83	Male	ICH	Left	Yes	Twitching of mouth	8	4	8	17
19	72	Male	ICH	Right	Yes		9	2.5	3.5	64
20	80	Female	GC	–	No	Twitching of mouth	5	36[a]	22	48
21	86	Female	SAH	Left	Yes		7	12	3	6
22	71	Female	Hydrocephalus, GC	–	Yes		11	24[a]	5	24
23	85	Male	ASDH	Left	No		10	12	23	1.5
24	39	Male	ICH	Left	Yes		6	6	4	1
25	91	Female	SAH	Left	No		5	1	7	43
26	62	Male	ICH	Right	Yes		6	5.5	4.5	2
27	75	Female	SAH	Right	Yes		10	12	1.5	14
28	78	Female	SAH	Left	Yes		9	9	6	17

[a]No recovery of consciousness after generalized convulsion.
[b]Episodes 16 and 17 were separate episodes in the same patient.
Abbreviations: ASDH, acute subdural haematoma; ASL, arterial spin labelling; CSH, chronic subdural haematoma; GC, generalized convulsion; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; NCSE, non-convulsive status epilepticus; SAH, subarachnoid haemorrhage.

Table 2 Diagnosis of NCSE by Salzburg criteria, EEG findings and hyperperfusion on ASL

Episode No.	Diagnosis of NCSE by Salzburg criteria	PDs Patterns	PDs Laterality	PDs Locations	PDs Frequency (Hz)	RDA Patterns	RDA Laterality	RDA Locations	RDA Frequency (Hz)	EEG seizures Locations	Brief rhythmic epileptiform discharges Laterality	Brief rhythmic epileptiform discharges Locations	Hyperperfusion on ASL Thalamus Laterality	Hyperperfusion on ASL Cerebral cortex Laterality	Hyperperfusion on ASL Cerebral cortex Locations
1	I	Lateralized	Right	T, P, O	I	Lateralized	Right	T, P	3–4	Right T → Right F, Right T	Right	T	Right	Right	T, P, O
2	2c	Lateralized	Right	F, C, T (STE)	1–2	Generalized	Bilateral	F, C, T	1.5				Right	Right	F
3	2b	Lateralized	Right > Left	P, O (Left); F, P, O (Right)	1.5–2	Lateralized	Right > Left	P, O (Left); F, P, O (Right)	1.5–2				Right	Bilateral	O
4	I	Lateralized	Left	P, O	1.5	Lateralized	Left	P, O	2	Left T, O	Left	P, O	Left	Left	F
5	I	Lateralized	Right	T	1.5	Lateralized	Right	T	2	Right T → Right T, O	Right	T, P	Left	Bilateral	P, O (Left); T (Right)
6	I	Lateralized	Left	F, T, P	I	Lateralized	Left	F, T		Left P → Left T, P	Left	T, P	Left	Left	F, T, P, O
7	2b										Left	F, T	Left	Bilateral	F, T, O (Left); T (Right)
8	I					Lateralized	Left	F, T	1.5	Right F, C → Generalized	Right	F		Right	F
9	I	Bilateral independent	Left > Right	F, T, P (Left); F, T (Right)	1–2								Right	Right	F, P
10	2b	Lateralized	Right	F, P, O (STE)	0.5–1.5	Lateralized	Right	F, T	1.5–2	Right C, P	Right	F, C, P	Right	Right	F, T, P, O
11	2c	Bilateral independent	Right > Left	F, T (Left); F, C, T (Right) (Fluct)	1–1.5	Lateralized	Right	F, C, T	0.5–1				Bilateral	Right	P, O
12	2e					Bilateral independent	Right > Left	F, T (Left); F, T (Right)	1.5		Bilateral	C	Left	Bilateral	O (Left); T (Right)
13	2b	Lateralized	Left > Right	T, P (Left); T, O (Right)	1–1.5						Right	F	Bilateral	Left	F
14	2b	Lateralized	Left	T, P	I	Lateralized	Left > Right	T, P (Left); T, O (Right)					Right	Right	T, O
15	2b					Lateralized	Right	F, C	2		Bilateral	O	Left	Left	T
16[a]	I									Left F → Left F, T, P	Left	F, P, O		Left	F, T, P, O
17[a]	2b	Lateralized	Right > Left	F, T (Left); F, T, P, O (Right)	I	Lateralized	Right > Left	F, T (Left); F, T, P, O (Right)	1–2		Right	P	Bilateral	Left	F, T
18	I	Lateralized	Left	F, C, P, O	I	Lateralized	Left	F, C, P, O	1.5–2	Left O → Left F, C	Left	F, P	Bilateral	Left	F
19	I									Right C, P → Right T	Right	C, P	Right	Right	F, T
20	2b	Lateralized	Left	F	2–2.5						Left	F	Left	Left	F, T, P
21	2e	Bilateral independent	Right > Left	F, T (Left); C, T, P (Right) (Fluct)	1–1.5						Left	F		Left	F, T
22	3					Generalized	Bilateral	Generalized	1–1.5						
23	3												Left	Left	F, T
24	3												Left	Left	F, T, O
25	3														
26	3														
27	3										Right	F, T	Left	Left	F
28	3														

[a]Episodes 16 and 17 were separate episodes in the same patient.

Abbreviations: C, central; F, frontal; Fluct, fluctuation; O, occipital; P, parietal; PDs, periodic discharges; RDA, rhythmic delta activity; SCP, subtle clinical phenomena; STE, spatiotemporal evolution; T, temporal.

