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Age-related morphological differences in the spike-and-wave complexes of absence epilepsy

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ABSTRACT

Objective: Absence epilepsy shows age-related clinical features, as is observed in childhood and juvenile absence epilepsy. Electroencephalogram (EEG) is characterized by bursts of 3 Hz spike-and-wave complex (SWC). We noticed a morphological variation of the slow-wave component of SWCs between patients. This study investigated whether the waveform of SWC might be associated with the child's age of this epilepsy.
Methods: Digitally-recorded EEGs under medication-free conditions were collected from 25 children who received the diagnosis of childhood or juvenile absence epilepsy. The morphology of slow wave in SWC in the frontal midline region was quantitatively compared between younger and older children using a cluster-based permutation test.
Results: At <7 years of age (2.9–6.5 years of age, n = 6), the electrical potential of the descending slope in the slow wave was positively correlated with age whereas this correlation was not observed in patients of ≥7 years of age (7.1–12.9 years, n = 19). A cluster-based permutation test confirmed the results—among the entire slow wave period (0–285 msec), the period of the descending slope (195–260 msec) showed significantly lower potential in patients of <7 years of age in comparison to patients of ≥7 years of age (sum of *t*-values: 46.57, *p*-value: 0.011).
Conclusions: The current study demonstrated an age-dependent morphological difference in the slow-wave components of SWCs in EEGs of patients with pediatric absence epilepsy. This finding may provide a clue to understanding the age-related clinical manifestations of this epilepsy.

1. Introduction

Absence epilepsy is the most common form of pediatric epilepsy (Berg et al., 2000; Jallon et al., 2001) and is characterized by absence seizures that are generalized, brief, non-motor seizures with impaired awareness (Fisher et al., 2017). Among various epilepsies, childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE) present primarily with absence seizures, and are the established syndromes of genetic generalized epilepsy in the recent classification of the International League Against Epilepsy (Scheffer et al., 2017). During an absence seizure, electroencephalography reveals repetitive discharges of the bilateral synchronous 3 Hz spike-and-wave complex (SWC) with a maximum amplitude in the frontal medial region (Mariani et al., 2011; Nordli et al., 2011).

In clinical practice in our pediatric department, we noticed a morphological variation in the slow-wave component of SWCs across patients with absence epilepsy. Patient age of this epilepsy is related to clinical features, such as seizure frequency, comorbidity of generalized seizures and the prognosis, as is observed in CAE and JAE (Guilhoto, 2017; Tenney and Glauser, 2013). Therefore, we hypothesized that the shape of slow wave may differ with respect to the child's age in absence epilepsy. To test this, we quantified the morphology of the slow wave

Abbreviations: CAE, childhood absence epilepsy; EEG, electroencephalogram; JAE, juvenile absence epilepsy; SWC, spike-and-wave complex.

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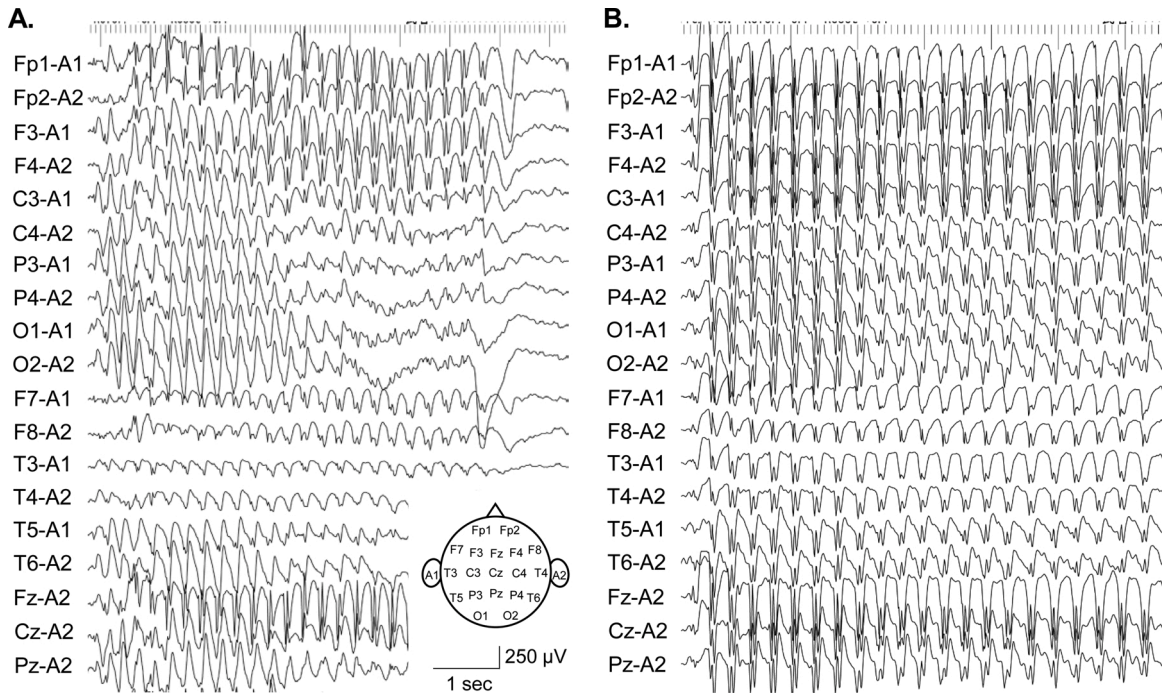

