



Symmetry and interhemispheric propagation of paediatric photoparoxysmal response

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ABSTRACT

Aim of the study. To investigate the speculated interhemispheric symmetry and the pattern of propagation of paediatric photoparoxysmal response.

Clinical rationale for the study. Quantitative analysis of the photoparoxysmal response (PPR) to intermittent photic stimulation is a promising method of assessing photosensitivity (PS). The pattern of PPR propagation underlies the model used for calculations. The generalisation of a discharge should correspond with the parameters objectively characterising the PPR in both cerebral hemispheres. However, to date no evidence of a postulated symmetry has been demonstrated.

Materials and methods. Our analysis was performed by comparing the EEG amplitude and interhemispheric coherence (ICoh) in both hemispheres in 100 non-epileptic individuals of both sexes, aged 5–18 years, with PS grade IV (the PPR group) and without PS (the control group). The amplitude and ICoh values were recorded and analysed statistically.

Results. The distribution of amplitude values between the hemispheres was comparable in both groups, but was significantly different between the PPR group and the control group. Individual tracks of propagation revealed hemispheric symmetry. Interhemispheric coherence values were significantly higher in occipital, temporal and fronto-polar areas in children with PS.

Conclusions and clinical implications. This study provides objective evidence of interhemispheric symmetry in paediatric PPR, which supports the link with generalised seizures. Interhemispheric propagation is facilitated in children with PS, and propagation is more likely in the occipital and temporal regions.

Key words: photoparoxysmal response, photosensitivity, interhemispheric symmetry, interhemispheric coherence

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Introduction

The issue of hemispheric symmetry of the photoparoxysmal response (PPR) has not been raised so far in neurological and epileptological literature. To date, understanding of the neurophysiological mechanism of photosensitivity (PS) has focused on the extent of discharge propagation towards frontal lobes, on which the only recognised classification of this phenomenon is still based [1].

Our previous study [2] drew attention to the internal differentiation of the route from the occipital to frontal areas, not disparaging the Waltz classification, but adding a quantitative

element to the pattern of the propagation within the hemisphere. The PPR, like other pathological discharges, reveals some predilection for a particular pathway, which probably has an anatomical or functional background [3, 4]. This raises the question as to whether similar conditions may affect the generalisation of a discharge or the propagation of the PPR between the hemispheres.

Interhemispheric coherence (ICoh) indices could answer this question indirectly. High coherence values characterise all the areas of well-developed connections [5, 6]. While ICoh does not explain the phenomenon of the generalisation of a discharge between the hemispheres, it can still give an

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indication if such propagation is possible. Therefore, coherence indices have been found to be useful in explaining the pathophysiology of certain neurological diseases such as dementia and Alzheimer's Disease [7].

Clinical rationale for the study

Recent concepts of visual cortex hyperexcitability as a primary generator of PPR [8] support the clinical observation that, once generated, the discharge is transmitted symmetrically in both hemispheres, although so far no electroencephalographic characteristic of this phenomenon has come to light. Additionally, in a standard EEG study, the visual assessment of bilateral response (discharge recorded in leads from both hemispheres) does not establish whether the response to intermittent photic stimulation (IPS) has the same power in each hemisphere.

Power spectra and coherence values have been studied in certain neurological entities [9, 10], but to date not a single description has concerned PPR. In our previous paper [2], several differences in amplitude values over left and right hemispheres were recorded, but none of the possible associations of that observation could have been matched to the purpose of that work.

The goal of the present study was to investigate whether the response to IPS is quantitatively comparable in both cerebral hemispheres, and whether there are significant differences in interhemispheric coherence values which might indicate a facilitated propagation between the hemispheres in photosensitive children.

Material and methods

The study was performed on anonymised EEG records of paediatric patients suffering from frequent episodic tension-type headache (type 2.2.2 according to ICHD-3 [11], not associated with pericranial tenderness) who were for this reason diagnosed at the EEG Laboratory of the Bogdanowicz Memorial Hospital for Children in Warsaw, Poland. Parents or legal guardians consented to the study. The study protocol was approved by the local Bioethics Committee.

Inclusion and exclusion criteria

The inclusion criteria for the studied (PPR) group were as follows: age ≤ 18 years and a PPR following IPS in EEG (photosensitivity). In all examined patients, a medical imaging (CT or MRI) of the head was performed prior to the EEG. EEG examinations were evaluated by two independent investigators. Patients with positive imaging studies, other types of headaches, recognised epilepsy or other EEG abnormalities, patients after head injury or brain surgery, and patients already receiving neurological treatment for other reasons, were all excluded from the study.

