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Bei Huang

*The Second Military Medical University - Shanghai*

Zhenying Qian

*Shanghai Mental Health Center-Shanghai*

Zongwen Wang

*The Second Military Medical University- Shanghai*

Jihui Zhang

*he Chinese University of Hong Kong*

Kun Chen

*The Second Military Medical University-Shanghai*

*See next page for additional authors*

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**Authors**

Bei Huang, Zhenying Qian, Zongwen Wang, Jihui Zhang, Kun Chen, Tao Xu, Jijun Wang, David F. Cechetto, Zhongxin Zhao, and Huijuan Wu

## RESEARCH ARTICLE

# Fluctuation of primary motor cortex excitability during cataplexy in narcolepsy

Bei Huang<sup>1,2</sup>, Zhenying Qian<sup>3</sup>, Zongwen Wang<sup>1</sup>, Jihui Zhang<sup>2</sup>, Kun Chen<sup>1</sup>, Tao Xu<sup>1</sup>, Jijun Wang<sup>3</sup>, David F. Cechetto<sup>4</sup>, Zhongxin Zhao<sup>1</sup> & Huijuan Wu<sup>1</sup>

<sup>1</sup>Department of Neurology, Changzheng Hospital, The Second Military Medical University, Shanghai, China

<sup>2</sup>Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong

<sup>3</sup>Department of EEG Source Imaging, Shanghai Mental Health Center, Shanghai, China

<sup>4</sup>Department of Anatomy & Cell Biology, University of Western Ontario, London, Ontario, Canada

## Correspondence

Huijuan Wu, Department of Neurology, Changzheng Hospital, 415 Fengyang Road, Shanghai 200003, China. Tel: 8621-8188-5461; Fax: 8621-8188-5458; E-mail: wuhj@smmu.edu.cn

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## Abstract

**Objective:** Cataplexy is a complicated and dynamic process in narcolepsy type 1 (NT1) patients. This study aimed to clarify the distinct stages during a cataplectic attack and identify the changes of the primary motor cortex (PMC) excitability during these stages. **Methods:** Thirty-five patients with NT1 and 29 healthy controls were recruited to this study. Cataplectic stages were distinguished from a cataplectic attack by video-polysomnogram monitoring. Transcranial magnetic stimulation motor-evoked potential (TMS-MEP) was performed to measure the excitability of PMC during quiet wakefulness, laughter without cataplexy, and each cataplectic stage. **Results:** Based on the video and electromyogram observations, a typical cataplectic attack (CA) process is divided into four stages: triggering (CA1), resisting (CA2), atonic (CA3), and recovering stages (CA4). Compared with healthy controls, NT1 patients showed significantly decreased intracortical facilitation during quiet wakefulness. During the laughter stage, both patients and controls showed increased MEP amplitude compared with quiet wakefulness. The MEP amplitude significantly increased even higher in CA1 and 2, and then dramatically decreased in CA3 accompanied with prolonged MEP latency compared with the laughter stage and quiet wakefulness. The MEP amplitude and latency gradually recovered during CA4. **Interpretation:** This study identifies four stages during cataplectic attack and reveals the existence of a resisting stage that might change the process of cataplexy. The fluctuation of MEP amplitude and MEP latency shows a potential participation of PMC and motor control pathway during cataplexy, and the increased MEP amplitude during CA1 and 2 strongly implies a compensatory mechanism in motor control that may resist or avoid cataplectic attack.

## Introduction

In narcolepsy type 1 (NT1), cataplexy is the most distinctive clinical manifestation, which is characterized by complete voluntary muscle atonia with full conscious awareness.<sup>1</sup> A typical cataplexy is most often triggered by strong emotions (such as laughter, anger, or being startled) with paralysis lasting for seconds to minutes, after which strength is restored without any sequelae.<sup>2,3</sup> However, cataplexy is not a simple and stable myoelectric inhibition status. Several studies have reported dynamic behavioral features during cataplectic attack, such as

stereotyped motor behaviors (facial movements and body swaying),<sup>2,4,5</sup> were accompanied with repeated brief enhanced myoelectric activity during initial cataplexy.<sup>6,7</sup> Therefore, it is very important to analyze the dynamic process of cataplectic attack.

Since active movement is mainly controlled by the primary motor cortex (PMC) during wakefulness,<sup>8,9</sup> it is important to understand how the PMC and motor conduction system work during the cataplectic process. Transcranial magnetic stimulation motor-evoked potentials (TMS-MEP) are a non-invasive measurement that would directly activate cortical interneurons as well as pyramidal neurons,<sup>10,11</sup> and

reflect the functional integrity of the whole motor conduction pathway.<sup>12</sup> To our knowledge, there have been only two single-case reports that have observed the motor control system alterations by using TMS-MEP during cataplexy, but the findings were contradictory.<sup>13,14</sup> Considering the complicated cataplexy process, it is essential to investigate the changes of motor control system during the cataplectic attack by a larger scale study.

To address these issues, we applied a video-polysomnogram monitoring to objectively classify different stages of cataplectic attack which were triggered by emotional stimuli at sleep center. Further, by using TMS-MEP, we aimed to determine the different characteristics of PMC excitability and the conductive functions of the pyramidal tract during the quiet wakefulness (QW) state, laughter without cataplexy state, and each cataplectic stage in order to verify the dynamic fluctuation of the PMC excitability and reveal the underline mechanism of PMC activity against the cataplectic attack.

## Methods

### Subjects

A total of 35 patients meeting the diagnostic criteria for NT1 by the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) and having typical and frequent cataplectic attack (more than once a month) were recruited in the sleep center at the Changzheng Hospital, Shanghai, China, from August 2012 to December 2017. Twenty-nine healthy volunteers from community-based sample were recruited as controls. The exclusion criteria for both patients and controls included: (1) obstructive sleep apnea syndrome (AHI > 10/h); (2) idiopathic hypersomnia; (3) a history of sleep restriction/deprivation; (4) shift work or jet lag; (5) drug abuse; (6) other neurological, psychiatric, or chronic medical conditions (such as diabetes or thyroid disease); and (7) taking psychotropic medications (including anticataplectic drugs) in the previous 3 weeks.

All subjects aged above 18 years gave written informed consent. For those subjects aged less than 18 years old, their parents gave written consents and the subjects gave written assents. The study was approved by the ethics committee of the Changzheng Hospital.

### Study protocol

This study contained two sections. Section 1 was a case-control design. We compared TMS-MEP between NT1 patients and controls during quiet wakefulness and laughter. Section 2 was a within-subject design. Cataplectic episodes of NT1 patients were segmented according to the video-polysomnogram (v-PSG), and then MEP amplitudes

were measured during cataplexy for further segmental analysis.

### TMS-MEP

Transcranial magnetic stimulation motor-evoked potential was performed at the Shanghai Mental Health Center, using a MagPro X100 magnetic stimulator and a MC-B70 butterfly coil (Medtronic, Denmark). Muscle responses were recorded in abductor pollicis brevis. Electromyograms (EMG) were obtained via Ag-AgCl surface electrodes and recorded by a key point myoelectricity-evoked potential apparatus (Medtronic, Denmark).