Fig. 1. Bursts of spike-and-wave complexes (SWCs) of a 6-year-old girl (**A**) and an 8-year-old girl (**B**). The slow-wave components are prominent in the frontal midline region and have a differential morphology between the two patients.

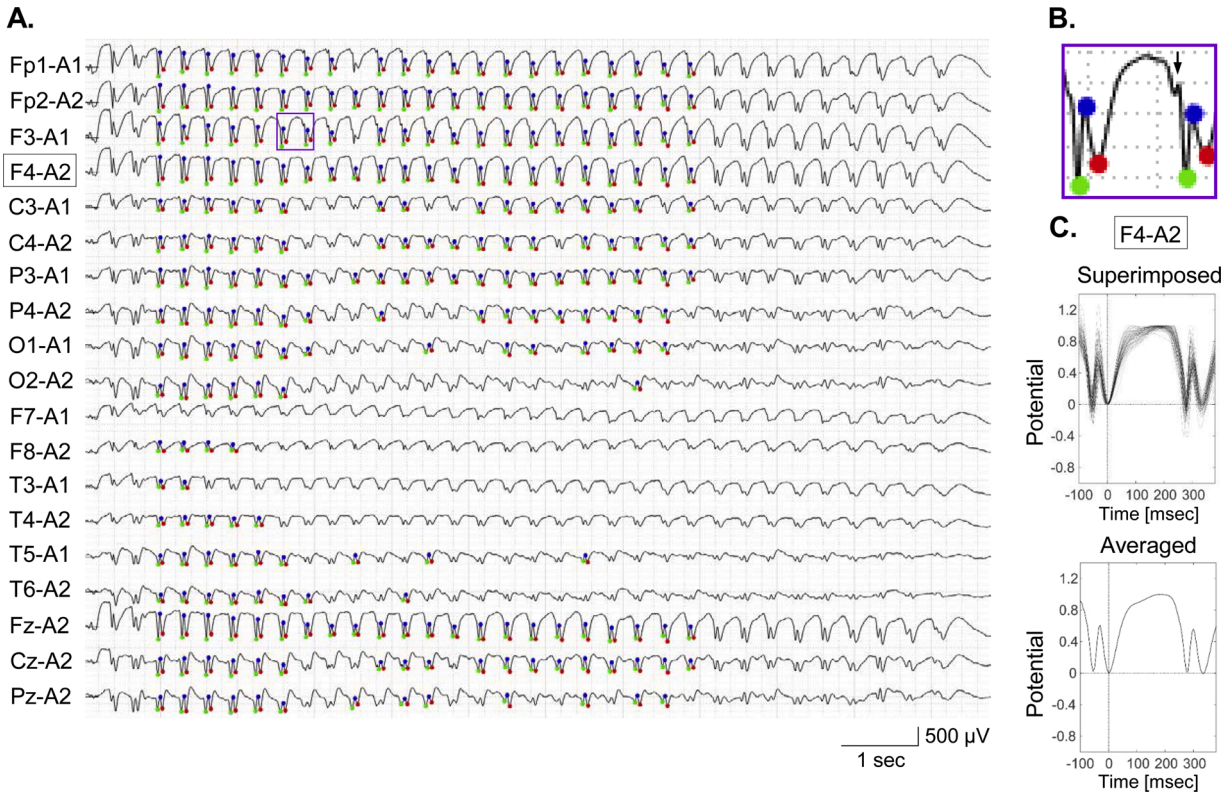

Fig. 2. The same burst in Fig. 1B on the custom MATLAB viewers. **A.** The SWC burst lasts 11.8 s. The MATLAB program identifies three time points in each SWC: the maximum of 'spike 2′ (blue), its preceding (green) and following (red) 'positive transient'. The SWC with the colored trios are eligible for analysis. The initial part (before 0.8 s) and the later part (over 8 s) are removed from the analysis. 'Spike 1′ is occasionally contaminated in the descending slope of the slow wave. **B.** An example of spike 1 is enlarged (arrow). **C.** *Top:* In electrode F4, each standardized SWC is time-locked to the onset of the slow wave (the red point in **A.**) and superimposed. *Bottom:* The standardized waveforms are averaged within the electrode. The potential is standardized and thus has no unit. 'Spike 1′, 'spike 2′ and 'positive transient' come from the terminology of Weir (1965).

using digitally-recorded electroencephalograms (EEGs) of patients with pediatric absence epilepsy.

2. Methods

2.1. Study population

A total of 44 children were consecutively diagnosed with CAE or JAE in the Department of Pediatrics, Kyushu University Hospital during the period of 2001–2018. The diagnoses were based on a recent proposal derived from the Panayiotopoulos's criteria (Guilhoto, 2017). According to the proposal, CAE includes the cases who show the onset age of absence seizures between 2–8 years and have no other types of epileptic seizures in early stages. Similarly, JAE contains the cases who have the onset age from 7 to 16 years and infrequent generalized tonic-clonic seizures. Their demographics, clinical and EEG findings were collected from medical records. Among these patients, we excluded 14 children whose EEGs were recorded under drug use or not saved digitally. We further excluded five children whose EEGs could not be reliably analyzed because of excessive noise (n = 1), insufficient duration of ictal burst (<5 s, n = 1), processing failure (n = 2) or highly fragmented bursts that were observed in a patient with JAE (n = 1). Thus, the remaining 25 patients were included in this study. The present study was approved by the Ethics Committee of the Graduate School of Medical Sciences, Kyushu University (#29−628).