Initially, 68 patients met the design criteria but, in order to standardise the analysis, 50 patients with the most common grade of PS (grade IV, according to Waltz) were enrolled, and 18 patients with PS grades I-III were excluded. The control group included children from the same population, meeting the same inclusion and exclusion criteria as the PPR group, but with no PS evident in EEG.

Material

Finally, 100 patients were enrolled into two groups of 50 patients each. The PPR group consisted of children with PS grade IV (Waltz). There were 14 boys (28%) and 36 girls (72%). The average age was 11.8 ± 3.9 years (range 5–18 years).

The control group included children without PS: 20 boys (40%) and 30 girls (60%) of a mean age of 14.2 ± 2.6 years (range 8–18).

Method

EEG was carried out using an Elmico EEG DigiTrack v.10 device according to an international 10–20 protocol [12]. The signal was recorded with 19 leads. The IPS was performed in the final part of the EEG, before hyperventilation, according to the 2012 European consensus on IPS guidelines [13].

For every patient, the artifact-free epoch of 2 seconds' duration including IPS was selected. The amplitude and interhemispheric coherence (ICoh) were calculated by EEG software. Power spectra for each lead were obtained with the Fast Fourier Transformation algorithm. The amplitudes were measured at 8 points for each hemisphere: O1, P3, T5, C3, T3, F3, F7, and Fp1 for the left side, and O2, P4, T6, C4, T4, F4, F8, and Fp2 for the right side. The ICoh was given by the equation: $ICoh = (S_{xy})^2 / (S_{xx} \times S_{yy})$, where S_{xy} , S_{xx} and S_{yy} were cross-spectrum estimates of leads x and y, respectively. Coherence indices were computed for 12 interhemispheric electrode pairs: O1–O2; P3–P4; C3–C4; F3–F4; T5–T6; T3–T4; F7–F8; and Fp1–Fp2. The amplitude and ICoh values were then registered in the study database.

In PS patients, an individual pattern of PPR propagation was established for every patient, according to the protocol described in our previous paper [2]. The PPR propagation pattern was based on amplitudes and characterised dominant tracks in the left and right cerebral hemispheres. Subsequently, the PPR group was divided into two subgroups: those with symmetric (the same in each hemisphere) tracks and those with asymmetric tracks.

Concept of the study

We designed a case-control study with two areas of interest. In the first, we attempted to directly compare the values of maximal discharge (measured by a maximal amplitude) between symmetric (respective) leads in the left and right cerebral hemispheres. This part of the analysis was implemented in both groups (PPR and control). We attempted to compare

the whole hemisphere to the other, with no regard to the dominant track in each. We tried to answer the question of comparability of the power of discharge in each hemisphere, and the significance of possible differences in amplitude and interhemispheric coherence values between the PPR group and the control.

The second area of interest aimed at a direct comparison of dominant tracks between the hemispheres. This was performed only in the PPR group. As each hemisphere was characterised by a different track, we designed two arms of this part of the study: 1) a comparison of symmetric dominant tracks; and 2) a comparison of asymmetric dominant tracks.

Statistical analysis

The results were analysed statistically using StatSoft Statistica 13.1 PL software. The normality was evaluated with Shapiro-Wilk test. The amplitude and ICoh values were compared among designed groups with respect to the side. The use of parametric and non-parametric tests is specified in the Results section below. We assumed a significance level at $p < 0.05$.

Results

Comparison of PPR amplitude between cerebral hemispheres

The distribution of amplitude values between the pairs of respective leads in both groups was comparable. In the PPR group, the highest values were observed in the rear leads (occipital (O1/O2), posterior temporal (T5/T6) and parietal (P3/P4)), but no significant difference was found between the left and right sides. Statistical analysis revealed that the amplitude values between symmetric leads were not significantly different (Mann-Whitney U-test; $p > 0.05$). The average amplitude values of every lead are presented in Tab. 1. In the control group, a symmetric distribution of amplitude values between the left and right sides was also observed, and no significant difference between the leads was noted. The distribution of

amplitude values in all leads for the PPR group and the control group is set out in Figure 1.