The following TMS measurements were evaluated by an experienced TMS technician: Rest motor threshold (RMT) was defined as the minimum stimulus intensity that TMS evokes at least five positive MEPs (amplitudes >50  $\mu$ V) out of ten trials; 1 mV motor threshold (1 mV MT) was a higher stimulus intensity that could evoke not less than five MEPs (amplitudes >1 mV) in ten trials; Cortical silent period (CSP) was conducted in the voluntary muscle contraction (20% of maximum contraction) under the intensity of 120% RMT, CSP was defined as the duration EMG silence. Intracortical facilitation (ICF) and short latency intracortical inhibition (SICI) were evoked by a paired-pulse stimulation which involved a conditioning stimulus (CS) followed by a test stimulus (TS). CS was a subthreshold stimulus (80% RMT) while TS was a suprathreshold (1 mV MT). ICF was induced at an inter-stimulus interval (ISI) of 10 msec and SICI of 3 msec. Average paired-pulse stimulation MEP amplitudes were compared with those produced by the TS alone (1 mV MT MEP) to assess intra-cortical facilitation and inhibition.

### Case-control design

Narcolepsy type 1 patients and controls were instructed to sit up straight in chair, a brief nap would be arranged for sleepy subjects (Stanford Sleepiness Scale score > 2<sup>15</sup>). MEP was recorded in dominant hands and stimulated by a coil located on the contralateral motor cortex. We measured 1 mV MT, RMT, CSP, ICF, and SICI successively during the QW state. Then all subjects were scheduled to watch humorous film clips. Typical laughter episodes (without cataplexy) were captured and measured under 1 mV MT stimulation.

### Within-subject design

#### Video-EMG and cataplectic stages

All NT1 patients were recruited for a video-PSG and trigger-test in a soundproof room. Video-PSG monitoring

(NIHON KOHDEN Inc, Polysmith 7.0 sleep analysis system) including electroencephalogram (EEG) derivations F3/C3/O1-A2 and F4/C4/O2-A1 (International 10–20 system), bilateral electro-oculogram (EOG), submental and anterior tibialis electromyograms (EMG), and 2-lead electrocardiogram (ECG). A three-minute quiet state with eyes closed was recorded as the QW stage. Then, the patients were triggered into cataplexy using specific stimulated scenarios (humorous and comedy videos, aerobic exercise, recollection of a happy or frightening memory, etc.). The recordings of cataplectic attack were simultaneously analyzed by two independent experienced sleep physicians to reach consensus on the confirmation of cataplectic attack.

### TMS-MEP under cataplectic stages

All NT1 patients were triggered and were under the close observation of two staff members. MEP would be measured under 1 mV MT as soon as any appearance of cataplectic behaviors. Research staff helped maintaining the standard MEP test position in case of excessive movements. As CSP, ICF, and SICI were time consuming, we only measured them during long cataplectic attacks.

### Statistical analysis

Statistical analyses were performed with SPSS 22.0. For a two-group comparison, continuous variables were compared by t-test or Mann–Whitney U test while categorical

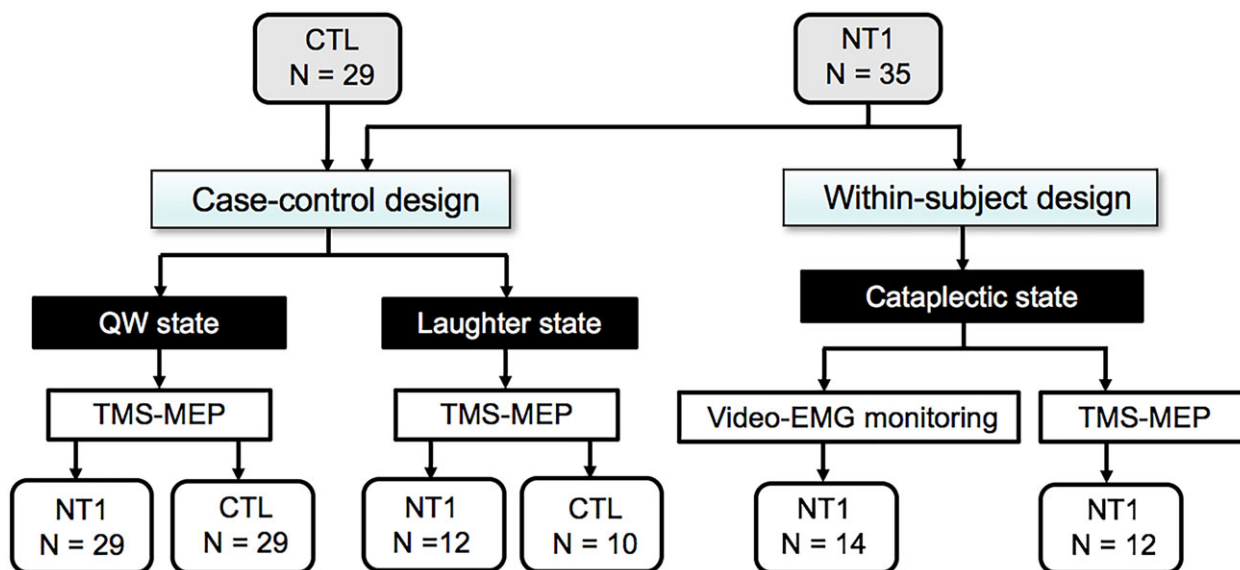
variables were compared by using Pearson’s chi-square test or Fisher’s exact test, where appropriate. To minimize the individual and intra-group differences, we used the magnitude of the MEP amplitude and of MEP latency rather than absolute value of these variables to run within individual comparisons between stages in section 2. The paired sample t-test was conducted for within-individual comparisons. For viewing multiple comparisons, a Bonferroni adjustment was used to control for false positives, where a  $P < 0.015$  was considered statistically significant.  $P < 0.05$  were taken as the statistically significant threshold for all other tests.

## Results

Thirty-five NT1 patients (23 males) and twenty-nine controls (21 males) were included in this study (Fig. 1). Among all, 28 patients were newly diagnosed and drug-naïve, seven patients had withdrawn drugs for at least 3 weeks prior. CSF Hypocretin-1 was tested in 11 patients and all of them showed significantly decreased concentration (Table 1, Table S1).

### During quiet wakefulness and laughter state

During quiet wakefulness, ICF significantly decreased in NT1 patients ( $109.8 \pm 54.4$  vs.  $184.7 \pm 73.2\%$ ,  $P < 0.001$ ) compared with 29 age-matched healthy controls. While 1 mV MT ( $46.6 \pm 7.7$  vs.  $46.1 \pm 5.6\%$ ,



**Figure 1.** Participant inclusion flowchart. This study contains two sections with two study designs: case-control design and within-subject design. NT1, narcolepsy type 1 patients; CTL, controls.

$P = 0.77$ ), RMT ( $35.1 \pm 5.5$  vs.  $37.2 \pm 5.6$ ,  $P = 0.15$ ), CSP ( $70.0 \pm 25.9$  vs.  $74.5 \pm 33.8$ ,  $P = 0.60$ ), and SICI [ $41.3$  ( $34.0, 57.1$ ) vs.  $41.9$  ( $24.3, 68.9$ ),  $P = 0.96$ ] did not differ between groups (Table 2).