2.2. EEG recording

For clinical purpose, scalp EEGs were recorded using a digital electroencephalography system (Neurofax series: EEG-1500 and -1200, Nihon Kohden, Japan) with the sampling frequencies of 200 and 500 Hz, high-cut filters of 60 and 120 Hz, and the time constants of 2 and 10 s, respectively. Electrodes were placed at the 19 scalp sites (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz), referenced to the ipsilateral ears (A1 or A2), with ground electrode at Fpz, according to the International 10–20 system. Electrode impedance was kept below 10 kΩ during recordings. The view settings were as follows: high-cut filter, 60 Hz; and time constant, 0.3 s. Fig. 1 shows representative SWC bursts of two patients on a Nihon Kohden Neurofax viewer in this setting.

2.3. EEG analysis

By means of the European Data Format (Kemp et al., 1992) and EEGLAB (Delorme and Makeig, 2004), recorded EEG data were extracted as time-series electrical potentials of the 19 channels with the above-noted EEG view settings. Data processing was performed in each patient using custom-designed scripts and graphical interfaces in MATLAB (MathWorks, USA). The data recorded at 500 Hz were resampled to 200 Hz.

We previewed EEG waveforms that included bursts of 2.5–4 Hz SWCs (Fig. 2A) and identified the onset and end of the bursts and then calculated the duration. The SWC contains subtle constituents such as small negative spikes, corresponding to 'spike 1′ in Weir's terminology (Weir, 1965) (Fig. 2B). We manually removed EEG data that contained noise, body and eye movements or drifting in each electrode by visual inspection. Further, we removed EEG data of the initial (0 to 0.5–2 s) and later parts (>8 s), in which the waveforms were unstable and inconsistent, as has been shown (Nordli et al., 2011). The slow-wave component with sufficient amplitudes was consistently observed in the frontal midline region but not always in other regions, as reported previously (Holmes et al., 2004; Lemieux and Blume, 1986; Seneviratne et al., 2016). Additionally, the waveforms in the frontopolar region (Fp1 and Fp2) often contained noises from the forehead. Therefore, our analysis was confined to the data of the three frontal electrodes (F3, F4 and Fz).