Comparison of PPR amplitude between PPR group and control group

The discharge values in the PPR group were significantly higher than in the control (U-test; $p < 0.05$) in all leads. The highest differences were noted in occipital, parietal and temporal leads. There was no significant difference among amplitude values in children without PS. The difference in values between the two groups can be best observed when comparing two extreme tracks: the most lateral (4L) and the most medial (4M) (Fig. 2A–B).

Comparison of ICoh values between PPR group and control group

Interhemispheric coherence values were significantly higher in occipital, temporal and fronto-polar areas in PS-affected children (U-test for O1–O2 and Fp1–Fp2; t-Student test for remaining pairs; $p < 0.05$). On the other hand, the ICoh values were significantly higher in the central region in the control group (t-Student test; $p < 0.05$). The ICoh indices in the parietal and frontal regions were of comparable value in both groups (Tab. 2).

Comparison of dominant tracks

In this part of the analysis, the PPR group was divided into two subgroups: patients with symmetric dominant tracks ($n = 24$, 48% of the PPR group), and patients with asymmetric dominant tracks ($n = 26$; 52% of the PPR group). The dominance of tracks was established using the method described in our previous paper [2]. Every lead at the course of a discharge was analysed and compared to the respective contralateral one. There were five leads on the route of a discharge: we numbered them from 1 to 5. Since every discharge started from the occipital region to reach the frontal pole areas, number 1 always corresponded to occipital leads (O), and number 5 always corresponded to fronto-polar leads (Fp). Numbers 2–4 had no

Table 1. Average amplitude values in left and right hemispheric leads in PPR and control groups

		PPR group						
Left hemisphere	O1	P3	C3	F3	Fp1	T5	T3	F7
[μ V]	170.24	113.55	83.81	67.11	71.39	140.28	101.86	81.63
Right hemisphere	O2	P4	C4	F4	Fp2	T6	T4	F8
[μ V]	164.66	120.16	86.88	68.94	73.45	140.46	111.67	92.23
		Control group						
Left hemisphere	O1	P3	C3	F3	Fp1	T5	T3	F7
[μ V]	14.71	13.48	13.56	12.12	10.36	15.18	14.39	14.51
Right hemisphere	O2	P4	C4	F4	Fp2	T6	T4	F8
[μ V]	16.21	12.86	13.06	12.02	11.06	14.91	13.50	13.09