Laughter episodes were recorded in 10 NT1 patients and 12 age-matched healthy controls. MEP amplitude notably increased in both patients [ $0.91$  ( $0.76, 1.3$ ) vs.  $1.7$  ( $1.3, 2.0$ ) mV,  $P = 0.005$ ] and controls [ $0.99$  ( $0.78, 1.24$ ) vs.  $2.3$  ( $2.0, 3.3$ ) mV,  $P = 0.005$ ], but the magnitude of

**Table 1.** Clinical characteristics and sleep study results of experimental groups.

	Controls (N = 29)	NC patients (N = 35)
Age (yr)	24.9 ± 14.0	23.2 ± 17.4
Sex (M/F)	19/10	23/12
BMI (Kg/m <sup>2</sup> )	20.7 ± 3.3	26.7 ± 4.4
Duration of illness (yr)	N.A.	3.82 ± 2.5
ESS score	8.1 ± 3.7	16.3 ± 2.7
Sleep paralysis	1/29	14/35
Treatment	N.A.	7/35
Nocturnal SE (%)	N.A.	81.8 ± 8.9
No. of SOREMPs	N.A.	3.3 ± 0.8
CSF hypocretin-1 <sup>1</sup>	N.A.	26.5 ± 28.1

N.A., not applicable.

<sup>1</sup>Results were based on 11 patients.

**Table 2.** TMS-MEP parameters during quiet wakefulness and laughter states.

	Controls	NT1 patients	P
<b>QW state</b>			
Number of subjects	29	29 <sup>1</sup>	
Sex (M/F)	19/10	21/8	0.57
Median age (years)	17 (16, 33.5)	15 (13, 34)	0.31
<b>TMS parameters</b>			
1 mV MT (%)	46.1 ± 5.6	46.6 ± 7.7	0.77
RMT (%)	37.2 ± 5.6	35.1 ± 5.5	0.15
CSP (msec)	74.5 ± 33.8	70.0 ± 25.9	0.60
ICF (%)	184.7 ± 73.2	109.8 ± 54.4	<0.001
SICI (%)	41.9 (24.3, 68.9)	41.3 (34.0, 57.1)	0.96
<b>LA state</b>			
Number of subjects	10	12	
Sex (M/F)	8/2	9/3	0.65
Median age (years)	14 (14, 29.8)	14 (12.3, 23.5)	0.46
<b>TMS parameters</b>			
QW MEP amp (mV)	0.99 (0.78, 1.24)	0.91(0.76, 1.3)	0.67
LA MEP amp (mV)	2.3 (2.0, 3.3)	1.7 (1.3, 2.0)	0.04
Magnitude of amp	2.5 ± 0.35	1.8 ± 0.62	0.008

TMS-MEP, Transcranial magnetic stimulation motor-evoked potential; NT1, narcolepsy type 1; QW, quiet wakefulness; 1 mV MT, 1 mV motor threshold; RMT, rest motor threshold; CSP, cortical silent period; ICF, intracortical facilitation; SICI, short latency intracortical inhibition; LA, laughter.

<sup>1</sup>Among 29 patients, 23 patients had CSP, ICF, and SICI measurements.

MEP amplitude was much lower in NT1 patients ( $1.8 \pm 0.62$  vs  $2.5 \pm 0.35$ ,  $P = 0.008$ ) (Table 2).

## During cataplectic stages

### Cataplexy stages based on the behavioral-EMG activity

Fourteen patients were successfully triggered under the video-PSG monitoring. We proposed a modified cataplexy staging focusing on the behavioral and EMG features: triggering (CA1), resisting (CA2), atonic (CA3), and recovering (CA4) stages. Ten patients experienced four stages with complete cataplectic episodes, while the other four patients showed partial cataplexy (without classical CA3). A typical complete cataplectic attack with four stages is shown in Figure 2. Behavioral and EMG characteristics of each stage are concluded and shown as follows.

**CA1 - Triggering stage.** In this stage, a cessation of previous behaviors was observed, such as ceasing to move or laugh, fixed or glazed eyes, drooping eyelids or a stiff facial expression. This stage is transient and shows no obvious or slight alterations of muscle tension.

**CA2 - Resisting stage.** After triggering, patients started twitching, flapping up and down of their body, and had postural instability. The complex behaviors may be during both the conscious (e.g., shaking and raising the head, supporting the body by hands) and unconscious state (e.g., flapped up and down motion of their body). The EMG showed paroxysmal enhanced EMG activities, which may occur against a background of muscle atonia.

**CA3 - Atonic stage.** Loss of muscle tone gradually extended to the neck, shoulders, trunk or knees, ending with partial or global paralysis. Typically, this stage shows that the EMG is silent, with occasional eye movement bursts.

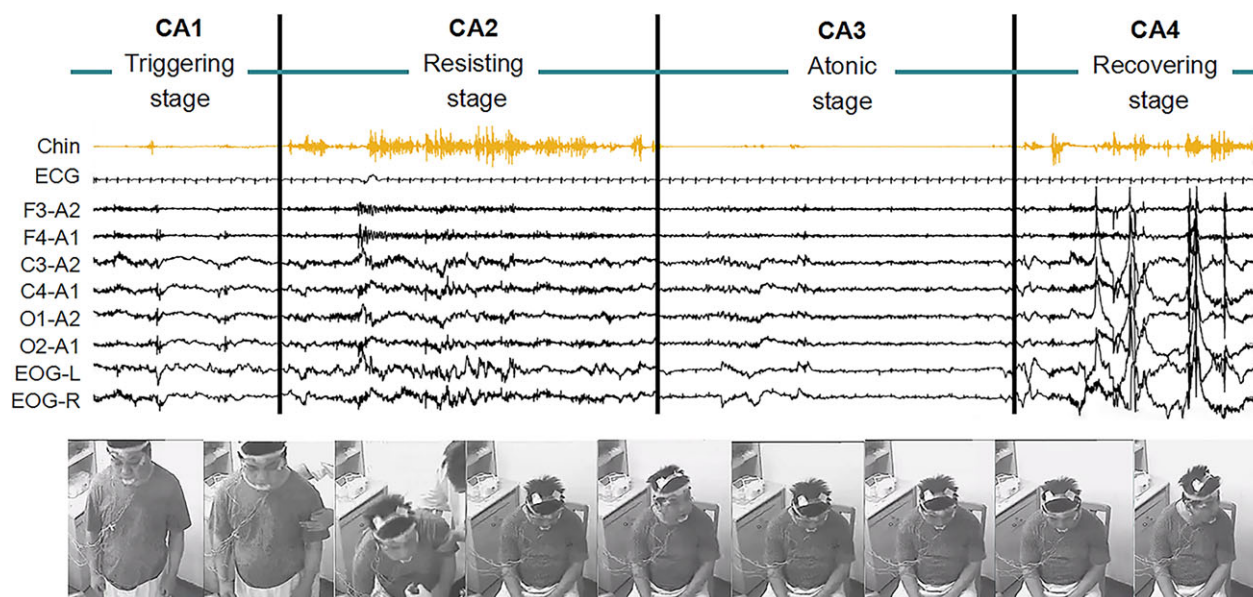
**CA4 - Recovering stage.** Postural tone recovers from CA3 gradually and normal motor control is restored.