Table 1
Clinical characteristics of the patients with childhood or juvenile absence epilepsy.

	All patients (n = 25)	<7 years[#] (n = 6)	≥7 years[#] (n = 19)	*P*-value	Effect size (*phi*, *r*)
Juvenile absence epilepsy (%)[†]	4 (16 %)	0 (0%)	4 (21 %)	0.540	0.25
Female (%)[†]	19 (76 %)	4 (67 %)	15 (79 %)	0.606	0.12
Age at onset, year (median [range])[¶]	7 [2–12]	4.5 [2–6]	7 [6–12]	$<1 \times 10^{-4}$	0.70
Generalized seizure (%)[†]	2 (8%)	0 (0%)	2 (11 %)	1.000	0.17
ID and/or DD (%)[†]	5 (20 %)	3 (50 %)	2 (11 %)	0.070	0.42
Control with AEDs (%)[†]	24/24 (100 %)	6/6 (100 %)	18/18 (100 %)	–	–
Successful discontinuation of AEDs (%)[†]	13/16 (81 %)	1/2 (50 %)	12/14 (86 %)	0.350	0.30
Observation period, year (median [range])[¶]	6.3 [0–14.2]	7.3 [5.7–11.6]	6.1 [0–14.2]	0.246	0.24

[#] The groups were categorized by the age at EEG monitoring.
[†] Fisher's exact test.
[¶] Mann-Whitney *U* test. Abbreviations: AED, antiepileptic drug; DD, developmental disorders; ID, intellectual disabilities.

In each electrode, we fractionated a burst into each SWC. The amplitude and frequency of SWCs varied during a burst within a given patient and between different patients. Thus, in order to statistically

Table 2
EEG characteristics.

	All patients (n = 25)	<7 years[#] (n = 6)	≥7 years[#] (n = 19)	*P*-value	Effect size (*phi*, *r*)
Age at EEG monitoring, year (median [range])[¶]	8.4 [2.9–12.9]	5.7 [2.9–6.5]	9.1 [7.1–12.9]	$<1 \times 10^{-4}$	0.73
Counts of analyzed SWC bursts per patient (mean [SD])[§]	3.6 [2.3]	2.8 [1.5]	3.8 [2.5]	0.384	0.18
Duration of SWC burst, sec (mean [SD])[§]	13.7 [4.8]	16.6 [5.8]	12.8 [4.3]	0.092	0.34
Patients with a duration of SWC burst less than 8 s (%)[†]	2 (8%)	0 (0%)	2 (11 %)	1.000	0.17
Counts of analyzed SWCs per patient (mean [SD])[§]	125.4 [110.7]	106.2 [82.6]	131.5 [119.5]	0.635	0.10
Original amplitude of slow wave in SWC, μV (mean [SD])[§]	623.7 [174.3]	606.3 [164.9]	629.2 [181.2]	0.785	0.06
Original frequency of SWC, Hz (mean [SD])[§]	3.03 [0.18]	2.95 [0.13]	3.05 [0.19]	0.235	0.25

[#] The groups were categorized by the age at EEG monitoring.
[¶] Mann-Whitney *U* test.
[§] *t*-test.
[†] Fisher's exact test. Abbreviations: EEG, electroencephalograpjy; SD, standard deviation; SWC, spike-and-wave complex.