Arterial spin labelling

The ASL findings are described in Table 2. Magnetic resonance angiography confirmed the absence of main artery stenosis or occlusion affecting CBF in all 27 patients in this study.

Thalamic hyperperfusion was identified in 16 (57%) of 28 episodes. The laterality of thalamic hyperperfusion was left in seven episodes, right in four and bilateral in five. Mean CBF of thalamic hyperperfusion was 70.1 ml/100 g/min in the lesion side and 70.5 ml/100 g/min in the non-lesion side (Supplementary Table 3).

Cerebral cortical hyperperfusion was identified in 24 (86%) of 28 episodes. The laterality of cerebral cortical hyperperfusion was left in 12 episodes, right in 8 and bilateral in 4. The locations of cerebral cortical hyperperfusion were focal in nine episodes, regional in seven, hemispheric in five and multifocal in three. Mean CBF of cerebral cortical hyperperfusion ranged from 81.9 to 85.9 ml/100 g/min in the lesion side and from 68.8 to 82.2 ml/100 g/min in the non-lesion side (Supplementary Table 3).

Comparison between ASL, and NCSE and EEG findings

The results of statistical analyses between thalamic hyperperfusion and NCSE and EEG findings are described in Table 3. Thalamic hyperperfusion was detected in 16 (76%) of 21 episodes with NCSE including two episodes with possible NCSE. Thalamic hyperperfusion was significantly associated with NCSE ($P = 0.0007$). The sensitivity of thalamic hyperperfusion for NCSE was 76.2% and the specificity was 100.0%. Thalamic hyperperfusion was detected in 14 (93%) of 15 episodes with PDs. Thalamic hyperperfusion was significantly associated with PDs consisting of lateralized and bilateral independent PDs ($P < 0.0001$; odds ratio, 77.0; 95% CI, 6.2–963.7). The sensitivity of thalamic hyperperfusion for PDs was 93.3% and the specificity was 84.6%. Thalamic hyperperfusion was detected in 12 (92%) of 13 episodes with RDA.

Thalamic hyperperfusion was significantly associated with RDA ($P = 0.0006$; odds ratio, 33.0; 95% CI, 3.2–342.3). The sensitivity of thalamic hyperperfusion for RDA was 92.3% and the specificity was 73.3%. In the subcategory of RDA, thalamic hyperperfusion was significantly associated with lateralized and bilateral independent RDA ($P = 0.0002$). The sensitivity of thalamic hyperperfusion for lateralized and bilateral independent RDA was 100.0% and the specificity was 70.6%. There was no significant association between thalamic hyperperfusion, and generalized RDA, EEG seizures and brief rhythmic epileptiform discharges (Table 3).

The results of statistical analyses between cerebral cortical hyperperfusion and NCSE and EEG findings are described in Table 4. Cerebral cortical hyperperfusion was detected in all 21 episodes with NCSE including two episodes with possible NCSE. Cerebral cortical hyperperfusion was significantly associated with NCSE ($P = 0.0017$). The sensitivity of cerebral cortical hyperperfusion for NCSE was 100.0% and the specificity was 57.1%. Cerebral cortical hyperperfusion was detected in all 15 episodes with PDs. Cerebral cortical hyperperfusion was significantly associated with PDs consisting of lateralized and bilateral independent PDs ($P = 0.0349$). The sensitivity of cerebral cortical hyperperfusion for PDs was 100.0% and the specificity was 30.8%. There was no significant association between cerebral cortical hyperperfusion, and RDA, EEG seizures and brief rhythmic epileptiform discharges (Table 4).

Comparisons of the receiver operating characteristic curves between thalamic and cerebral cortical hyperperfusion for NCSE, PDs and RDA are shown in Fig. 1. For NCSE, the AUC of thalamic hyperperfusion was 0.8810 and AUC of cerebral cortical hyperperfusion was 0.7857, with no difference between thalamic and cerebral cortical hyperperfusion (0.0952, $P = 0.3938$) (Fig. 1A). For PDs, the AUC of thalamic hyperperfusion was 0.8897 and AUC of cerebral cortical hyperperfusion was 0.6538, with a significant difference between thalamic and cerebral cortical hyperperfusion (0.2359, $P = 0.0029$; 95% CI, 0.08–0.39). Thalamic hyperperfusion showed

Table 3 Association between thalamic hyperperfusion and NCSE and EEG findings

	N	Thalamic hyperperfusion, N (%)		P value	Odds ratio (95% CI)	Sensitivity (%)	Specificity (%)
		Yes	No				
NCSE	21	16 (76)	5 (24)	0.0007	N/A	76.2	100.0
EEG findings							
PDs (lateralized and bilateral independent)[a]	15	14 (93)	1 (7)	<0.0001	77.0 (6.2–963.7)	93.3	84.6
RDA	13	12 (92)	1 (8)	0.0006	33.0 (3.2–342.3)	92.3	73.3
Lateralized and bilateral independent	11	11 (100)	0 (0)	0.0002	N/A	100.0	70.6
Generalized	2	1 (50)	1 (50)	0.8254	0.7 (0.0–13.0)	50.0	42.3
EEG seizures	9	5 (56)	4 (44)	0.7014	0.9 (0.2–4.5)	55.6	42.1
Brief rhythmic epileptiform discharges	17	11 (65)	6 (35)	0.2693	2.2 (0.5–10.4)	64.7	54.5

[a]Generalized PDs were not found in any episodes.
Abbreviations: CI, confidence interval; N/A, not applicable.