### Fluctuations of TMS-MEP during cataplectic stages

Considering the brief duration and quick conversion of CA1 stage, we took the data of the CA1 and 2 stages together for analyses. CA3 and CA4 stages were successfully recorded in 12 patients, but typical CA1 and 2 stage episodes were only recorded in eight patients because cataplexy could not be triggered in four patients in situ and the CA1 and 2 data were missed.

The MEP amplitudes between the QW and the cataplectic stages showed remarkable fluctuations. Figure 3A, B shows the typical MEP fluctuations of the complete and partial cataplexy in two patients. Compared with the





**Figure 2.** Video polysomnogram-monitoring during a typical complete cataplectic attack (Patient No. 8), exhibiting four stages: triggering, resisting, atonic, and recovering. Chin EMG (yellow) showed paroxysmal enhanced activity synchronized with twitching and postural instability during CA2, while gradually recovered during CA4.

QW, the magnitude significantly increased during the CA1 and 2 stages ( $2.7 \pm 0.86$  vs. 1,  $P < 0.001$ ), then reduced below baseline in the CA3 stage ( $0.37 \pm 0.17$  vs. 1,  $P = 0.004$ ), and gradually recovered during the CA4 stage ( $1.1 \pm 0.36$  vs. 1,  $P = 0.235$ ); Particularly, the increase during the CA1 and 2 stage was remarkable, even higher than the laughter stage ( $2.7 \pm 0.86$  vs.  $1.8 \pm 0.62$ ,  $P = 0.02$ ) (Fig. 4A).

The MEP latency during the CA3 stage was notably prolonged during the cataplectic attack (CA3 vs. QW:  $23.7 \pm 1.1$  vs.  $21.0 \pm 1.5$  msec,  $P < 0.001$ , Fig. 3C), and the magnitude fluctuation of MEP latency was as shown in Figure 4B. Notably, an increase of 6 msec during the CA3 stage was recorded from a new-onset, middle-aged male patient (No.18), with a cataplectic frequency that varied from several to dozens of times a day.

Four patients, who experienced long duration attacks, had further examinations of the ICF, SIC1, and CSP during the CA3 stage. Compared with the QW, notable prolonged CSP duration ( $123.7 \pm 9.9$  vs.  $72.0 \pm 4.2$  msec,  $P = 0.04$ ) was observed in patients. However, the attenuation of ICF ( $73.0 \pm 38.5$  vs.  $95.8 \pm 45.0\%$ ,  $P = 0.36$ ) and the increase of SIC1 ( $26.3 \pm 12.9$  vs.  $49.7 \pm 11.8\%$ ,  $P = 0.09$ ) were not significant due to the small sample size.

## Discussion

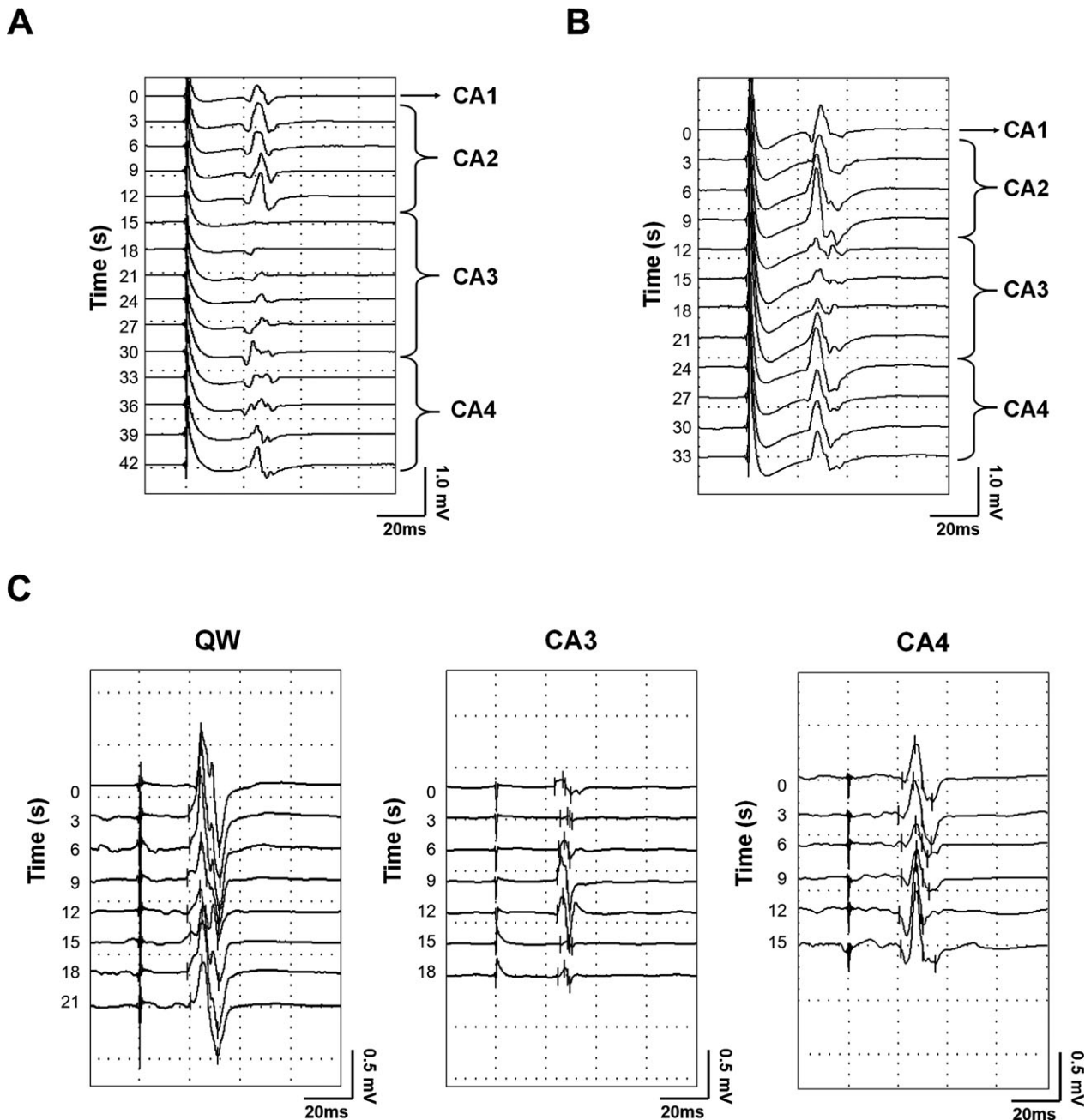
This is the first study to reveal the dynamic changes of PMC excitability by TMS-MEP during four modified

cataplectic stages in NT1 patients based on the behaviors and muscular features. Besides the decreased intracortical facilitation in PMC during QW, we discovered dynamic changes of PMC in patients: the MEP amplitude increased during laughter, and even higher during CA1 and 2, then significantly decreased with obvious prolonged latency during CA3; MEP amplitude was gradually restored in CA4. The fluctuations of excitability in the PMC and the motor conduction pathway, as continuously detected by TMS-MEP, reveal comprehensive interbrain coordination during the cataplectic process.