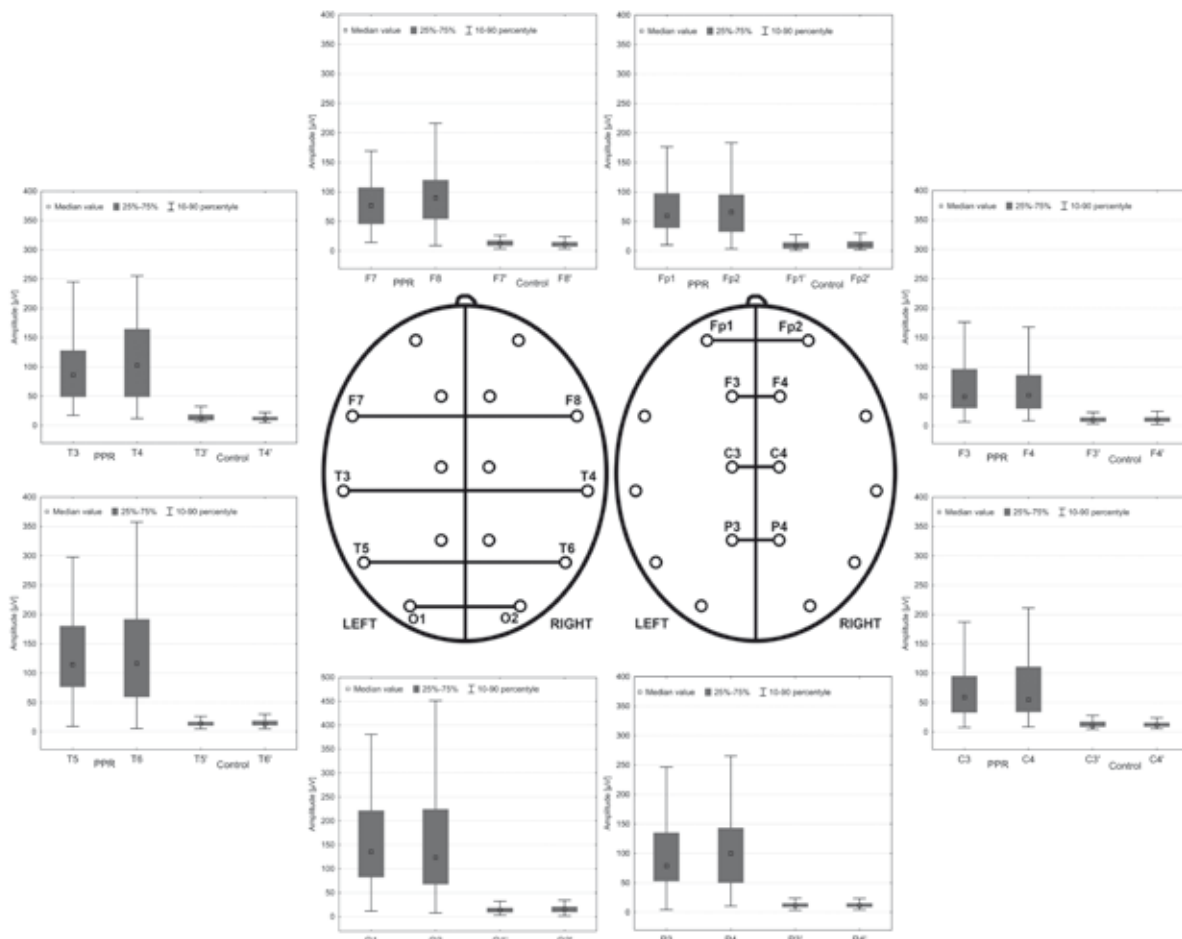


Figure 1. Distribution of amplitude values in PPR and control groups; PPR – photoparoxysmal response

Table 2. Values of interhemispheric coherence (ICoh) in PPR and control groups

ICoh	PPR group	Control group	p-value
O1–O2	0.8057	0.6973	0.00007 (U-test)
P3–P4	0.7221	0.7298	0.71394 (t-test)
C3–C4	0.6771	0.7489	0.00031 (t-test)
F3–F4	0.6606	0.7070	0.06085 (t-test)
T5–T6	0.7223	0.6452	0.00026 (t-test)
T3–T4	0.6787	0.6313	0.01533 (t-test)
F7–F8	0.6719	0.6387	0.13145 (t-test)
Fp1–Fp2	0.7104	0.6616	0.02270 (U-test)

specific lead assigned, as in every case these numbers could be matched to different areas.

In the subgroup of symmetric dominant tracks, no specific differences were found between the hemispheres (U-test for all pairs except the fourth; $p < 0.05$). This proved quantitative hemispheric symmetry. Median values of amplitudes on the

left side tended to be slightly lower than on the right, but no statistical significance was found (Fig. 2C).

The symmetry between the hemispheres was also confirmed quantitatively in the subgroup of patients characterised by asymmetric dominant tracks (U-test for all pairs except the fourth; $p < 0.05$). In these patients, no hemispheric tendencies were noted (Fig. 2D).