Table 4 Association between cerebral cortical hyperperfusion and NCSE and EEG findings

	N	Cerebral cortical hyperperfusion, N (%)		P value	Odds ratio (95% CI)	Sensitivity (%)	Specificity (%)
		Yes	No				
NCSE	21	21 (100)	0 (0)	0.0017	N/A	100.0	57.1
EEG findings							
PDs (lateralized and bilateral independent)[a]	15	15 (100)	0 (0)	0.0349	N/A	100.0	30.8
RDA	13	12 (92)	1 (8)	0.3556	3.0 (0.3–33.1)	92.3	20.0
Lateralized and bilateral independent	11	11 (100)	0 (0)	0.1162	N/A	100.0	23.5
Generalized	2	1 (50)	1 (50)	0.9841	0.1 (0.0–2.7)	50.0	11.5
EEG seizures	9	9 (100)	0 (0)	0.1893	N/A	100.0	21.1
Brief rhythmic epileptiform discharges	17	16 (94)	1 (6)	0.1531	6.0 (0.5–67.3)	94.1	27.3

[a]Generalized PDs were not found in any episodes.
Abbreviations: CI, confidence interval; N/A, not applicable.

significantly higher association with PDs than cerebral cortical hyperperfusion (Fig. 1B). For RDA, the AUC of thalamic hyperperfusion was 0.8282 and AUC of cerebral cortical hyperperfusion was 0.5615, with a significant difference between thalamic and cerebral cortical hyperperfusion (0.2667, $P < 0.0001$; 95% CI, 0.14–0.40). Thalamic hyperperfusion showed significantly higher association with RDA than cerebral cortical hyperperfusion (Fig. 1C).

Illustrative case: Episode 3

An 87-year-old female with a traumatic brain injury was diagnosed with NCSE. She was hit by an automobile at an intersection. Initial brain CT showed thin right temporo-occipital acute subdural haematoma. She presented with generalized convulsion 9 days later. The convulsive seizures were controlled by fosphenytoin sodium and levetiracetam, but her consciousness with GCS 5 had not recovered 24 h later. EEG showed bilateral 1.5–2 Hz PDs and RDA with right hemispheric predominance (Fig. 2A). Her eyes deviated to the left during the periods of PDs and RDA. ASL showed right thalamic and bilateral occipital cortical hyperperfusion (Fig. 2B). After additional administration of propofol, her consciousness recovered to GCS 14.

Illustrative case: Episode 6

An 81-year-old female with subdural haematoma was diagnosed with NCSE. She was admitted with complaints of right paresis and motor aphasia without impaired consciousness with GCS 12. Initial brain CT showed left hemispheric idiopathic acute subdural haematoma due to blood coagulation disorder. Her consciousness deteriorated to GCS 9 2 days later. Continuous EEG showed 1 Hz lateralized PDs over the left hemisphere (Fig. 3A) as well as EEG seizure pattern over the left temporo-parietal regions. ASL showed left thalamic and left hemispheric cortical hyperperfusion (Fig. 3B). After administration of levetiracetam and midazolam, her consciousness recovered

to GCS 14 with resolving right paresis and motor aphasia.

Illustrative case: Episodes 16 and 17

An 80-year-old female with subarachnoid haemorrhage was twice diagnosed with NCSE during separate periods. She was admitted with complaints of headache, right paresis, aphasia and moderately impaired consciousness with GCS 10. Initial brain CT showed subarachnoid haemorrhage with left frontal subcortical haematoma due to a ruptured aneurysm of the left anterior cerebral artery. We immediately performed clipping of the aneurysm and removal of the haematoma. Her consciousness deteriorated to GCS 5 with eye deviation to the right over the next 3 days. Continuous EEG showed several EEG seizure patterns from the left frontal to left temporo-parietal regions (Fig. 4A). ASL showed left hemispheric cortical hyperperfusion (Fig. 4B). After administration of levetiracetam and midazolam, her consciousness improved to GCS 9. However, her consciousness deteriorated to GCS 7 with eye deviation to the right again after 13 days. Subsequent continuous EEG showed bilateral 1 Hz PDs and 1–2 Hz RDA with right hemispheric predominance (Fig. 4C). Repeat ASL showed bilateral thalamic hyperperfusion and left fronto-temporal cortical hyperperfusion (Fig. 4D). After additional administration of lacosamide, her consciousness recovered to GCS 10.

