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Electroencephalography quadratic phase self-coupling correlates with consciousness states and restoration in patients with disorders of consciousness

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HIGHLIGHTS

- EEG quadratic phase self-coupling correlates with a behaviour assessment of disorders of consciousness.
- Theta quadratic phase self-coupling significantly differentiates between consciousness states.
- Frontal theta quadratic phase self-coupling shows a predictive value for consciousness recovery.

ABSTRACT

Objective: The objective of this study was to explore the role for quadratic phase coupling within electroencephalography (EEG) oscillations in the diagnosis of consciousness and consciousness restoration for disorders of consciousness (DOC).
Methods: Fifty-one DOC patients were enrolled in this study. For each patient, a Coma Recovery Scale-Revised (CRS-R) score and 20-min resting-state EEG were recorded. Consciousness recovery was assessed with a CRS-R score at a three-month follow-up. Twenty healthy subjects were included as controls. General harmonic wavelet transform-based bicoherence was used to quantify the quadratic phase coupling characteristics of the EEG oscillations.
Results: Quadratic phase self-coupling (QPSC) at the delta (QPSC_delta), theta (QPSC_theta) and alpha (QPSC_alpha) bands were closely correlated with patient CRS-R scores. Particularly, the QPSC_theta value could significantly differentiate between vegetative state (VS) patients, minimally conscious state (MCS) patients and healthy control subjects. As compared to VS patients, patients with MCS had a lower QPSC_theta value on the left as well as a higher QPSC_alpha value in right frontal regions. The frontal QPSC_theta value showed significant differences between recovered and unrecovered patients.
Conclusion: QPSC characteristics could differentiate between consciousness states and show a predictive ability for the recovery of consciousness in DOC patients.
Significance: Changes in QPSC accompany consciousness injury and restoration in DOC patients. A QPSC assessment is helpful in the diagnosis and prognosis of DOC patients.

1. Introduction

A large body of research has been conducted on altered states of consciousness (e.g., anaesthesia, sleep, epileptic seizures) (Purdon et al., 2013; Tononi and Edelman, 1998). Progress has been made, but the understanding of human consciousness is still insufficient. Limited knowledge on the contents, mechanisms and markers of consciousness has led to significant challenges in the treatment of consciousness-related disorders, including disorders of consciousness (DOC) such as coma, vegetative state (VS) and minimally conscious state (MCS) (Gosseries et al., 2014; Gosseries

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et al., 2011). Unlike anaesthetics or sleep-induced consciousness fading, DOC are caused by irreversible neural injuries (e.g., trauma, stroke, anoxia, etc.) (Giacino et al., 2014; Schiff, 2010). The differential diagnosis and treatment of patients with DOC have been problems of great difficulty for neuroscientists and clinicians for decades and can thus provide an ideal field for consciousness research.

In clinics, behavioural assessment scales, such as the Coma Recovery Scale-Revised (CRS-R), are often used to classify the consciousness states of DOC patients. The CRS-R requires that a seasoned doctor use the scale to score the conscious behaviour of a patient once per day over five days. However, this type of assessment gradually reveal defects through problems such as a high ratio of misdiagnoses (Gosseries et al., 2016; Schnakers et al., 2009). Recently, an increasing number of studies have attempted to use neuroimaging measurements to improve consciousness detection. These methods have included MRI (Huang et al., 2014; Soddu et al., 2011; Vanhaudenhuyse et al., 2010), PET (Laureys et al., 2000; Stender et al., 2015; Tommasino et al., 1995) and electroencephalography (EEG) (Fernandez-Espejo and Owen, 2013; Gantner et al., 2013). Among these, EEG is an attractive option for clinical use for DOC as it is portable and cost-effective, and it is relatively feasible to deploy at the patient's bedside. Some features derived from EEG recordings have been proposed as indicating the electrical features of the brains of those with DOC (Casali et al., 2013; Schartner et al., 2015; Thul et al., 2016). Among these features, as neural oscillation regulates the integration of the brain (Lakatos et al., 2005; Palva et al., 2005) and coordinates neuronal computation, communication and learning (Canolty and Knight, 2010), the features describing oscillatory coupling could be potential EEG markers for consciousness detection. A growing body of evidence suggests that the oscillatory coupling in EEG closely correlates with the consciousness states of DOC patients. For example, delta and alpha band coherence and variant methods such as the imaginary part of coherence and partial directed coherence could significantly distinguish different consciousness states in DOC patients (Lehembre et al., 2012; Varotto et al., 2014). The phase coupling of alpha oscillations have been closely correlated with the behavioural awareness and metabolism of patients (Chennu et al., 2017; Chennu et al., 2014).

Bicoherence is a power-independent bispectral method. It detects the quadratic phase coupling of neural oscillations by measuring phase relations within frequency components. Quadratic phase coupling is closely correlated with the neural activities of consciousness in anaesthesia and sleep studies (Bullock et al., 1997). For example, a quadratic phase coupling of theta-alpha bands and quadratic phase self-coupling (QPSC) of the delta band represent a shift in sleep stages (Li et al., 2009). In isoflurane or sevoflurane-induced anaesthesia, consciousness fading is accompanied by changes in QPSC characteristics (Hagihira et al., 2002; Hayashi et al., 2008; Li et al., 2011). Specifically, the quadratic phase coupling of delta-theta bands and the QPSC of the alpha band have been found to be well correlated with anaesthetic concentrations (Hagihira et al., 2002; Morimoto et al., 2006; Pritchett et al., 2010). Thus, the above studies of QPSC on sleep and anaesthesia prove that it has a close correlation with fading consciousness. This facilitates a further issue worth considering: what are the characteristics of the alterations of this phase coupling in a loss of consciousness caused by brain injury? Understanding the relationship of quadratic phase coupling with consciousness state and consciousness recovery is an important issue for the study of DOC. It could both improve our knowledge of the EEG reflection of a loss of consciousness with different causes and contribute to the clinical application of EEG in this area.