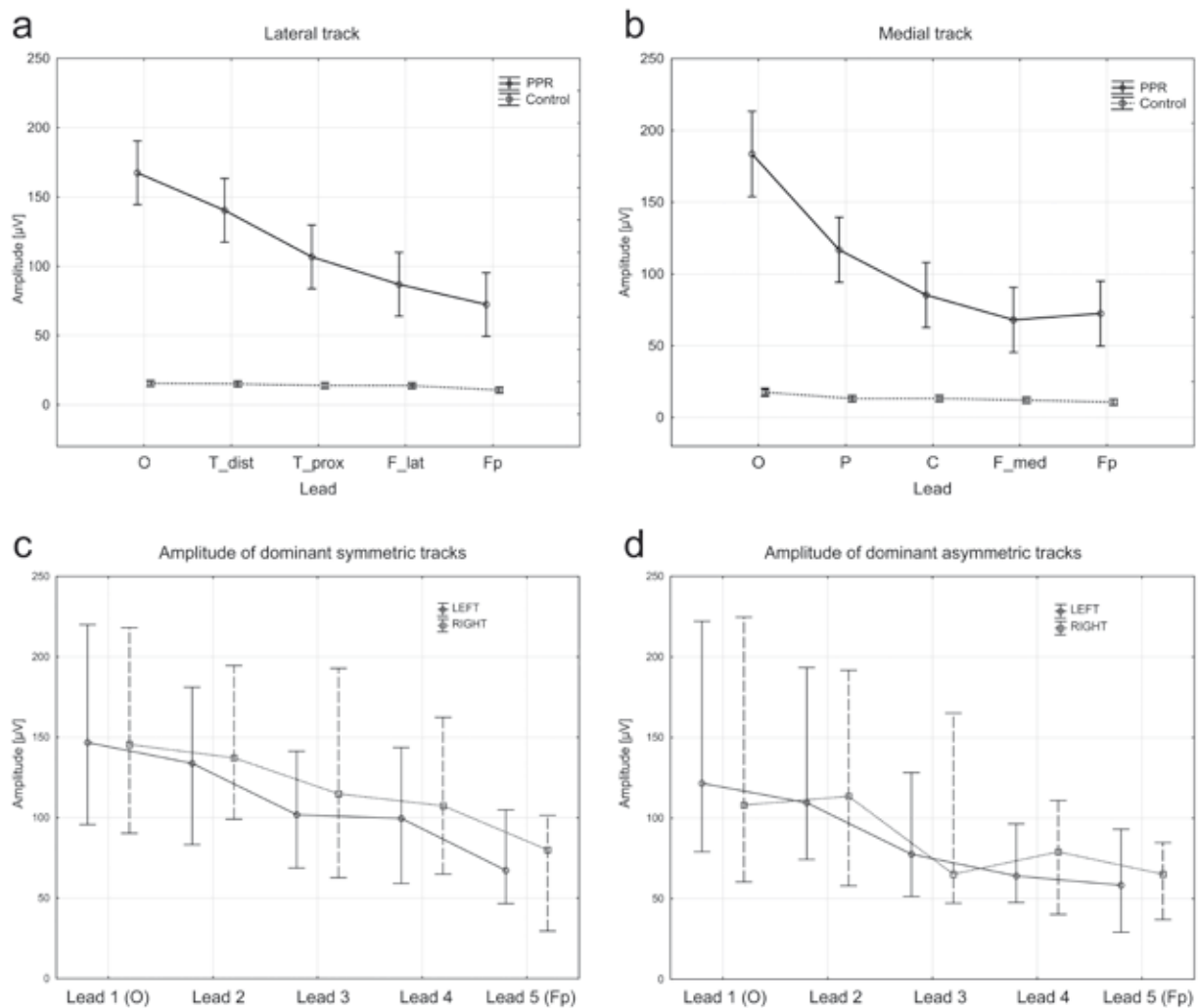


Figure 2. Amplitude in the most lateral (A) and the most medial (B) tracks in PPR and control groups (median and interquartile range); Amplitude of symmetric (C) and asymmetric (D) dominant tracks in the PPR group (median and interquartile range); O – occipital lead (O1 or O2); T_dist – distal temporal lead (T5 or T6); T_prox – proximal temporal lead (T3 or T4); F_lat – lateral frontal lead (F7 or F8); P – parietal lead (P3 or P4); C – central lead (C3 or C4); F_med – medial frontal lead (F3 or F4); Fp – fronto-polar lead (Fp1 or Fp2)

Discussion

Methodology and limitations

Hemispheric symmetry of the PPR has not been quantitatively defined in the neurological literature. To date, no convincing model of the generalisation of PPR has been proposed, despite several attempts to implement the PPR into the model of generalised and focal seizures [14–17]. From a clinical point of view, it seems important to establish a link between the PPR and a pattern of photosensitive epilepsy; however, to date only a few papers have referred to the background of PPR and the mechanisms of its propagation [3, 4, 16, 17]. Although bilateral spread of PPR is usually observed in the EEG, and PS grade IV has been categorised as a model for generalised seizures, the literature lacks quantitative analysis of this phenomenon.

While our previous paper considered possible pathways of propagation of the PPR within one hemisphere [2], in the present

study we have focused on a direct comparison of the response to IPS in both cerebral hemispheres. For the purpose of analysis, we adopted the hypothesis that the discharge begins in occipital areas and usually spreads forwards. This assumption is supported by other papers pointing to the hyperexcitability of the visual cortex as a primary generator of the PS [18, 19]. Structural data also sheds light on the potential facility of the PPR to propagate from the occipital to fronto-polar regions [3, 4] and between other areas including interhemispheric pathways [20, 21].

Our analysis includes a simultaneous comparison of the maximal amplitude values recorded in all leads. This approach allowed for investigation of the potential lateralisation or theoretical hemispheric preference, with no regard to the electrophysiological track revealed by the quantitative EEG analysis. Although necessary for analysis, this approach has, in our opinion, a substantial limitation because it does not specifically characterise the PPR.