Discussion

Summary of findings

The thalamic hyperperfusion demonstrated by ASL was significantly associated with NCSE, PDs and RDA on scalp EEG with high sensitivity and specificity in critically ill patients who presented with impaired awareness without convulsions. The cerebral cortical hyperperfusion demonstrated by ASL was significantly associated with NCSE and PDs with high sensitivity but lower specificity than the thalamic hyperperfusion. The cerebral cortical
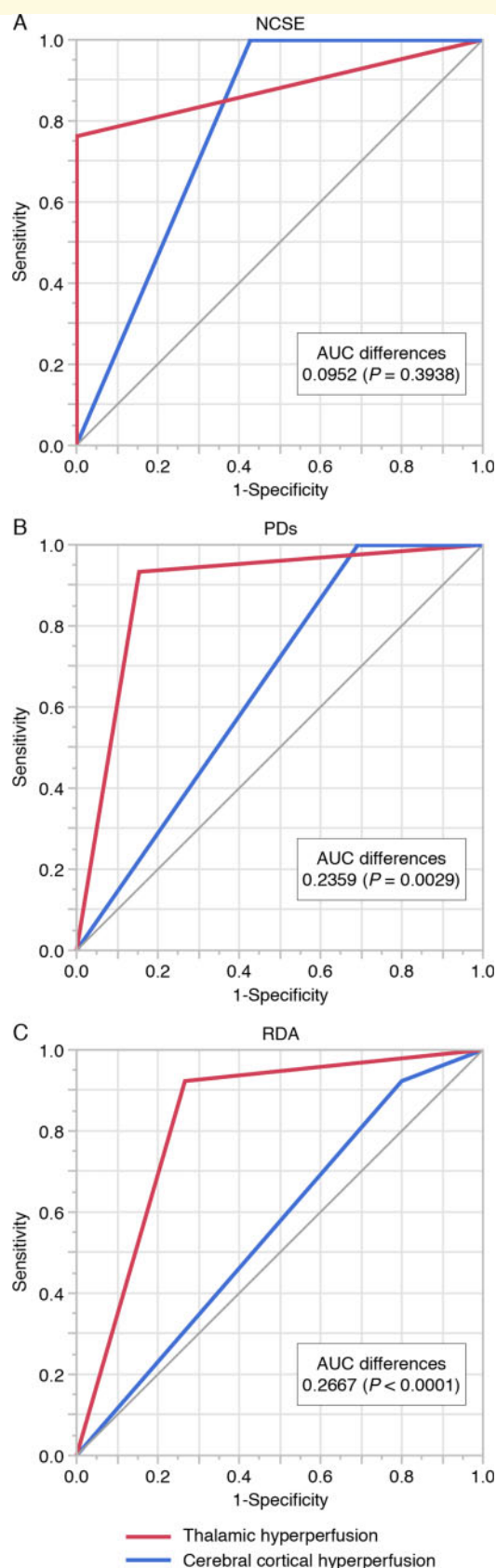
Figure 1 Comparisons of receiver operating characteristic curves between thalamic and cerebral cortical hyperperfusion for NCSE, PDs and RDA. (A) Receiver operating characteristic curve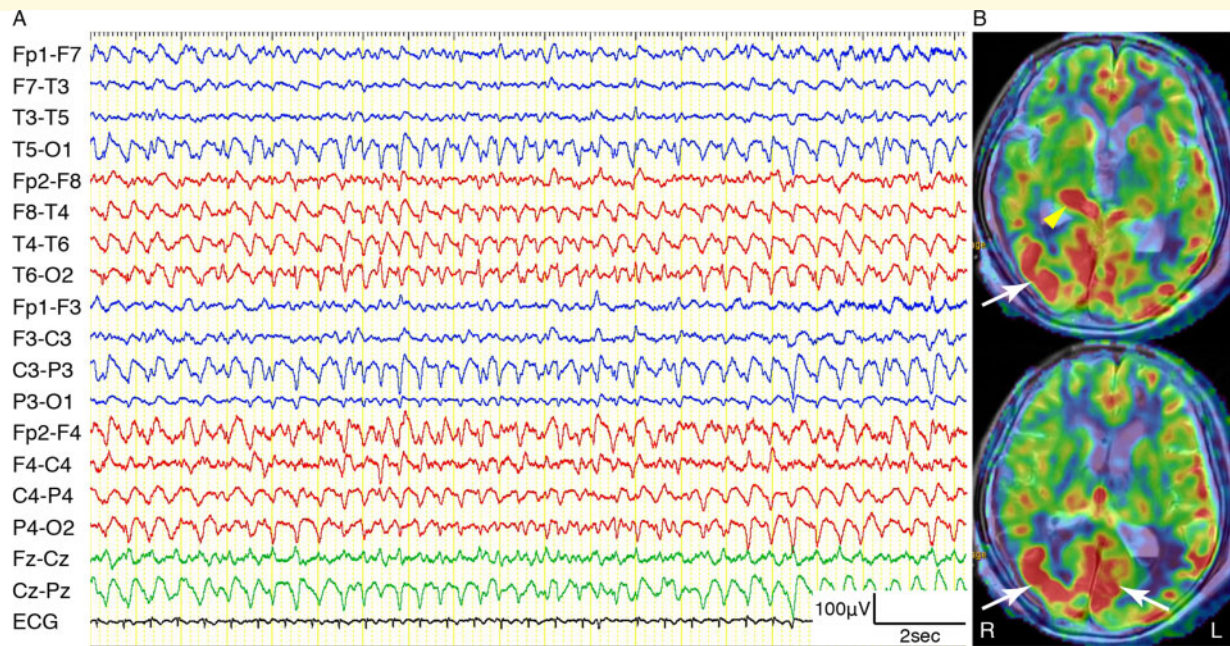s of thalamic (red line) and cerebral cortical hyperperfusion (blue line) for NCSE. Area under the curve (AUC) of thalamic hyperperfusion was 0.8810 and AUC of cerebral cortical hyperperfusion was 0.7857, with no difference for NCSE between thalamic and cerebral cortical hyperperfusion (0.0952, $P = 0.3938$). (B) Receiver operating characteristic curves of thalamic (red line) and cerebral cortical hyperperfusion (blue line) for PDs. AUC of thalamic hyperperfusion was 0.8897 and AUC of cerebral cortical hyperperfusion was 0.6538, with a significant difference between thalamic and cerebral cortical hyperperfusion (0.2359, $P = 0.0029$). (C) Receiver operating characteristic curves of thalamic (red line) and cerebral cortical hyperperfusion (blue line) for RDA. AUC of thalamic hyperperfusion was 0.8282 and AUC of cerebral cortical hyperperfusion was 0.5615, with a significant difference between thalamic and cerebral cortical hyperperfusion (0.2667, $P < 0.0001$).

hyperperfusion demonstrated by ASL showed no association with RDA. ASL hyperperfusion over both the thalamus and the cerebral cortex was associated with NCSE without significant difference. The PDs and RDA on EEG were significantly more associated with thalamic hyperperfusion than cerebral cortical hyperperfusion.