2. Materials and methods

2.1. Participants

Fifty-one DOC patients (31 VS and 20 MCS, 21 females and 30 males) were enrolled as subjects in this study (Table 1). The aetiologies of the brain damage were traumatic injury (n = 10), anoxia (n = 18), brain stem haemorrhage (n = 9) and other types of brain injury (n = 14) such as haemorrhagic infarction and stroke. Detailed clinical-demographic characteristics of the patients are summarized in Supplementary Table S1. Clinical assessment was carefully conducted by trained neurologists using the CRS-R (Giacino et al., 2004). It was confirmed that the patients included in this study had no history of epilepsy or epileptiform EEG activity. All the patients were diagnosed as being either MCS or VS and free of any acute comorbidity (e.g., acute pneumonia) for at least two weeks prior to the study. Three patients (two MCS and one VS) had received a craniotomy to reduce intracranial pressure, but none had undergone craniotomy reconstructive surgery. Forty-eight patients were re-assessed by the CRS-R three months after the EEG recording as a follow-up. Patients who had either progressed into a higher state of consciousness or had CRS-R scores that increased by at least three points at the follow-up were defined as recovered patients. If not, they were defined as unrecovered patients. Twenty age-matched healthy subjects (13 females and seven males) were included to form the control group for this study. Caffeine or nicotine were forbidden one day before the recordings. Written informed consent to participate in the study was obtained from the subjects (controls) or the legal representatives of the patients. This study was approved by the ethical committee of PLA Army General Hospital, clinical registration: ChiCTR1800017548.

Table 1
Patients enrolled in the study.

Diagnosis	Age	Sex	Etiology	Post-injury (Months)	CRS-R
MCS n = 20	23–68 mean = 45.35	Female n = 8 Male n = 12	Anoxia (n = 4) Hemorrhage (n = 4) TBI (n = 6) BSH (n = 4) Stroke (n = 2)	1.5–35 mean = 7.57	7–17 mean = 9
VS n = 31	17–79 mean = 45.68	Female n = 13 Male n = 18	Anoxia (n = 14) Hemorrhage (n = 5) TBI (n = 4) BSH (n = 5) Stroke (n = 3)	1.5–30 mean = 5.21	2–7 mean = 5.52
Healthy n = 20	18–73 mean = 37.50	Female n = 13 Male n = 7			

CRS-R = Coma recovery scale-revised; TBI = traumatic brain injury; BSH = Brain stem hemorrhage; MCS = Minimally conscious state; VS = Vegetative state.

2.2. EEG recordings and pre-processing

For this study, a 20-min EEG was acquired continuously from each patient and healthy subject on 62 channels (BrainAmp 64 MR plus, Brain Products) with the positions of the international 10–20 system. The equipment used sintered Ag/AgCl-pin electrodes. We set a bandpass filtered at DC to 1000 Hz in the recorder, and the EEG signal was digitized at a sampling rate of 2.5 kHz. During the recording, skin/electrode impedance was maintained below 5 kΩ. The patients were laying in their hospital beds during the EEG recording. We monitored them so that if any possible EEG signs of drowsiness or sleep onset (e.g., an increase of tonic theta rhythms, sleep spindles) were displayed, an arousal procedure was performed to keep the patients in vigilance. During the EEG recording, the healthy subjects were also lying in a comfortable bed and kept their eyes open. Strenuous exercise or eating were forbidden at least one hour before the recording.

The off-line analysis was performed with EEGLAB 12.0.2.5b, running in a MATLAB environment (Version 2013b, MathWorks Inc., Natick, MA, USA). An independent component analysis (ICA) function was used to identify and remove artefact components, such as from eye movement and muscle activities (Bai et al., 2016a). The EEG data were down-sampled to 500 Hz and bandpass filtered (1–45 Hz). Then, the EEG data were divided into epochs of 10 seconds. Artefact-free epochs were preserved and recorded for further analysis. In order to overcome the volume-conduction of the EEG signals, we analysed current source density (CSD) (Kayser and Tenke, 2006, Trujillo et al., 2017) before calculating the EEG features.

2.3. Relative spectral power

Relative power was calculated at five frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–45 Hz). The relative power of each given band was calculated by

$$Relative\ power(f_1,f_2) = \frac{Power(f_1,f_2)}{Power(1,45)} \times 100\% \quad (1)$$

where $Power(f_1,f_2)$ indicates the power between low f_1 and high f_2 frequency estimated by periodogram method. $Power(1,45)$ means sum of power (1–45 Hz).