Taking this into consideration, in the second part of the study we adapted a simplified linear model of the PPR and based its characteristic on five points, representing areas from occipital to fronto-polar regions. This model may be another limitation of this study, as the possibility of various types and pathways of excitation has been postulated in other papers [22]. However, unlike experimental works, our study was performed in the course of standard neurological diagnostics, suitable to be carried out with the use of devices available in most EEG laboratories. This allows simple models to be repeatedly validated in other institutions.

The inequality of age subgroups between the PPR and the control groups may be considered another limitation of our study. It is established that PS more often concerns girls than boys under the age of 10 [23], which corresponds with our studied group. The prevalence of boys aged 11–14 in the control group did not closely match the PPR group, and therefore we decided not to analyse directly the age subgroups, focusing rather on the results as a whole. In this study, neither did we analyse such clinical data as a child's left- or right-handedness, recognising that its impact on PS remains undefined [24].

Results discussion

The results of our analysis objectively confirmed the theory of symmetric propagation of the PPR in both cerebral hemispheres. Despite the specific origin, a discharge attains the same amplitude on both sides, regardless of the intra-hemispheric track it spreads towards fronto-polar areas. This observation seems to support the thesis that the quantitative nature of the PPR is different from that observed in focal epilepsy, which every time originates in a well-defined area [3]. The amplitude of the PPR in our study revealed a repeatable and consistent symmetry between the sides, something which has already been declared typical for models of generalised seizures [25]. In our opinion, this finding underlines the concept of functional generalisation but does not explain the mechanism of bilateral spread of the PPR.

A structural insight might possibly add certain missing data on the local connectivity and its relation to interhemispheric pathways of neuronal activation. Recent studies on the topographical distribution of EEG activity in response to photic stimulation have revealed that provocative stimulus leads to cortical synchronisation of many neurons [26]. This synchronisation begins in the visual cortex, corresponding with areas where alpha activity is recorded in EEG [27]. In a healthy brain, at the beginning of IPS, the beta and gamma synchronisation suddenly rises for about one second and disintegrates immediately thereafter. In a photosensitive brain, the disintegration of synchronisation is much slower [28], enabling the neuronal activation to be expanded to other brain areas, as reviewed by Singer [29].

Despite various attempts to propose a convincing model, an increase in connectivity typically encountered across PS-affected patients has been demonstrated mainly in

occipito-temporal regions [30]. Our study seems to support this finding, given that the amplitude of the PPR in our population was the highest precisely in the occipital and temporal regions. Further evidence comes from analysis of the inter-hemispheric coherence indices. This indirect determinant of brain connectivity rises in the regions where neuronal activation takes advantage over remaining cortical areas. ICoh values differ significantly between the PS group and the control in the rear, lateral, fronto-polar and central leads. This finding seems to suggest that an interhemispheric propagation in PS patients may be facilitated in the regions where ICoh values were significantly higher. In contrast, significantly higher ICoh values in central regions in the control group may reflect a normal pattern of callosal interhemispheric conduction and may highlight a preference for other directions in PS-affected individuals.

In the course of our analysis, in addition to comparing the amplitudes alone, we also aimed to assess the power of the real PPR in each hemisphere, represented by the dominant track. This evaluation was designed to assess if and/or how the symmetry of dominant pathways is associated with hemispheric symmetry in response to IPS. This aspect of the PPR has not been studied previously, and is an important part of this work.

Individual PPR patterns showed that the PPR group was divided almost equally between patients with identical tracks in each hemisphere and patients with different dominant tracks. The hypothesis of the potential asymmetry of amplitudes in response to IPS in patients with asymmetric dominant pathways, however, was not reflected in the obtained results. Both patients with identical (symmetric) dominant tracks as well as those with different (asymmetric) dominant tracks did not show a significant difference in amplitude values.

This fact unambiguously indicates hemispheric symmetry in response to IPS.

Clinical implications

Our data suggests that PPR in children with PS shows a symmetry between the left and right hemispheres of the brain.

An interhemispheric propagation is facilitated in children with PS, and the propagation is more probable in the occipital and temporal regions.

In light of our results, the concept of PPR lateralisation suggested in our previous paper seems to be unfounded, since the discharge amplitudes in one hemisphere are not significantly higher than in the opposite one. Nevertheless, the revealed symmetry creates the possibility of averaging the amplitudes for the particular tracks. In this way, it becomes possible to simultaneously compare the values of all dominant amplitudes between the PS and the control groups.

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