Thalamic hyperperfusion in NCSE involved with impaired consciousness

We hypothesized that thalamic hyperperfusion in NCSE indicated hyperexcitability of the thalamocortical network and was associated with impaired consciousness. The degree of thalamocortical synchrony by stereotactic EEG is correlated with loss of consciousness (Guye *et al.*, 2006). Secondary involvement of the thalamus during focal impaired awareness seizures may play a major role in impaired consciousness in temporal lobe epilepsy (Blumenfeld *et al.*, 2004). Excessive synchronization of the thalamocortical networks by stereotactic EEG is correlated with the degree of impaired consciousness (Arthuis *et al.*, 2009). Thalamic hyperperfusion was demonstrated during focal impaired awareness seizures by SPECT, suggesting that thalamic hyperactivity was associated with impaired consciousness during seizures (Lee *et al.*, 2002; Blumenfeld *et al.*, 2004).

Altered level of consciousness during focal seizures requires hypersynchrony between the thalamus and the association cortices (Bartolomei *et al.*, 2014). Among the thalamic nuclei, the medial pulvinar nucleus functionally connects with the association cortex of the temporoparietal junction, frontoparietal opercular cortex, insula and both lateral and mesial temporal regions (Rosenberg *et al.*, 2009). Perfusion MRI (Szabo *et al.*, 2005) and SPECT studies (Lee *et al.*, 2002) in patients with focal impaired awareness seizures disclosed hyperperfusion of the pulvinar nucleus during the sequelae of prolonged ictal brain activity. Regions of thalamic hyperperfusion

Figure 2 Example of thalamic and cerebral cortical hyperperfusion on ASL in an 87-year-old female with NCSE (Episode 3).
(A) EEG recording on a longitudinal bipolar montage showing bilateral 1.5–2 Hz continuous RDA with right hemispheric predominance. **(B)** ASL superimposed onto the T2-weighted MRI showing right thalamic hyperperfusion (yellow arrowhead) and bilateral occipital cortical hyperperfusion (white arrows).
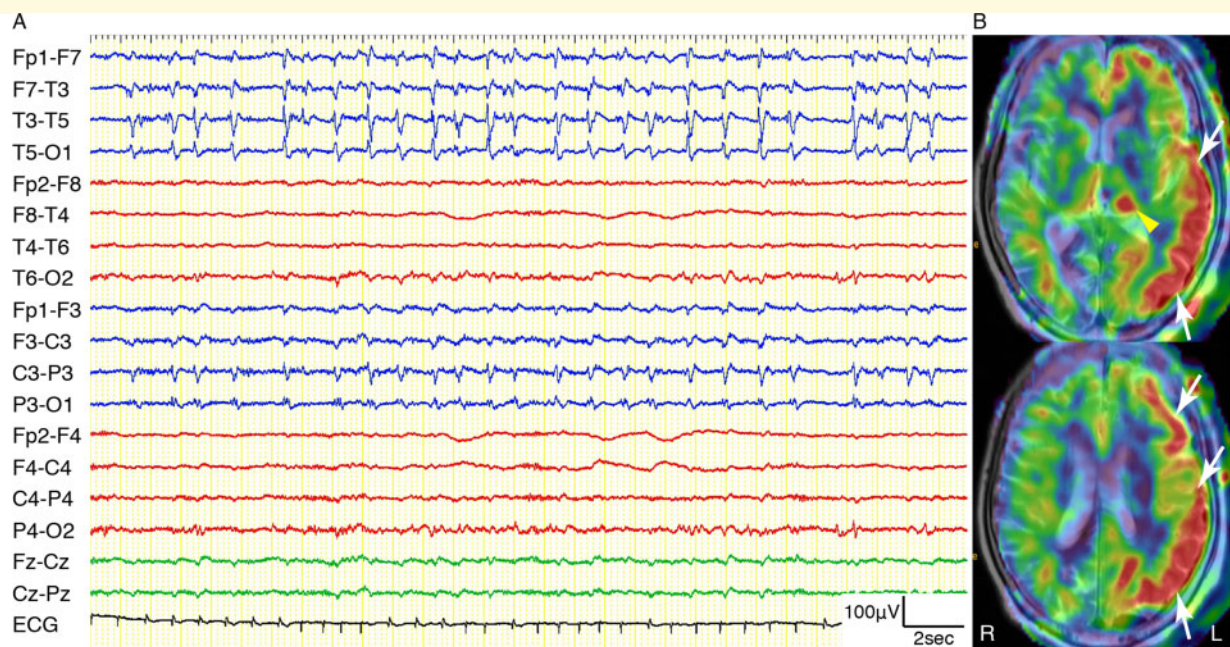
Figure 3 Example of thalamic and cerebral cortical hyperperfusion on ASL in an 81-year-old female with NCSE (Episode 6).
(A) EEG recording on a longitudinal bipolar montage showing 1 Hz lateralized PDs over the left hemisphere. **(B)** ASL superimposed onto the T2-weighted MRI showing left thalamic hyperperfusion (yellow arrowhead) and left hemispheric cortical hyperperfusion (white arrows).