2.4. Quadratic phase coupling

The present study used general harmonic wavelet transform (GHWT) based wavelet bicoherence with segment-averaging approach (Bai et al., 2017; Hagihira et al., 2001; Li et al., 2009) to quantify the quadratic phase coupling of EEG. Bicoherence was computed on wavelet coefficients $a(f,t)$ in all pairs of frequencies from 1 to 45 Hz, with a step of 1 Hz and a bandwidth of 1 Hz.

Firstly, GHWT was conducted at the EEG epoch $X_k(t)$ (k means the number of epochs), obtaining the wavelet coefficients $a_k(f_p,\mathrm{t})$ corresponding to the signal component at frequency f_p. In order to reduce edge effects, we padded data with zeros to get N up to the next higher power of two, and removed the corresponding time points after transform. Then, the normalized squared wavelet bicoherence, which characterizes the quadratic phase coupling between component with frequencies f_p and f_p in $X_k(t)$, is calculated as

$$b_k(f_p,f_q) = \frac{|B_k(f_p,f_q)|^2}{\sum_{t=1}^{N}|a_k(f_p,\mathrm{t})a_k(f_q,\mathrm{t})|^2\sum_{t=1}^{N}|a_k(f_p+f_q,\mathrm{t})|^2} \quad (2)$$

where the phase randomized wavelet bi-spectrum is given by the expression

$$B_k(f_p,f_q) = \sum_{t=1}^{N} a_k(f_p,\mathrm{t})a_k(f_q,\mathrm{t})a_k{}^*(f_p+f_q,\mathrm{t})e^{iR\varnothing_k(f_p,f_q,t)} \quad (3)$$

$R \in (-\pi,\pi]$ is a random variable and the biphase is

$$\varnothing_k(f_p,f_q,t) = \varnothing_k(f_p,t) + \varnothing_k(f_q,t) - \varnothing_k(f_p+f_q,t) \quad (4)$$

Then, we used a surrogate method to correct the false coupling. Using a new biphase $\varnothing_k{}^{\#}(f_p,f_q,t) = \varnothing_k(f_p,f_q,t) + \theta$ to replace $\varnothing_k(f_p,f_q,t)$, $\theta \in (-\pi,\pi]$, a new surrogated bicoherence value can be obtained. After surrogating over N_{sum} times ($N_{sum} > 30$), bicoherence values greater than 95% statistical threshold (mean plus 1.96 times standard deviation) will be preserved, and the other is set to zero. Finally, for all the epochs, Q-test is applied to remove the outlier bicoherence values to obtain a reliable bicoherence value.

Then, a symmetrical bicoherence matrix could be obtained, with each element $b(f_p,f_q)$, denoting the bicoherence value at bifrequency pair ((f_p,f_q)), where $1 \le f_p,f_q \le 45$ Hz. The diagonal line values of the bicoherence matrix reveal QPSC. Averaged diagonal line values within 1–4 Hz, 4–8 Hz and 8–13 Hz respectively represent QPSC at delta, theta and alpha, identifying as QPSC_delta, QPSC_theta and QPSC_alpha.

2.5. Statistics

The comparisons of the QPSC delta (QPSC_delta), theta (QPSC_theta) and alpha (QPSC_alpha) values within the different conscious groups (MCS, VS and control) were conducted by a two-way repeated measures ANOVA with post-hoc tests and a Bonferroni correction. A correlation of the features with the CRS-R scores was measured by a Kendall's tau coefficient. Receiver operating characteristic (ROC) curves plotted the false-positive rates as a function of true-positive rates. The area under the ROC curve (AUC) was measured to test the performance of the features in classifying the consciousness groups, with a bigger AUC implying a more efficient discrimination of groups. Student's t-tests corrected with a false discovery rate (FDR) were conducted at the electrode level for each feature within the consciousness groups. A Wilcoxon rank-sum test (WR-test) was used to test the significance of the differences of the features averaged at the different brain regions and of the QPSC_theta values at the electrode level between the recovered and unrecovered patients. An FDR correction ($Q = 0.05$) was used to correct the p values after the comparisons of the electrodes.

3. Results

Quadratic phase coupling was measured for each data epoch, and the quadratic phase coupling matrix that was derived from each electrode was averaged across epochs. Fig. 1(A) shows an EEG epoch from the Fp1 electrode for a healthy control, MCS patient and VS patient. The corresponding quadratic phase coupling matrix for all three groups are shown in Fig. 1(B). For the healthy control group, a relatively stronger coupling shows in the high-frequency bands (alpha and beta bands) than in the patient group. The MCS and VS patients demonstrated a primary coupling in the low bands (delta and theta bands), and the VS patients had peak power of coupling in the lower frequency band. Fig. 1(C) shows the diagonal value of the corresponding quadratic phase coupling matrix, and the bars present the QPSC mean at the delta, theta and alpha bands. Distinct differences in the QPSC at the delta, theta and alpha bands could be found between the healthy controls and the patients. The healthy control group showed relatively higher QPSC at the alpha band and the lowest QPSC at the delta and theta bands. On the contrary, the MCS and VS patients showed