### Four-stage cataplectic attack

Cataplexy was first segmented according to EEG characteristics in animal studies, from a stage resembling wakefulness to a REM-like stage, and a final stage dominated by mixed amplitude and frequency activity.<sup>16,17</sup> Then a scholar focused on the behavioral features of cataplectic episodes in one NT1 patient and identified three phases of cataplexy — namely, initial phase, falling phase, and atonic phase.<sup>6</sup> In addition, autonomic functions also indicate a segmental cataplexy, for example, heart rate significantly increased prior to the muscle atonia of cataplexy, and then decreased along with increased muscle sympathetic nervous activity, systolic blood pressure and decreased skin sympathetic reaction.<sup>18,19</sup>

Our study segmented cataplexy based on a larger sample size, which included different phenotypes, triggers and

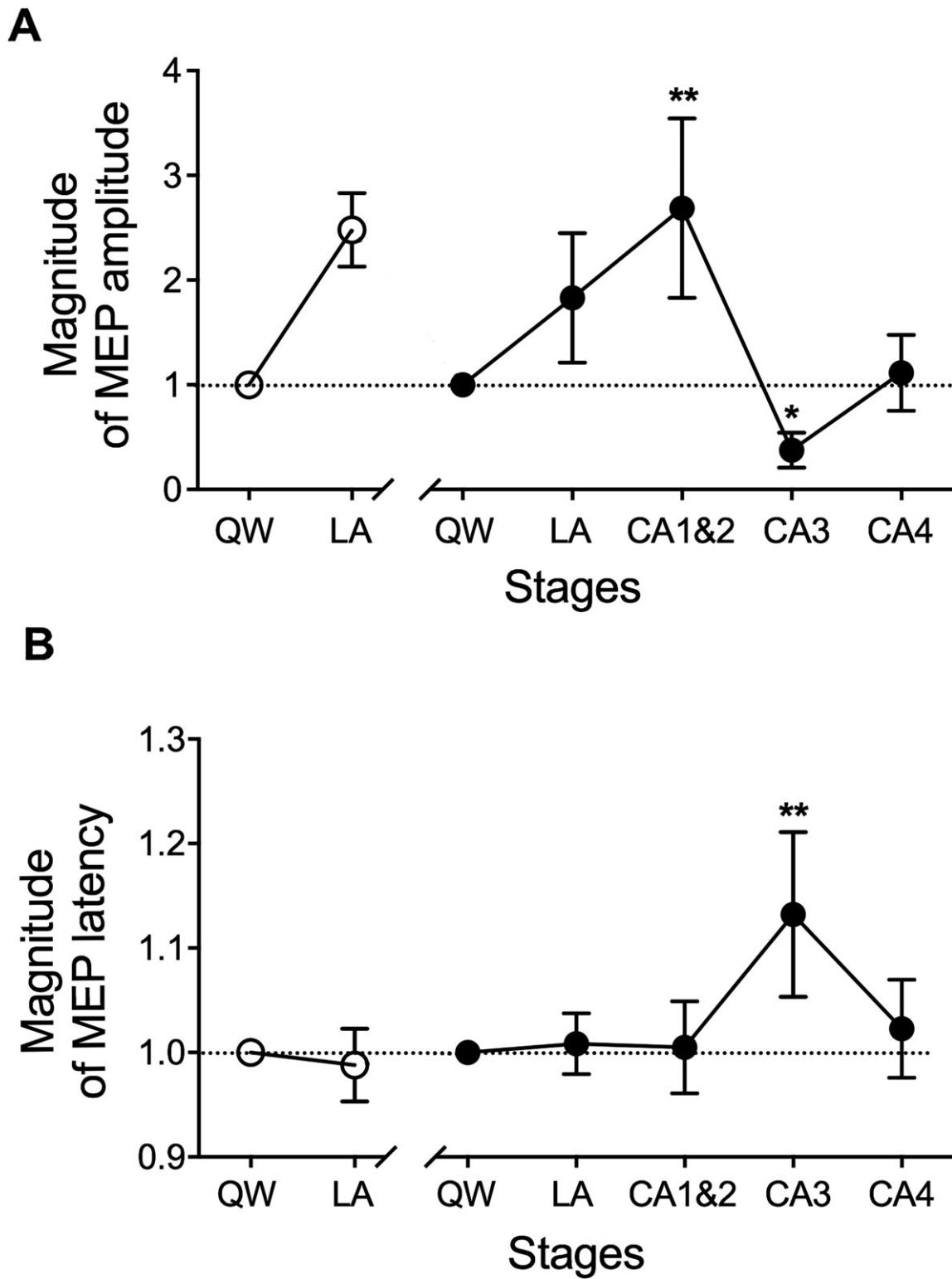


**Figure 3.** (A) Fluctuations of MEP amplitude during complete cataplexy (patient No.10) and (B) partial cataplexy (patient No.14) under the stimulus intensity of 1 mV MT. (C) MEP latency immediately prolonged in CA3 compared with QW, then shortened back to normal level during CA4. QW, quiet wakefulness; MEP, Motor evoked potentials.

onset age. Triggering stage (CA1) is more like a state that converts into cataplexy, which is consistent with the description by Wilson<sup>4</sup> that patient said “it’s coming on now” in a slightly indistinct voice just before the cataplectic attack. Resisting stage (CA2) resembled previous initial and falling stage, opposite to the “enacted intentional movements in response to the segmental postural

lapses”.<sup>7</sup> Patients fight against the inner uncontrolled change and display complex movement<sup>5</sup>. At the same time, EMG shows paroxysmal enhanced activity. So CA2 is regarded as a “fighting process”. Atonia stage (CA3) is the most distinct stage with postural collapse and atonia/lower muscle tone and is the state of most concern. Recovering stage (CA4) is usually neglected; it indicates a





**Figure 4.** (A) In patients with NT1, Magnitudes of MEP amplitude increased during LA, even higher during CA1 and2, then dramatically decreased during CA3, and recovered gradually during CA4. (B) Magnitudes of MEP latency only significantly prolonged during CA3 compared with QW. \* indicate  $P < 0.05$  and \*\* indicate  $P < 0.001$ . Error bars indicate SD. NT1, narcolepsy type 1; CTL, controls; QW, quiet wakefulness; LA, laughter; MEP, Motor evoked potentials; MT, motor threshold.

gradual recovery from atonia to normal muscle tone, also accompanied with a gradual recovery of heart rate and muscle sympathetic nervous activity.<sup>15</sup> However, in fact, it is very hard to distinguish CA1 from CA2 using available biomarkers, and sometimes CA2 and CA3 are mixed by persistent resistance and abolishment due to the efforts of the patients' motivation. In general, the four stages we proposed here are quite different from previous reports, which has comprehensively described and summarized the process of cataplectic attack.

### The excitability of PMC during QW and laughter

A notable decrease in ICF was observed during QW, suggesting a potential inhibition of the motor cortex in NT1 patients.<sup>20</sup> Previous studies (Table 3) have reported higher MT, decreased MEP amplitude, prolonged CSP duration, and more significant SICI in drug-naive narcoleptic patients, which supports a coincidence conclusion of PMC hypoexcitability in the QW.<sup>21–24</sup> The increased MEP amplitude during laughter identified in this study is also consistent with the previous study; which showed laughter caused the mean MEP area to increase by 60% in healthy subjects.<sup>25</sup> However, a relatively low increase in MEP magnitude in patients also implies the latent inhibition of PMC activity during laughter in NT1.