were observed to some extent and contained multiple nuclei including the pulvinar of the thalamus. Hyperexcitability of the reciprocal connectivity between the thalamus and the cerebral cortex might elicit the impaired consciousness of NCSE in critically ill patients.
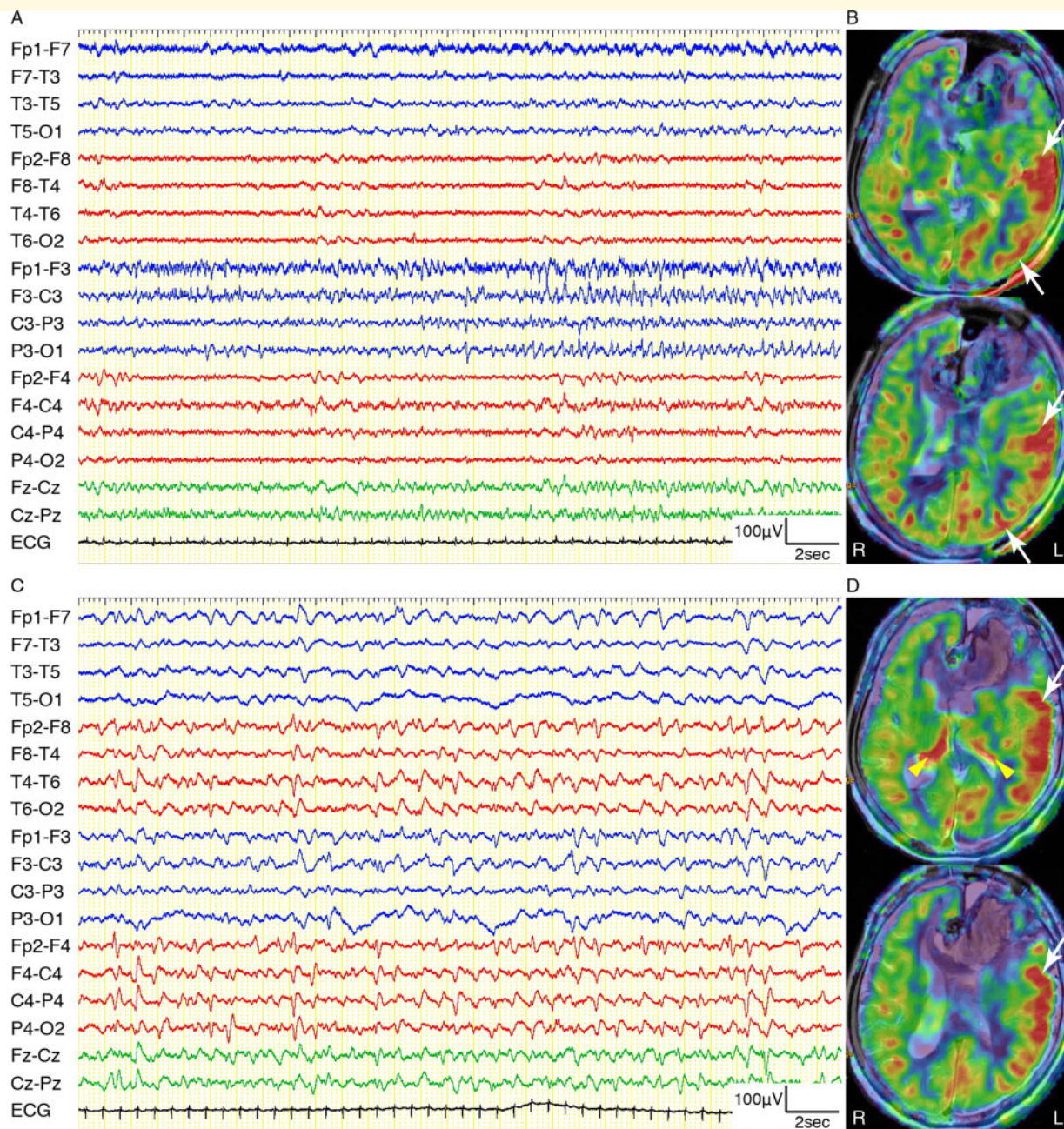
Figure 4 Example of thalamic and cerebral cortical hyperperfusion on ASL in an 80-year-old female with separate two NCSE episodes (Episodes 16 and 17). (A, B) Episode 16; (C, D) Episode 17. **(A)** EEG recording on a longitudinal bipolar montage showing EEG seizure patterns with apparent spatiotemporal evolution from the left frontal to left temporo-parietal regions. **(B)** ASL superimposed onto the T2-weighted MRI showing left hemispheric cortical hyperperfusion (white arrows) without thalamic hyperperfusion. **(C)** EEG recording on a longitudinal bipolar montage showing bilateral 1 Hz PDs with right hemispheric predominance. **(D)** ASL superimposed onto the T2-weighted MRI showing bilateral thalamic hyperperfusion (yellow arrowheads) and left fronto-temporal cortical hyperperfusion (white arrows).