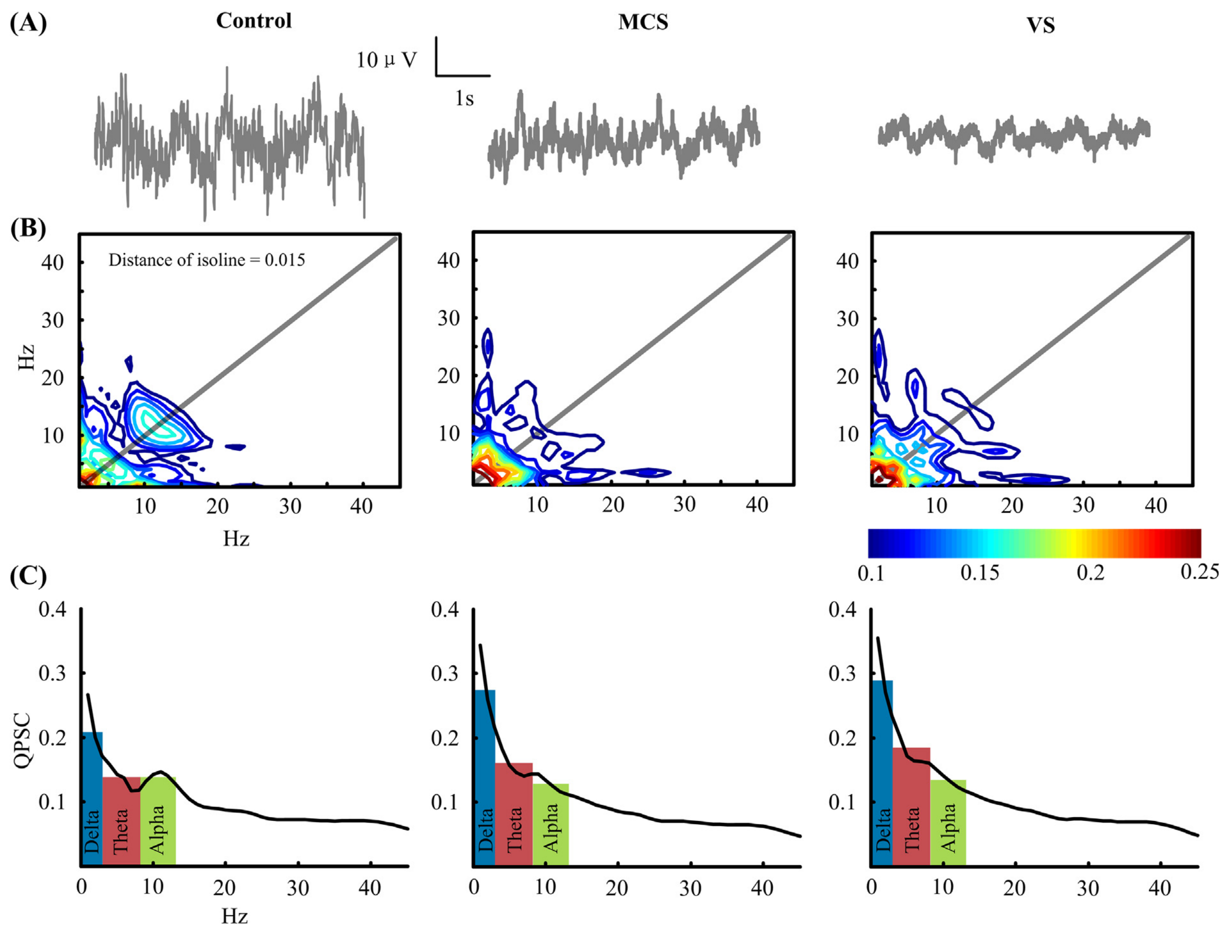

Fig. 1. EEG signal and the corresponding bicoherence of an MCS patient, VS patient and healthy control. Shown are the (A) EEG signal, (B) quadratic phase coupling matrix and (C) quadratic phase self-coupling (QPSC), with bars indicating QPSC_delta, QPSC_theta and QPSC_alpha values.

higher QPSC at the delta and theta bands and lower QPSC at the alpha band.

In the group tests, the relative spectral power values at the delta, theta and alpha bands averaged over all electrodes showed a difference between the different consciousness groups (Fig. 2(A)). Healthy subjects showed significantly lower delta ($p < .001$) and theta ($p = .024$) and higher alpha ($p = .009$) powers than that of the MCS patients and significantly lower delta ($p < .001$) and higher alpha ($p < .001$) powers than that of the VS patients. However, there was no significant difference in the relative spectral power values between the MCS and VS patients. For the QPSC features, the averaged QPSC_delta, QPSC_theta, and QPSC_alpha values could be differentiated between the different consciousness states. As shown in Fig. 2 (B), the QPSC_delta ($r = -0.24$, $p = .020$) and QPSC_theta ($r = -0.31$, $p = .002$) values of the patients showed a significant negative Kendall's tau correlation to their CRS-R scores. Patients with higher CRS-R scores were found to have lower QPSC_delta and QPSC_theta values. Meanwhile, QPSC_delta and QPSC_alpha values suggest negative and positive correlation tendencies with the CRS-R scores, respectively. Fig. 2(C) shows statistics on the QPSC_delta, QPSC_theta and QPSC_alpha values of the patients and healthy controls. The statistical tests imply a significant difference between the QPSC_delta values of the controls and the DOC patients (control–MCS: $p = .003$, control–VS: $p < .001$). The QPSC_theta values were significantly distinguishable between the three consciousness states (control–MCS: $p < .001$, control–VS: $p < .001$, MCS–VS: $p = .015$). The QPSC_alpha value showed a significant difference between the controls and VS patients ($p < .001$). Overall, the controls showed lower QPSC_delta and QPSC_theta and higher QPSC_alpha values than that of the DOC patients.