The orexinergic projection system is highly involved in sleep/wake transitions and reinforces behavioral wakefulness, with a widespread distribution in the whole motor control system.<sup>26</sup> In cortex, orexinergic afferent was reported a direct modulation in the motor cortex layer

VI-b.<sup>27</sup> Therefore, absence of orexinergic output in NT1 may lead to a mild decrease of excitability in the PMC during QW and laughter.

### The fluctuation of PMC excitability during cataplexy

Previously, the studies of the main mechanisms of cataplexy focused on the suppression of brainstem neural circuits promoting rapid eye movement (REM) sleep-like muscle atonia, which is induced by the activations of medial prefrontal cortex (mPFC) and amygdala.<sup>28–30</sup> Our study observed a fluctuation of MEP amplitude during the cataplectic process, which indicates that PMC takes part in the process of cataplexy attack. The significantly increased MEP amplitude during CA2 accompanying the voluntary motor movement, implies that the hyperexcitability of PMC aims to resist the loss of muscle tone. The inhibition during CA3 is presented as dramatically decreased MEP amplitude and prolonged MEP latency, and the latter had not been reported before. The prolonged MEP latency may also suggest a strong para-inhibition of the whole corticospinal tract, which is consistent with the changes that deep-tendon reflexes were abolished during global cataplexy attacks and were partially inhibited during partial cataplexy.<sup>31,32</sup>

Since the PMC is the dominating control center of the voluntary motor movements with consciousness,<sup>5</sup> we hypothesize that the PMC works as a compensatory/resistant mechanism in the brain during a cataplectic attack: when the NT1 patient encounters laughter, most of the time, cataplexy could not be triggered because of

**Table 3.** Main findings of the study exploring motor cortex excitability in patients with narcolepsy.

	Patients	CTL	State	Transcranial magnetic stimulation						
				MCT	Amp	MT	CSP	SICI	ICF	Other
Current research	29	29	QW	N	–	N	N	N	↓	
	12	10	LA	N	↑ <sup>1</sup> ↓ <sup>2</sup>	–	–	–	–	
	12	–	CA	↑	↑↓ <sup>3</sup>	–	↑	↑	↓	
Rosler et al.(1994)	1	–	CA	–	N	–	–	–	–	
Oliviero et al. (2005)	13	12	QW	N	N	↑ <sup>4</sup>	N	–	N	SICF: N, ICI:↑
Nardone et al. (2010)	24	20	QW	N	–	↑	–	↑	N	
Joo et al. (2010)	19	25	QW	–	N/↓ <sup>5</sup>	N	↑	–	–	
Joo et al. (2011)	1	–	CA	–	↓	–	–	–	–	
Vijayakumari et al.(2013)	8	8	QW	N	–	↑	↑	–	–	

CTL, controls; MCT, motor conduction time; Amp, peak-to-peak MEP amplitude; RMT, resting motor threshold; 1 mV MT, 1 mV motor threshold; CSP, cortical silent period; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation; SICF, short latency intracortical facilitation; ICI, intracortical inhibition; QW, quiet wakefulness; CA, cataplexy; LA, laughter; N, normal; –, not evaluated.

<sup>1</sup>If compared with QW state, MEP amplitude increased in laughter without cataplexy episodes, <sup>2</sup>but still lower than normal controls.

<sup>3</sup>MEP amplitude was fluctuant during cataplexy compared with QW level, which increased in CA1&2 stage, while notable decreased during CA3.

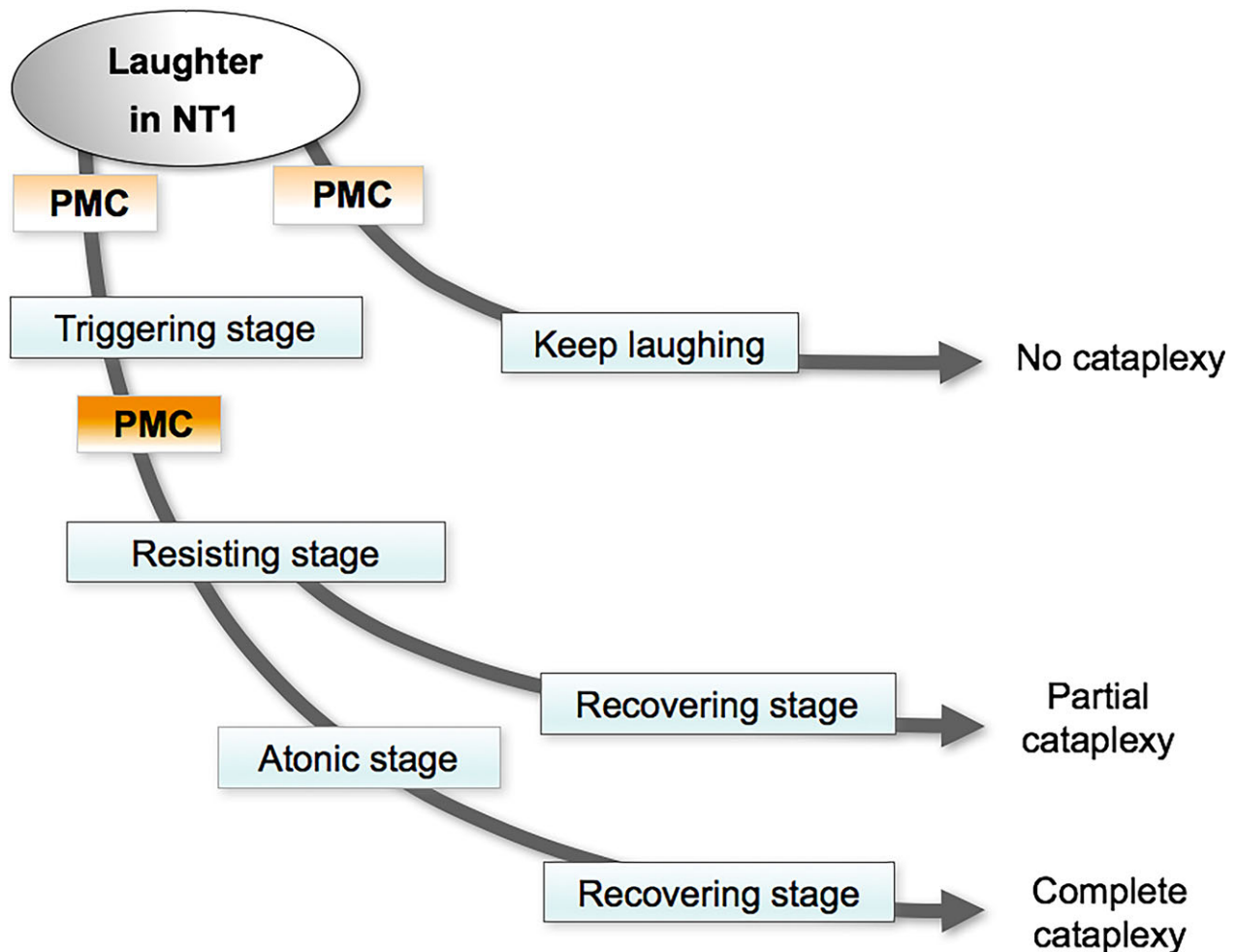
<sup>4</sup>Both RMT and active motor threshold (AMT) increased in this research. AMT was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 200  $\mu$ V in 50% of trials) during isometric contraction of the tested muscle at about 20% maximum.