Anatomical studies in monkeys demonstrated that the re-ciprocal connections of the medial pulvinar nucleus reached all cerebral lobes (Romanski *et al.*, 1997). Thalamic con-nectivity in the human brain corresponds to the findings from monkeys (Rosenberg *et al.*, 2009). DWI hyperinten-sities were found in both the cerebral cortex and the thal-amus in patients with status epilepticus (Lansberg *et al.*, 1999; Szabo *et al.*, 2005; Toledo *et al.*, 2008; Huang *et al.*, 2009; Katramados *et al.*, 2009; Chatzikonstantinou *et al.*, 2011; Ohe *et al.*, 2014; Nakae *et al.*, 2016; Rennebaum *et al.*, 2016; Jabeen *et al.*, 2017; Giovannini *et al.*, 2018). Among 225 patients with seizures, 17 patients exhibited DWI abnormalities of the pulvinar corre-sponding to status epilepticus (Ohe *et al.*, 2014). Such

DWI abnormalities of pulvinar can be expected to cause hyperexcitability of the thalamus connecting various areas of cerebral cortex. The medial pulvinar nucleus is mainly connected with the association cortices of the temporal and parietal lobes and to a lesser degree with those of the frontal and occipital lobes (Rosenberg et al., 2009).

Thalamic hyperperfusion associated with PDs and RDA

Thalamic hyperperfusion on ASL was significantly associated with PDs and RDA, especially lateralized PDs and lateralized RDA during NCSE. Thalamic hyperexcitability could modulate PDs and/or RDA associated with NCSE. The PDs and RDA often occurred without apparent EEG seizures during NCSE, and were often indistinguishable from EEG seizures as well. The Salzburg criteria are the breakthrough for the diagnosis of NCSE by combining the frequency of epileptiform discharges and clinical symptoms to differentiate NCSE, possible NCSE and no NCSE (Trinka and Leitinger, 2015; Leitinger et al., 2016). The PDs and RDA consist of epileptiform discharges with the frequency of ≤2.5 cycles per second without evolution. The diagnosis of NCSE using the Salzburg criteria has been confirmed in 220 cases (Leitinger et al., 2016). This study has now demonstrated the ASL findings associated with NCSE, PDs and RDA under the Salzburg criteria.

Lateralized PDs were formerly called periodic lateralized epileptiform discharges (PLEDs). However, lateralized PDs are not consistently associated with epileptiform discharges. Therefore, the American Clinical Neurophysiology Society standardized EEG terminology discarded the 'E' of epileptiform discharges (Hirsch et al., 2013). PLEDs are associated with both cortical lesions, and subcortical grey- and white-matter lesions in diffuse encephalopathies (Gloor et al., 1968). Acute lesions may be the most common structural abnormalities seen in PLEDs, whereas chronic lesions, subcortical lesions and non-lesions are not uncommon (Kalamangalam et al., 2007). Thalamic hyperintensities on DWI were associated with PLEDs in various cases of status epilepticus (Huang et al., 2009; Rennebaum et al., 2016). Other studies of DWI showed thalamic hyperintensities associating with seizure propagations other than PLEDs (Katramados et al., 2009; Giovannini et al., 2018). The thalamus is involved in the propagation and synchronization of epileptic discharges on EEG (Szabo et al., 2005; Guye et al., 2006; Rosenberg et al., 2006). PLEDs represent an abnormal response of both cortical and thalamocortical neurons to the rhythmic burst firing generated by the reticular nucleus of the thalamus (Gross et al., 1998). Consequently, the thalamus could modulate lateralized PDs with ictal nature.

Our results indicated that thalamic hyperperfusion is associated with lateralized RDA in addition to lateralized PDs. Lateralized RDA in critically ill patients is indicated to have similar clinical significance to lateralized PDs (Gaspard et al., 2013). Lateralized RDA reflects the presence of a focal lesion and is associated with a high risk of acute non-convulsive seizures (Gaspard et al., 2013). Lateralized RDA in critically ill patients is associated with seizures if the frequency is 1.5 Hz or higher (Rodriguez Ruiz et al., 2017). The study of cat models demonstrated that unilateral diffuse polymorphic delta activity appears on the side of thalamic or hypothalamic lesions (Gloor et al., 1977), whereas the reticular thalamic nucleus can generate synchronous delta oscillations (Steriade et al., 1993). Our results indicated that lateralized RDA with 1.5 Hz or higher frequency mainly dominated in episodes with thalamic hyperperfusion. We speculated that thalamus is involved in modulating the rhythmicity of delta activity in addition to PDs in critically ill patients with NCSE.

Cerebral cortical hyperperfusion associated with NCSE

The cerebral cortical hyperperfusion on ASL was associated with all NCSE episodes in our series, and was also associated with PDs during NCSE. However, cortical hyperperfusion was not significantly associated with RDA. Regional cortical hyperperfusion on SPECT was associated with PLEDs representing a form of focal status epilepticus (Assal et al., 2001). Cerebral cortical hyperintensities on DWI were associated with PLEDs in patients with focal seizures (Narayanan, 2016).

The sensitivities of both thalamic and cerebral cortical hyperperfusion for NCSE were high, but the specificity of cerebral cortical hyperperfusion for NCSE was low. Cortical hyperperfusion was demonstrated in all 15 patients with NCSE (Shimogawa et al., 2017), whereas cortical hyperperfusion has been widely detected on ASL during seizure-related events including ictal or peri-ictal periods other than NCSE (Pizzini et al., 2013; Matsuura et al., 2015; Yoo et al., 2017). The sensitivity and specificity of cortical hyperperfusion on ASL to identify the seizure focus were 74 and 0%, respectively (Kim et al., 2016). In our results, cerebral cortical hyperperfusion was not associated with RDA, whereas thalamic hyperperfusion was associated with lateralized PDs and lateralized RDA. We speculated that cerebral cortical hyperperfusion in critically ill patients reflects cortical functional abnormality. Thalamic hyperperfusion might indicate the hyperexcitability of thalamocortical networks due to specifically recognized lateralized PDs and lateralized RDA during NCSE. Such cortical dysfunction might be modulated by the thalamus.