Fig. 3 shows the ROC plots for the QPSC_delta, QPSC_theta and QPSC_alpha features in classifying the control group and the MCS and VS patients along with the Z values of the comparisons at the electrical level. These three features demonstrate a high performance for distinguishing the control group from the MCS (QPSC_delta: AUC = 0.856, QPSC_theta: AUC = 0.881, QPSC_alpha = 0.628) and VS (QPSC_delta: AUC = 0.914, QPSC_theta: AUC = 0.929, QPSC_alpha = 0.765) patients. In the spatial distribution, the controls show large-scale lower QPSC_delta and QPSC_theta values and primarily higher parietal QPSC_alpha values than the MCS and VS patients. In addition, the MCS patients show a lower QPSC_theta (AUC = 0.739) value primarily on the left hemisphere than the VS patients.

Seven patients (six MCS and one VS) showed marked clinical improvement (a more than three level score increase in the CRS-R or a transformation of the conscious state) at the three month follow-up (Table 2). Among the recovered patients, at the baseline assessment, six were diagnosed as MCS and one as VS. All showed an improvement in auditory tests, and five patients (patients 7, 19, 22, 28 and 38) showed an improvement in their conscious state. Patient 7 showed a great increase in consciousness with the total increase of 12 points and finally emerged from the MCS. Table 3 shows the QPSC_delta, QPSC_theta and QPSC_alpha values of the recovered and unrecovered patients at the five regions defined according to electrode placement. The QPSC_theta values averaged at frontal region of the recovered patients were significantly lower