<sup>5</sup>Amplitude normal in 120% RMT, decrease in 140% and 150% RMT

increased PMC activity. If the laughter triggered an attack successfully, it may lead into a resisting stage with even higher PMC activity. If the PMC resisted the attack successfully, the patient may enter recovery stage immediately. If resisting failed, the patient enters the atonic stage and thus presents as complete cataplexy (Fig. 5). Furthermore, four stages of cataplexy may hardly be regarded as four distinguishable phases. For example, some patients with partial cataplexy may have only the CA1 and 2, and recover easily. Some patients with status cataplecticus have mixed components of CA1, CA2, and CA3, with a very difficult CA4.

During CA3, decreased MEP amplitude, prolonged MEP latency, together with other biomarkers indicate the inhibition of the whole motor conduction pathway. As we know, neurons in locus coeruleus (LC), dorsal raphe (DR) and laterodorsal tegmental nucleus (LDT) will be inhibited by amygdala in patients with NT1 since the

absence of orexinergic excitatory inputs.<sup>33</sup> Nevertheless, LC ∨ DR ∨ LDT are part of the wake-promoting network which helps drive cortical activation. Inhibition of these nuclei will inhibit the excitability of the PMC. Reduction in PMC excitability may also be due to the partial inhibition of the ascending arousal system during cataplexy; loss of consciousness would not occur since most part of the network is still working. In addition, cataplexy can be regarded as an intrusion of REM sleep atonia into wakefulness. Spinal motor neuron, as a target of PMC, is under a strong inhibitory input at the same time, and sublaterodorsal nucleus (SLD) neurons play a critical role in its generation.<sup>34</sup> During REM sleep, SLD activates premotor neurons in the medial medulla and spinal cord that strongly inhibits motor neurons, and it falls silent during wakefulness and NREM sleep.<sup>33–35</sup> However, due to orexin deficiency in patients with NT1, inappropriate activation of SLD neuron could occur during wakefulness



**Figure 5.** When triggered by laughter, patients with NT1 showed three conditions with varied activity of PMC. To some extent, PMC might affect the process of cataplexy. PMC, primary motor cortex; NT1, narcolepsy type 1 patients.

which may generate muscle atonia and accompanied by depression of PMC.

Our findings highly confirm the evidence of neuroimaging studies in narcolepsy. It was clear that there was no evidence of structure alterations in PMC during quite wakefulness<sup>36</sup> in magnetic resonance imaging (MRI). Consistent with increased PMC activity, the blood oxygenation level dependent contrast signal was found to increase in the bilaterally motor-premotor cortex and anterior cingulate cortex during laughter without cataplexy episodes.<sup>37</sup> Interestingly, functional neuroimaging studies showed significantly higher metabolism and higher perfusion in bilateral pre-postcentral gyri during cataplectic attacks.<sup>29,38,39</sup> These could very well be interpreted by hyperexcitability of PMC during CA1 and 2, and during CA3. We speculate that the attenuated MEP amplitude in CA3 may not be due to the inhibited PMC neuron itself, but to a strong para-inhibition from the brainstem and spinal cord. In addition, patients treated with psychostimulant and/or anticataplectic drugs also showed hypermetabolism in pre-postcentral gyri compared with untreated patients.<sup>33</sup>

Clinically, narcolepsy symptoms, such as excess daytime sleepiness, 24 h sleep time, and the severity of cataplexy<sup>40–42</sup> were relieved over time in patients with or without treatment. The alleviated phenomena imply the existence of compensatory mechanisms. Thus, enhanced PMC activity resisting the process of cataplexy might be a useful acquisition method to alleviate the severity and frequency of cataplectic attacks. On the other hand, from the therapeutic perspective, antidepressants, especially selective norepinephrine reuptake inhibitors (SNRIs), are reported as the most effective drugs to alleviate cataplexy via the adrenergic system.<sup>43</sup> The dopaminergic system is involved in the regulation of cataplexy via the D2-like receptor in mouse models of narcolepsy.<sup>44</sup> Cholinergic systems are demonstrated to be very important in the regulation of cataplexy in animal models.<sup>45</sup> Since close relationships were found between the PMC and these neurotransmitter systems,<sup>46,47</sup> the work of the PMC may be to integrate the outputs of adrenergic, dopaminergic, and cholinergic systems.

There are several limitations to this study. Firstly, MEP amplitude and latency were influenced by the whole motor conduction pathway, spinal activity, and the individual muscle strengths, which could have an impact on MEP results. Being aware of this, we also measured the ICF, SIC1, and CSP to confirm the excitability of the PMC. Secondly, only some of the patients were triggered into cataplectic attack in the test conditions, which might cause some selective bias. Thirdly, considering the time-consuming MEP tests and the transient cataplectic attack, we could not complete all trials of the MEP parameters. We selected 1 mV MT as the preferred during cataplexy.

Lastly, because of technology limitations we were not able to record the EEG and EMG synchronously with TMS-MEP. Because the attack of cataplexy is very complex, ranging from complete cataplexy to mild attacks with undetectable symptoms, it is a challenge to distinguish the specific stages of cataplexy in each patient. In addition, other criteria including EEG, heart rate, and blood pressure are needed for further analysis.

In conclusion, this is an important study to demonstrate the dynamic process of cataplectic attacks and to analyze the excitability of the PMC through TMS during each cataplectic stage. The four distinct stages of cataplexy reveal the important evolution of the cataplectic process. The fluctuation of the MEP amplitude and the prolonged MEP latency during cataplexy shows that PMC and motor control pathway participate in cataplectic attacks. And more importantly, the increased MEP amplitude during CA1 and 2 indicates that the PMC may act as a resisting regulator to struggle against the loss of muscle tone or postural collapse in patients with full consciousness. The activity of the PMC may help patients avoid or alleviate cataplectic attack. These findings broaden our knowledge about the integration and compensatory mechanism in the brain during cataplectic attack in NT1 patients.

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## Author Contributions

HJW BH ZWW JJW ZXZ contributed to the conception and design of the study; BH ZYQ ZWW KC HJW contributed to the acquisition and analysis of data; BH HJW JHZ DFC TX contributed to drafting the text and preparing the figures.

## Conflicts of Interest

The authors have no conflicts of interest to disclose.

## References

1. Scammell TE. Narcolepsy. *N Engl J Med* 2015;373:2654–2662.
2. Dauvilliers Y, Siegel JM, Lopez R. Cataplexy—clinical aspects, pathophysiology and management strategy. *Nat Rev Neurol* 2014;10:386–395.