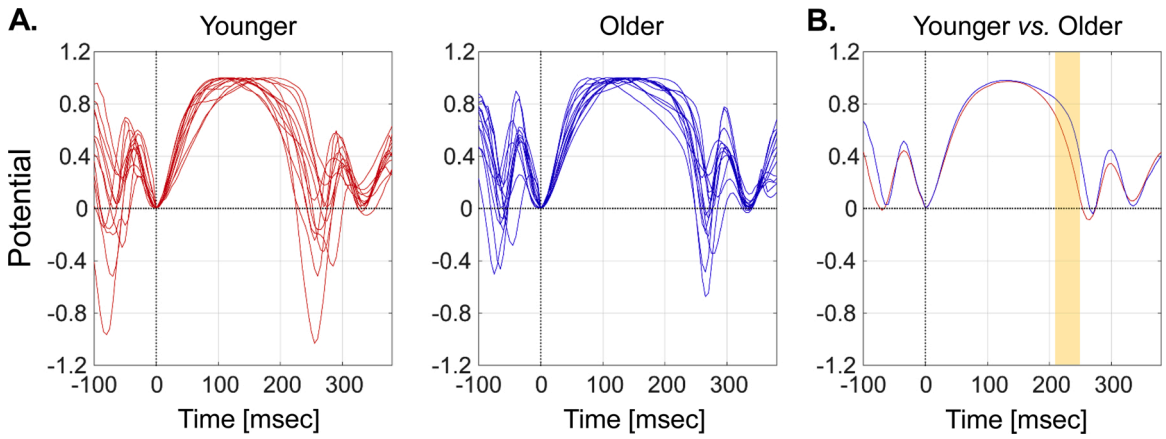

Fig. 3. Comparison of the waveform between the younger (red, n = 12) and older (blue, n = 13) groups. **A.** Waveforms averaged across F3, F4 and Fz are shown in individual patients. **B.** The averaged waveforms are further averaged in the younger and older groups. The orange bar indicates a marginally significant temporal cluster of 210–250 msec in the difference between the two groups. The potential has no unit.

analyze the morphology of slow wave, we standardized the waveform of each SWC: the frequency of the SWC was resampled to 3 Hz and the amplitude of the slow-wave component was adjusted with a maximum of 1 (Fig. 2C). Within an electrode, we averaged the standardized waveforms, time-locked to the onset of the slow wave and further averaged these data across the three frontal electrodes. These averaging procedures made the waveform smooth with the disappearance of the components of spike 1.

Statistical differences in the potential of the processed slow wave between different age groups were tested by means of a cluster-based permutation test (Groppe et al., 2011; Maris and Oostenveld, 2007) using FieldTrip toolbox (Oostenveld et al., 2011) on MATLAB. The test was performed between the onset (0 msec) and the end (285 msec) of the slow wave. The cluster threshold was set to 0.05 in *t*-test and the false alarm rate was 0.05 in a two-tailed permutation test with 5000 repetitions.

3. Results

3.1. Clinical characteristics of the patients

The demographics and clinical characteristics are shown in Table 1. We analyzed a total of 25 patients—21 patients with CAE and 4 patients with JAE. The age at onset of absence seizures recollected by parents at the diagnosis, which could be ambiguous, ranged from 2 to 12 years of age (median: 7 years); however, the majority (n = 21) were ≤8 years of age. The phenotypes of two patients in whom the onset was before 4 years of age (2 and 3 years) met the criteria for childhood absence epilepsy, as reported previously (Shahar et al., 2007; Verrotti et al., 2011). In all patients, with the exception of one who dropped out just after the diagnosis, absence seizures were well controlled with antiepileptic drugs, which were successfully discontinued in 81 % of the patients within the average observation period of 6.3 years.

3.2. EEG findings

EEGs were monitored at various timings from immediately after to 6 years after the onset of absence seizures (median age, 8.4 years [range, 2.9–12.9 years], Table 2). On average, we analyzed 3.6 bursts with the duration of 13.7 s per patient. The mean durations of SWC burst were sufficiently long (≥ 8 s) in majority of the patients while those in two were shorter (6.4 s and 6.9 s). To obtain an overview of the trends in morphological differences associated with age, we preliminarily divided the 25 participants into a younger group (n = 12; age, 2.9–8.1 years) and an older group (n = 13; age, 8.4–12.9 years) according to the age at EEG monitoring. The processed waveforms of the frontal midline region in each patient were provided separately for the younger and older groups (Fig. 3). Overall, the descending slope of the slow wave seemed to decay more rapidly in the younger group in comparison to older group. A cluster-based permutation test revealed that the younger group had marginally lower EEG potentials with a temporal cluster of 210–250 msec in comparison to the older group (the sum of the *t*-values: 21.71, *p*-value: 0.060).