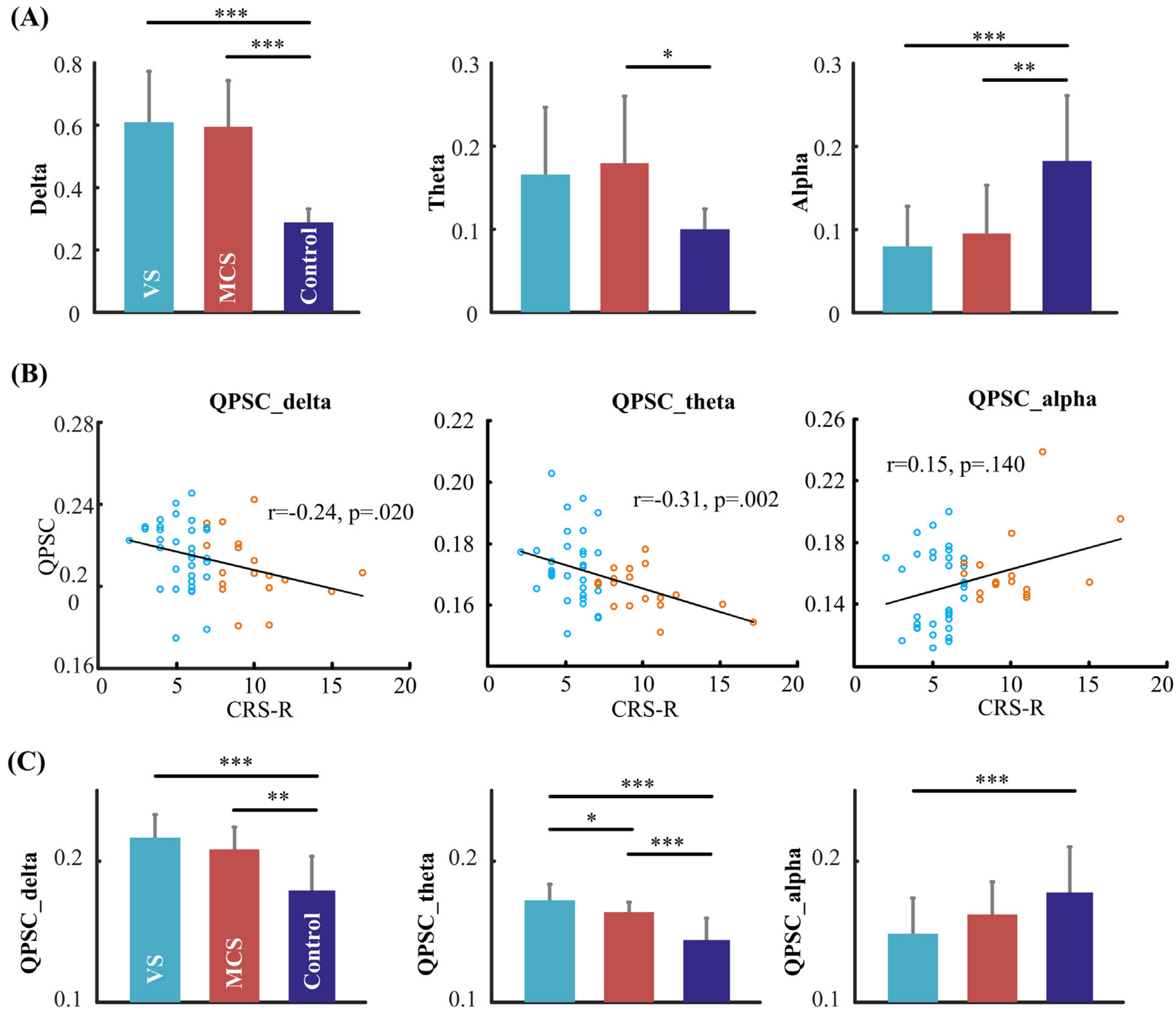

Fig. 2. Averaged relative spectral power values and quadratic phase coupling values of patients and healthy controls. (A) Relative spectral power values of patients and healthy controls at the delta, theta and alpha bands. (B) Scatter plot and Kendall's tau correlation of the QPSC_delta, QPSC_theta and QPSC_alpha values of the patients along with their CRS-R scores. Blue circles show VS patients; orange circles show MCS patients. (C) The values of QPSC_delta, QPSC_theta and QPSC_alpha of the patients and healthy controls. The test was conducted by two-way repeated measures ANOVAs with a Bonferroni correction, *means $p < 0.05$, **means $p < 0.01$, ***means $p < 0.001$.

than that of the unrecovered patients ($p = 0.03$, WR–test; Fig. 4(A)). Fig. 4(B) shows the Wilcoxon rank-sum tests at the electrode level. It shows that the electrodes that could significantly differentiate between recovered and unrecovered patients were primarily located at the anterior brain. Demographic factors could not have responsible for the difference in the frontal QPSC_theta values between the recovered and non-recovered patients.

4. Discussion

The variation of quadratic phase coupling characteristics under anaesthesia and sleep have been reported in several studies (Hayashi et al., 2008; Morimoto et al., 2006). Specifically, features derived from quadratic phase coupling were suggested to be capable of assessing the depth of anaesthesia (Li et al., 2011, 2013). However, the relationships between the interactions within the neural oscillations and consciousness or consciousness recovery have not been systematically investigated. The present study found a relationship between the quadratic phase coupling within neural oscillations and consciousness by measuring the EEG bicoherence of DOC patients. The QPSC values of QPSC_delta, QPSC_theta and QPSC_alpha were found to correlate with levels of consciousness. Specifically, the QPSC_theta value effectively differentiated between VS patients, MCS patients and healthy subjects. In addition to diagnostic utility, the present study also demonstrated that the frontal QPSC_theta value was also significantly correlated with the recovery of consciousness of patients at the follow-up, suggesting a promising prognostic utility of quadratic phase coupling characteristics for DOC.

Neural oscillatory activities that are generated by the synchronized activities of thousands of neurons are the fundamental basis of both functional expression and information transfer in a normal neural system (Gray, 1994). Because there is a dependent relationship between the communication of distributed brain regions and brain oscillatory activities, neural oscillations express the integration of the brain. As an EEG characteristic derived from the spectrum, bicoherence indicates interactions between different neural oscillations and thus captures the intrinsic coupling between neural activities. Information integration theory states that consciousness depends on the integrated activities of distributed areas within the thalamo-cortical system (Markowitsch and Kessler, 2000; Mataró et al., 2001; Schiff, 2010), suggesting a possible relationship between bicoherence and consciousness. Previous investi-