3. Overeem S, van Nues SJ, van der Zande WL, et al. The clinical features of cataplexy: a questionnaire study in narcolepsy patients with and without hypocretin-1 deficiency. *Sleep Med* 2011;12:12–18.
4. Wilson SA. Cataplexy. *J Neurol Psychopathol* 1933;14:45–51.
5. Plazzi G, Pizza F, Palaia V, et al. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. *Brain* 2011;134:3477–3489.
6. Rubboli G, d’Orsi G, Zaniboni A, et al. A video-polygraphic analysis of the cataplectic attack. *Clin Neurophysiol* 2000;111(Suppl 2):S120–S128.
7. Vetrugno R, D’Angelo R, Plazzi G, et al. Behavioural and neurophysiological correlates of human cataplexy: a video-polygraphic study. *Clin Neurophysiol* 2010;121:153–162.
8. Muellbacher W, Ziemann U, Wissel J, et al. Early consolidation in human primary motor cortex. *Nature* 2002;415:640–644.
9. Ebbsen CL, Brecht M. Motor cortex - to act or not to act? *Nat Rev Neurosci* 2017;18:694–705.
10. Salvador R, Silva S, Bassar PJ, Miranda PC. Determining which mechanisms lead to activation in the motor cortex: a modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry. *Clin Neurophysiol* 2011;122:748–758.
11. Opitz A, Legon W, Rowlands A, et al. Physiological observations validate finite element models for estimating subject specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex. *NeuroImage* 2013;81:253–264.
12. Rossini PM, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071–1107.
13. Rosler KM, Nirkko AC, Rihs F, Hess CW. Motor-evoked responses to transcranial brain stimulation persist during cataplexy a case report. *Sleep* 1994;17:168–171.
14. Joo EY, Hong SB, Han SJ, Suh M. Suppression of motor evoked potential during cataplexy. *Sleep Med* 2011;12:306–307.
15. Hoddes E, Zarcone V, Smythe H, et al. Quantification of sleepiness: a new approach. *Psychophysiology* 1973;10:431–436.
16. Kushida CA, Baker TL, Dement WC. Electroencephalographic correlates of cataplectic attacks in narcoleptic canines. *Electroencephalogr Clin Neurophysiol* 1985;61:61–70.
17. Vassalli A, Dellepiane JM, Emmenegger Y, et al. Electroencephalogram paroxysmal  $\theta$  characterizes cataplexy in mice and children. *Brain* 2013;136:1592–1608.
18. Donadio V, Plazzi G, Vandi S, et al. Sympathetic and cardiovascular activity during cataplexy in narcolepsy. *J Sleep Res* 2008;17:458–463.
19. Siegel JM, Fahringer H, Tomaszewski KS, et al. Heart rate and blood pressure changes associated with cataplexy in canine narcolepsy. *Sleep* 1986;9:216–221.
20. Ziemann U. TMS and drugs. *Clin Neurophysiol* 2004;115:1717–1729.
21. Oliviero A, Della Marca G, Tonali PA, et al. Functional involvement of cerebral cortex in human narcolepsy. *J Neurol* 2005;252:56–61.
22. Nardone R, Bergmann J, Lochner P, et al. Modafinil reverses hypoexcitability of the motor cortex in narcoleptic patients: a TMS study. *Sleep Med* 2010;11:870–875.
23. Joo EY, Hong SB, Kim HJ, et al. The effect of modafinil on cortical excitability in patients with narcolepsy: a randomized, placebo-controlled, crossover study. *Sleep Med* 2010;11:862–869.
24. Vijayakumari AA, Khan FR, Varma RP, Radhakrishnan A. Can transcranial magnetic stimulation be used to evaluate patients with narcolepsy? *Neurol Sci* 2013;34:1411–1420.
25. Overeem S, Reijntjes R, Huyser W, et al. Corticospinal excitability during laughter: implications for cataplexy and the comparison with REM sleep atonia. *J Sleep Res* 2004;13:257–264.
26. Anaclet C, Parmentier R, Ouk K, et al. Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. *J Neurosci* 2009;29:14423–14438.
27. Hu B, Yang N, Qiao QC, et al. Roles of the orexin system in central motor control. *Neurosci Biobehav Rev* 2015;49:43–54.
28. Mahoney CE, Agostinelli LJ, Brooks JN, et al. GABAergic neurons of the central amygdala promote cataplexy. *J Neurosci* 2017;37:3995–4006.
29. Oishi Y, Williams RH, Agostinelli L, et al. Role of the medial prefrontal cortex in cataplexy. *J Neurosci* 2013;33:9743–9751.
30. Schwartz S, Ponz A, Poryazova R, et al. Abnormal activity in hypothalamus and amygdala during humour processing in human narcolepsy with cataplexy. *Brain* 2008;131:514–522.
31. Wilson SA. Discussion on narcolepsy. *Proc R Soc Med* 1928;21:1239–1248.
32. Barateau L, Pizza F, Lopez R, et al. Persistence of deep-tendon reflexes during partial cataplexy. *Sleep Med* 2018;45:80–82.
33. Boissard R, Gervasoni D, Schmidt MH, et al. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur J Neurosci* 2002;16:1959–1973.
34. Lu J, Greco MA. Sleep circuitry and the hypnotic mechanism of GABAA drugs. *J Clin Sleep Med* 2006;2:S19–S26.
35. Krenzer M, Anaclet C, Vetrivelan R, et al. Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PLoS ONE* 2011;6:e24998.



36. Dang-Vu TT. Neuroimaging findings in narcolepsy with cataplexy. *Curr Neurol Neurosci Rep* 2013;13:349.
37. Meletti S, Vaudano AE, Pizza F, et al. The brain correlates of laugh and cataplexy in childhood narcolepsy. *J Neurosci* 2015;35:11583–11594.
38. Dauvilliers Y, Comte F, Bayard S, et al. A brain PET study in patients with narcolepsy-cataplexy. *J Neurol Neurosurg Psychiatry* 2010;81:344–348.
39. Hong SB, Tae WS, Joo EY. Cerebral perfusion changes during cataplexy in narcolepsy patients. *Neurology* 2006;66:1747–1749.
40. Pizza F, Franceschini C, Peltola H, et al. Clinical and polysomnographic course of childhood narcolepsy with cataplexy. *Brain* 2013;136:3787–3795.
41. Wang Z, Wu H, Stone WS. Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. *Sleep Med* 2017;25:139–144.
42. Wang Z, Wu H. Body weight changes in early onset narcolepsy: implying compensatory. *Sleep Med* 2017;32:278–279.
43. Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. *Eur J Neurol* 2006;13:1035–1048.
44. Burgess CR, Tse G, Gillis L, Peever JH. Dopaminergic regulation of sleep and cataplexy in a murine model of narcolepsy. *Sleep* 2010;33:1295–1304.
45. Reid MS, Nishino S, Tafti M, et al. Neuropharmacological characterization of basal forebrain cholinergic stimulated cataplexy in narcoleptic canines. *Exp Neurol* 1998;151:89–104.
46. Chandler DJ, Gao WJ, Waterhouse BD. Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proc Natl Acad Sci U S A* 2014;111:6816–6821.
47. Henny P, Jones BE. Projections from basal forebrain to prefrontal cortex comprise cholinergic, GABAergic and glutamatergic inputs to pyramidal cells or interneurons. *Eur J Neurosci* 2008;27:654–670.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Clinical characteristics and sleep study result of the narcoleptic patients.