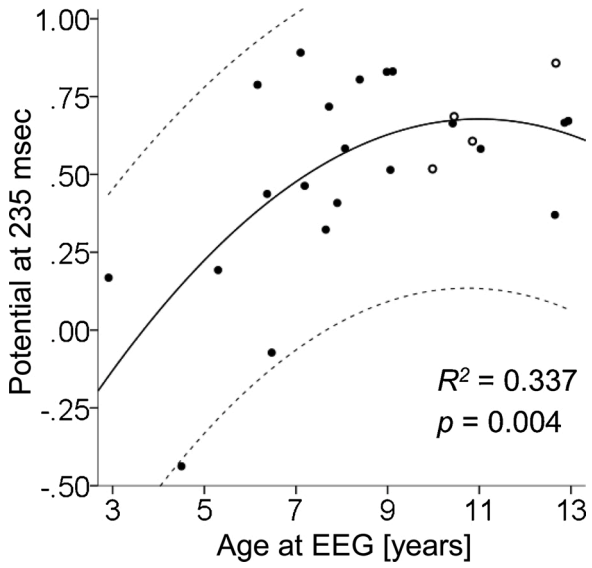

Fig. 4. A scatter diagram between the patient's age and the processed potential at 235 msec from the onset of slow wave. A quadratic regression curve (solid line) and 95 % prediction intervals (dashed lines) are shown in the diagram. Closed and open circles indicate CAE and JAE patients, respectively. The potential has no unit.

To examine whether the child's age and the EEG potentials of the descending slope were correlated linearly or not, we drew a scatter plot of age *vs.* the processed potential at the time (235 msec) of the maximum *t*-value (2.585) among the abovementioned clusters (Fig. 4). The potential was positively correlated with age <7 years, but reached a plateau thereafter. All JAE patients were ≥7 years of age and their potentials were as high as those on the EEGs of CAE patients of ≥7 years of age. A quadratic polynomial regression model fitted to the data with statistical significance (adjusted $R^2 = 0.337$, *F*-value = 7.094, *p*-value = 0.004).

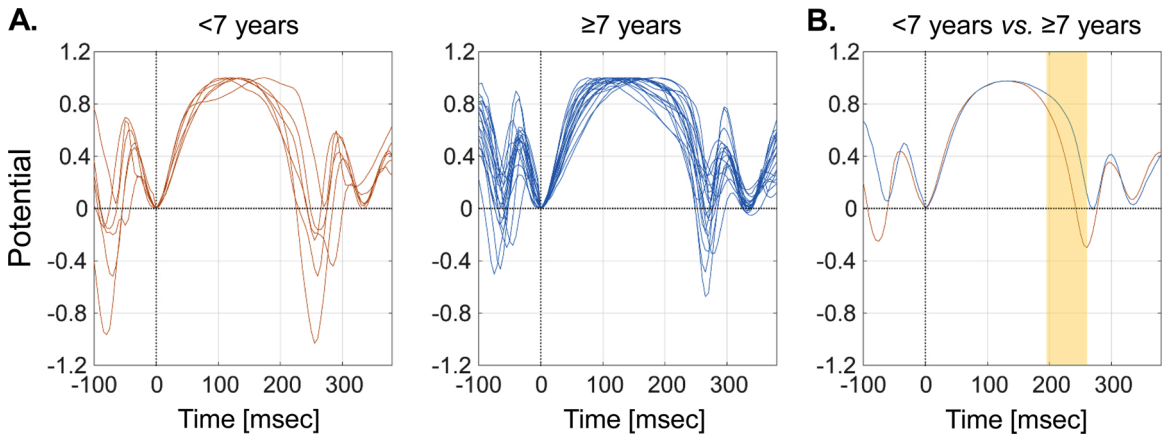

Fig. 5. Comparison of the waveforms between patients of <7 years of age (chocolate, n = 6) and patients ≥7 years of age (navy blue, n = 19). **A.** Waveforms averaged across F3, F4 and Fz are shown in individual patients. **B.** The averaged waveforms are further averaged in each of the groups. The orange bar indicates a significant temporal cluster of 195–260 msec in the difference between the groups. The potential has no unit.

Based on this result, we categorized the children into 6 patients of <7 years of age (2.9–6.5 years old) and 19 patients of ≥7 years of age (7.1–12.9 years). Another cluster-based permutation test demonstrated that the patients of <7 years of age had significantly lower EEG potentials with a temporal cluster of 195–260 msec in comparison to those of ≥7 years of age (sum of *t*-values: 46.57, *p*-value: 0.011, Fig. 5). Between the two groups, there were no significant differences in the clinical and other EEG characteristics including the number of patients with a duration of SWC burst less than 8 s, the counts of analyzed SWCs per patient, the original amplitude of slow wave in SWC, and the original frequency of SWC (Tables 1 and 2).