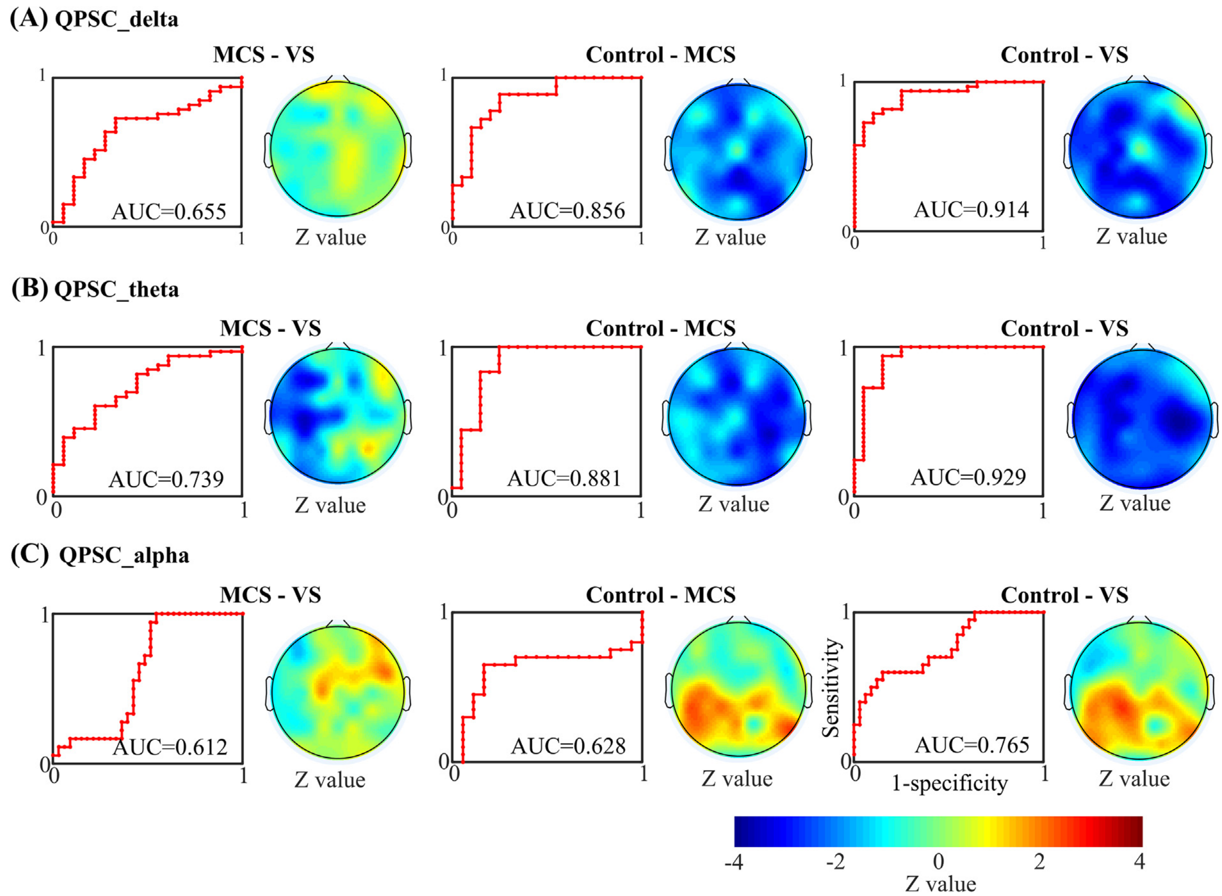

Fig. 3. Receiver operating characteristic (ROC) curves and comparisons of the averaged QPSC_delta (A), QPSC_theta (B) and QPSC_alpha (C) values of the VS patients, MCS patients and healthy controls. The area under the curve (AUC) is used to quantify the classification performance of the features within these three groups. Mann-Whitney U tests of the QPSC_delta, QPSC_theta and QPSC_alpha values in pair-wise groups were conducted at the electrode level. Z values are corrected based on a false discovery rate (FDR) for multiple comparisons with q = 0.05.

Table 2
CRS-R improvement of the recovered patients.

	CRS-R improvement						Total CRS-R	State
	A	V	M	O	C	Ar		
Patient 7	3	3	1	2	2	1	7/19	MCS-/EMCS
Patient 19	3	2	0	0	1	1	8/15	MCS-/MCS+
Patient 22	1	2	1	0	0	0	6/10	VS/MCS-
Patient 24	1	0	1	0	1	1	11/15	MCS+/MCS+
Patient 26	1	0	1	0	1	0	12/15	MCS+/MCS+
Patient 28	2	1	1	1	0	0	8/13	MCS-/MCS+
Patient 38	1	1	2	1	1	1	9/16	MCS-/MCS+

CRS-R = Coma recovery scale-revised; A = Auditory; V = Visual; M = Motor; O = Oro-motor; C = Communication; Ar = Arousal; MCS = Minimally conscious state; EMCS = Emergence from minimally conscious state; VS = Vegetative state.

gations on this topic were only conducted in animals and healthy subjects. The present study validated the correlation of QPSC with consciousness by investigating EEG bicoherence in DOC patients. The results showed that patients with lower CRS-R scores had higher QPSC_delta and QPSC_theta and lower QPSC_alpha values. Specifically, the QPSC_theta value significantly differentiated between different consciousness states: QPSC_theta values were the highest in healthy subjects, lower in MCS patients and the lowest in VS patients. This finding was consistent with studies on anaesthesia and sleep: the lower level of consciousness induced by deep anaesthesia caused an increase of the bicoherence in the theta band (Hagihira et al., 2002; Hayashi et al., 2008; Li et al., 2011), while in sleep, phase coupling within the theta band was a major marker to distinguish between slow-wave and rapid eye movement sleep (Li et al., 2009). The evidence of these studies combined with our results suggests that the QPSC_theta value is related to different states of consciousness in subjects under anaesthesia and in sleep and in patients with DOC, and it is thus a critical indicator of consciousness. However, the shift in the peak of the QPSC_alpha value (a primary feature of consciousness depression in anaesthesia (Hayashi et al., 2008; Morimoto et al., 2006)) in VS patients varied insignificantly with MCS patients and healthy subjects. Therefore, despite the similar QPSC characteristics of general anaesthesia, normal deep sleep and VS, different QPSC expressions still exist within the decline of consciousness.

Abnormal spectral power values occur as a distinct property of DOC patients. The results for the relative spectral power values were consistent with previous studies (Lehembre et al., 2012;

Table 3
QPSC_delta, QPSC_theta and QPSC_alpha values (mean±std) of recovered and unrecovered patients at frontal, central, parietal and occipital regions.

Features	Regions	Recovered	Unrecovered	p values (uncorrected)
QPSC_delta	Frontal	0.157 ± 0.011	0.167 ± 0.015	0.109
	Central	0.212 ± 0.017	0.220 ± 0.019	0.159
	Parietal	0.212 ± 0.014	0.223 ± 0.019	0.073
	Occipital	0.210 ± 0.015	0.215 ± 0.025	0.175
QPSC_theta	Frontal	0.157 ± 0.011	0.167 ± 0.012	0.030 *
	Central	0.162 ± 0.009	0.172 ± 0.014	0.050
	Parietal	0.170 ± 0.015	0.178 ± 0.015	0.223
	Occipital	0.167 ± 0.017	0.171 ± 0.018	0.575
QPSC_alpha	Frontal	0.147 ± 0.015	0.150 ± 0.019	0.691
	Central	0.170 ± 0.028	0.165 ± 0.021	0.924
	Parietal	0.179 ± 0.040	0.171 ± 0.019	0.989
	Occipital	0.168 ± 0.037	0.161 ± 0.024	0.945