Thalamocortical hyperperfusion as a new biomarker of NCSE

PLEDs represent an EEG signature of a dynamic pathophysiological state involving unstable neurobiological

processes described as the 'ictal–interictal continuum' applied for uncertain EEG falling between ictal EEG features with evolution and interictal periodic/rhythmic activities without evolution (Pohlmann-Eden *et al.*, 1996). Since continuous EEG monitoring has been established in the intensive care unit for patients with suspected NCSE, an indistinguishable pattern is often observed between EEG seizures, and PDs and RDA. Lateralized PDs in critically ill patients are highly associated with clinical seizures regardless of the frequency of epileptiform discharges (Rodriguez Ruiz *et al.*, 2017). The concept of ictal–interictal continuum was naturally accepted for such ambiguous EEG findings (Pohlmann-Eden *et al.*, 1996). The spectrum of PDs together with ictal–interictal continuum is well known to associate with impaired awareness seizures and altered mental status with or without seizures (Chong and Hirsch, 2005).

Delayed diagnosis and treatment of NCSE lead to poor outcomes (Young *et al.*, 1996). Prolonged video EEG monitoring is essential for the diagnosis of NCSE since the clinical signs are very subtle (Claassen *et al.*, 2004). The cohort study of 2111 participants with continuous EEG showed that any highly epileptiform discharges during the first hour of EEG (i.e. a 2HELPS2B score of ≥ 2) indicated that at least 24 h of recording was recommended to detect seizures (Struck *et al.*, 2020). In 121 critically ill children, the first non-convulsive seizures were all captured within 24 h in 28 non-convulsive seizures (McCoy *et al.*, 2011). In contrast, the acquisition time of ASL in MRI requires only about 3 min. Initial use of ASL could promote the early diagnosis of NCSE (Shimogawa *et al.*, 2017). The prompt application of ASL for critically ill patients may be valuable to establish a diagnosis of NCSE.

No evidence-based guidelines have been established for the treatment of ictal–interictal continuum patterns in critically ill patients. If the spectrum of ictal–interictal continuum together with PDs and RDA is one of the diagnoses of NCSE, aggressive treatment would be required. Lateralized PDs regardless of frequencies and lateralized RDA with high frequencies are associated with seizures (Rodriguez Ruiz *et al.*, 2017). Brief potentially ictal rhythmic discharges may indicate ictal–interictal continuum for consideration of the treatment of seizures (Yoo *et al.*, 2014; Struck *et al.*, 2020). One of the ictal EEG criteria must persist for longer than 10 s under the Salzburg criteria (Leitinger *et al.*, 2016). We can often identify brief periodic or rhythmic epileptiform discharges shorter than 10 s with and without evolution in critically ill patients. Thalamic hyperperfusion on ASL was most sensitive to PDs and RDA. Single brief potentially ictal rhythmic discharges might be shorter for ASL. If ASL demonstrates cerebral cortical hyperperfusion during the period of frequent brief potentially ictal rhythmic discharges, impaired awareness may associate with micro-seizures in NCSE.

The mean regional CBF of the hyperperfusion area was about 70 ml/100 g/min in the thalamus and 80 ml/100 g/min in the cerebral cortex. Magnetic resonance angiography confirmed the absence of main artery stenosis or occlusion in all patients in this study. The regional CBF of the deep brain structures on ASL is not influenced by the anatomic variant types of the circle of Willis (Hendrikse *et al.*, 2010). Previous ASL study has indicated resting CBF in normal aging subjects (>60 years) is 45.1 ± 9.4 ml/100 g/min in the thalamus and 42.7 ± 8.8 ml/100 g/min in the cortex on average (Chen *et al.*, 2011). Our reference data in the thalamus (non-lesion side) were 48.5 ± 6.4 ml/100 g/min, which was in the same range as the normal perfusion values in a similar age group (Supplementary Table 1). Our reference data in the cerebral cortex (non-lesion side) were ranged from 47.1 ± 7.2 to 51.7 ± 7.9 ml/100 g/min (Supplementary Table 1). Because the control subjects were matched with the patients according to brain disease, the values of CBF in the cerebral cortex may have slightly increased compared to the normal perfusion values shown in the previous study (Chen *et al.*, 2011).

Limitations

This retrospective study showed no consistent time course of ASL and EEG for patients with impaired consciousness. We used the shortest interval possible between ASL and EEG. Early or delayed studies may impact the associations between thalamic hyperperfusion, and PDs and RDA. However, medications and treatments were not started before both ASL and EEG.

The inconsistent duration of EEG monitoring might impact some of the EEG findings. Continuous EEG monitoring was not routinely performed at the beginning of the study. For consistency of EEG findings, we selected suspected NCSE cases with more than 1 h EEG recording.

The various characteristics examined in this study, such as hyperperfusion, NCSE and EEG findings, were evaluated at discrete times. Evaluation of these characteristics as continuous variables may identify correlations between thalamic and cerebral cortical hyperperfusion and NCSE, PDs and RDA.

Conclusion

ASL findings of hyperperfusion in both the thalamus and the cerebral cortex may be a new biomarker of NCSE according to the Salzburg criteria in critically ill patients with impaired consciousness level without convulsions. Thalamic hyperexcitability might modulate the PDs and RDA associated with NCSE. The prompt application of ASL and evidence of thalamocortical abnormalities in critically ill patients may be valuable to identify and treat NCSE.

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Supplementary material

Supplementary material is available at *Brain Communications* online.

Competing interests

The authors report no competing interests.

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