4. Discussion

The present study quantitatively analyzed the waveform of slow waves in SWCs in children with absence epilepsy and found that the shape of the descending slope showed a significant difference according to age. At <7 years of age, the younger the patient, the more rapidly the slope decayed; however, this correlation was not observed in older patients. To the best of our knowledge, this is the first time that an age-related morphological difference in SWCs has been reported in human absence epilepsy. This subtle difference might have been unrecognized because of the enormous amplitudes of SWCs on conventional EEG viewers.

The neurobiology of the age-dependent morphological difference in the slow wave is uncertain. Animal and human studies have attributed the repetitive discharges of SWC to the interaction between the cortex and thalamus, demonstrating the strong contribution of a local cortical zone as the initiator and rhythm generator of the discharges as well as the role of the thalamus as a relevant resonator for the maintenance (Luttjohann and van Luijtelaar, 2015; Meeren et al., 2002; Polack et al., 2007; Westmijse and Ossenblok, 2009). Similar to childhood changes in background activity and epileptiform discharges (Aanestad et al., 2020; Petersen and Eeg-Olofsson, 1971; Riviello et al., 2011), this paroxysmal activity of absence epilepsy may change as individuals age, reflecting the maturational process of the developing brain. Such morphological changes are also observed in developmental epileptic encephalopathies (*e.g.*, transition from West syndrome to Lennox-Gastaut syndrome) (Calvo et al., 2020; Kotagal, 1995) although the change appears much more trivial in absence epilepsy.

Unfortunately, there was a considerable time interval between the seizure onset and EEG monitoring in several cases. Absence seizures can be noticed early but are often not recognized as seizures for a long time because they are usually brief and the patient does not exhibit apparent motor symptoms. These characteristics often delay hospital visits and EEG monitoring. Within a patient, in our study, the EEG waveform might change during the interval. Thus, the time interval as well as the insufficient number of JAE patients precluded a justifiable comparison between CAE and JAE. A larger number of EEGs monitored just after the seizure onset would be needed to clarify whether the types of absence epilepsy are associated with the EEG morphology.

Several decades ago, a few studies quantitatively analyzed the paroxysmal discharges associated with the diagnosis and severity of childhood epilepsy with centrotemporal spikes (Frost et al., 1992; van der Meij et al., 1993; Wong et al., 1988). All of these studies focused on the peak/bottom points of the spike and/or slow wave and calculated the amplitude, duration and their derivatives, yielding inconsistent results. The present study used the computerized systematic quantification of digitally-recorded EEG to examine the entire waveform of the slow wave and found an age-related difference. The clinical implications of this result are currently unclear but would be revealed by further electrophysiological and neuropharmacological investigations in the animal and human brain.

The present study was associated with some limitations. First, the number of cases was relatively small after the rigorous selection of patients who fulfilled both the strict diagnostic criteria and who were in a medication-free condition in our tertiary university hospital. Second, subtle EEG constituents were missed in our analysis regarding the averaged waveforms. For instance, spike 1 was often mixed in the descending slope of a slow wave (Fig. 2B), as reported previously (Weir, 1965). However, this occurred at variable times and thus disappeared in the averaging procedures. Such constituents could—to some extent—influence the morphology of the slow wave. Third, the main result of the morphological difference between groups might be compromised by our methodology of analysis—the resampling of the SWC to 3 Hz and the extraction of differential duration of SWC bursts. However, there were no significant intergroup differences in the original frequency of SWC and the number of patients who had shorter durations, suggesting the limited effects on the result. Finally, this cross-sectional study showed a difference between different age groups but not age-dependent longitudinal trajectories. During the follow-up time, we could not obtain medication-free EEGs because we always administered antiepileptic drugs after the diagnosis of this epilepsy.

In conclusion, the current study demonstrated that absence epilepsy patients of <7 years of age are more likely to show a rapid decay of the slow wave in the SWC, in comparison to older patients. Although its neurobiology and clinical significance remain unclear, this finding may provide a clue to understanding the age-related clinical manifestations of this epilepsy. Such a quantitative morphological analysis might be similarly useful for elucidating the pathophysiological mechanisms of

various epileptic syndromes.

Declaration of competing interest

None.

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