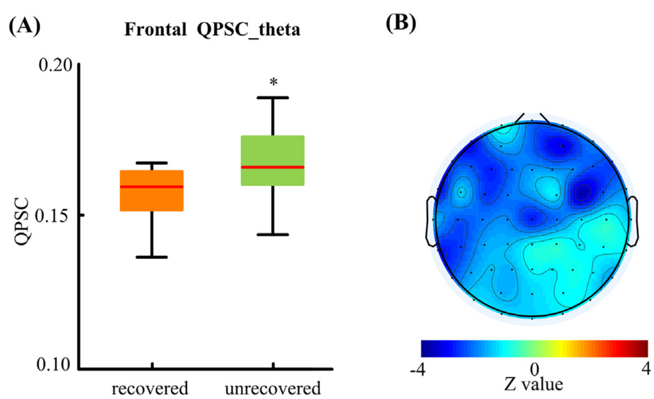

Fig. 4. Averaged QPSC_theta values at the frontal region of recovered and unrecovered patients. (A) Averaged QPSC_theta values at the frontal region of recovered and unrecovered patients. Comparison was conducted with a Wilcoxon rank-sum test, **means $p < 0.01$. (B) Wilcoxon rank-sum tests of the QPSC_theta value at each electrode comparing recovered and unrecovered patients. A false discovery rate (FDR) was conducted after multiple tests with q = 0.05.

Piarulli et al., 2016). The DOC patients had a decreased alpha power and increased delta and theta powers as compared to healthy subjects. The present study also showed a metamorphosis in the EEG phase coupling of the DOC patients. In particular, when comparing MCS patients with VS patients, spectral power values could not distinguish them significantly; however, phase coupling in the theta band showed a significant difference. Using the methodology of this study, bicoherence measures the inherent coupling relationship within a phase of oscillations and avoids an impact from spectral power. This study is also different from previous studies because in this study, the QPSC directly measures the coupling within the neural rhythms at each scalp location, while previous studies focused on spatial connectivity when measuring phase coupling, such as by using the phase lag index (Lehembre et al., 2012). Moreover, the present study indicates that the QPSC_theta value has ability to predict the follow-up consciousness recovery of DOC patients. The patients who obtained a distinct recovery showed a lower QPSC_theta value at frontal region. This implies a possible correlation of phase coupling at the theta band with the neural rehabilitation. This correlation may provide an explanation for the finding that the theta phase synchronization of a MCS patient can decrease after taking Midazolam (Carboncini et al., 2014).

The present study indicates that the QPSC_theta value at the frontal region has a potential prognostic value. Previous studies have demonstrated that activity in the frontal cortex correlates with the recovery of consciousness in DOC patients (Yang et al., 2017). Based on these findings, the frontal cortex has frequently been used as the target point in neuromodulation research (Angelakis et al., 2014; Bai et al., 2016b; Thibaut et al., 2014). In addition, the microcircuit hypothesis has been proposed as an explanation of transitions across the DOC continuum (Giacino et al., 2014; Schiff, 2010). The frontal cortex has been identified as a primary cortical node participating in the consciousness circuit. Studies that have focused on the contrasts between different levels of consciousness have revealed that conscious brain activities have a distinct association with widely distributed brain regions within the prefrontal cortex (Giacino et al., 2014). Therefore, the findings of the present study provide further evidence supporting that the frontal cortex plays a significant role in the evaluation of consciousness and the prediction of consciousness recovery. It also provides a fundamental hypothesis for studies of the frontal cortex based on neural modulations.

In the past, a number of EEG based algorithms and characteristics have been applied to improve the accuracy of the diagnosis and prognosis of DOC patients. The present study demonstrated that QPSC characteristics could provide a close correlation to both consciousness level and consciousness recovery, which was difficult to achieve using other EEG characteristics. Therefore, we suggest that QPSC, especially QPSC_theta, can be a crucial electrophysiological characteristic for the evaluation of consciousness in DOC patients. However, there were some limitations to this study. For example, the number of recovered patients may have been limited by the short-term follow-up. It is necessary to perform a further investigation on the prognostic value of QPSC_theta value using a larger sample and long-term tracking. Nevertheless, the present study has revealed that the QPSC characteristics of an EEG closely correlate with levels of consciousness and consciousness recovery, which is of great value for the diagnosis and prognosis of DOC patients.

5. Conclusion

The present study measured the characteristics of quadratic phase coupling in the EEGs of DOC patients and investigated their role in consciousness disorders and recovery from them. Furthermore, the findings supported that QPSC characteristics, especially of QPSC_theta, closely correlate with the degree of consciousness injury and restoration in DOC patients. Patients with a lower QPSC value at the delta and theta bands and a higher QPSC value at the alpha band showed higher consciousness levels. Meanwhile, a lower frontal QPSC value at the theta band denoted a higher possibility for consciousness recovery at follow-up. Since QPSC values reflects the interaction and integration of neural oscillations, these findings support information integration theory. In addition, although few patients recovered, the QPSC values highlighted the critical role of the frontal cortex in consciousness recovery. Overall, in consideration of the close correlation of QPSC characteristics with consciousness, a QPSC assessment can be of great value for the diagnosis and prognosis of DOC patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.04.710.

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