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Neurophysiological signatures reflect differences in visual attention during absence seizures

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HIGHLIGHTS

- Absence seizures affect visual attention and eye movements variably.
- Deficits in visual attention during absences are associated with differences in EEG features and network activation.
- Our findings can be employed in clinical practice for tailored risk assessment in patients.

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ABSTRACT

Objective: Absences affect visual attention and eye movements variably. Here, we explore whether the dissimilarity of these symptoms during absences is reflected in differences in electroencephalographic (EEG) features, functional connectivity, and activation of the frontal eye field.
Methods: Pediatric patients with absences performed a computerized choice reaction time task, with simultaneous recording of EEG and eye-tracking. We quantified visual attention and eye movements with reaction times, response correctness, and EEG features. Finally, we studied brain networks involved in the generation and propagation of seizures.
Results: Ten pediatric patients had absences during the measurement. Five patients had preserved eye movements (preserved group) and five patients showed disrupted eye movements (unpreserved group) during seizures. Source reconstruction showed a stronger involvement of the right frontal eye field during absences in the unpreserved group than in the preserved group (dipole fraction 1.02% and 0.34%, respectively, $p < 0.05$). Graph analysis revealed different connection fractions of specific channels.
Conclusions: The impairment of visual attention varies among patients with absences and is associated with differences in EEG features, network activation, and involvement of the right frontal eye field.
Significance: Assessing the visual attention of patients with absences can be usefully employed in clinical practice for tailored advice to the individual patient.

1. Introduction

Absence seizures affect 10% to 17% of all cases of pediatric epilepsy (Matricardi et al., 2014). Absences usually manifest behaviorally through staring and poor responsiveness, which are the most prominent symptoms of absence epilepsy (Mirsky et al., 1986; Stefan and Trinka, 2022; Unterberger et al., 2018). Characteristically, absences impact eye movements and visual attention (Asato et al., 2011; Lunn et al., 2016; Bedoin et al., 2012; Panayiotopoulos et al., 1989), i.e., the selection of visual stimuli based on spatial location and visual characteristics (Vecera and Rizzo, 2003). Furthermore, absences can result in oculomotor syndromes, such as myoclonic movements (Galli et al., 2018; Vaudano et al., 2014; Unterberger et al., 2018; Matsuoka et al., 2000), or paroxysmal tonic upgaze of childhood (Verrotti et al., 2010).

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The changes in attention observed during an absence (Fonseca Wald et al., 2019; Mitchell et al., 1992; Blumenfeld, 2005; Tian et al., 2010; Touloumes et al., 2016; Barone et al., 2022) presumably result from a transient impairment of specific brain areas during seizures (Landi et al., 2019), in particular, networks involved in consciousness and attention (Posner, 2012; Posner, 1994; Blumenfeld, 2005). These networks - when subdivided into partial, operational definitions, such as state, awareness, and volition - have both physiological (e.g., cortico-thalamic network, anterior cingulate, frontal areas) and phenomenological (e.g., awareness, orienting, selection of external or internal inputs, voluntary control) overlapping characteristics (Posner, 2012; Posner, 1994). There exists an intricate relationship between eye movements, attention, and consciousness. Indeed, characteristic eye movements correlate with disorders of consciousness (Kwan-Chun Ting et al., 2014; Johanson et al., 2011; Nani and Cavanna, 2014). Therefore, determining the functional patterns of eye movements during absences may reveal useful information about the conscious and attentive state.

The anatomo-functional link between visual attention, the oculomotor system, and absence seizures is not trivial to elucidate and has not been specifically addressed, yet. Several neural networks are involved in attention and eye movements (Amso and Scerif, 2015; Vernet et al., 2014). In particular, the frontal eye field (FEF) has a leading function in eye movement preparation and triggering, but also in visual orientation, awareness, perceptual performance, and conscious access (Vernet et al., 2014; Stefan and Trinka, 2022). Given its functional characteristics and the predominance of ocular symptoms in absence seizures, the FEF may play a role in the symptomatology of absences (Stefan and Trinka, 2022). Among the key regions of visual attention, frontal areas and thalamic nuclei (e.g., reticular nuclei and relay nuclei) are involved in the generation of absence seizures, too (Marten et al., 2009; Saalmann and Kastner, 2011).

The selective deficits of visual attention and oculomotor functions in patients with absences probably result from variations in the extent and type of cortical networks involved in the generation and propagation of the seizure, including the frontal eye field (Blumenfeld, 2005; Vuilleumier and Jallon, 2000; Goldie and Green, 1961; Tian et al., 2010). Several studies suggest that symptoms caused by absences may be associated with a precise focal involvement of frontal areas (e.g., orbital and mesial frontal cortex) (Rodin et al., 1994; Vuilleumier and Jallon, 2000; Holmes et al., 2004; Bai et al., 2010; Carney and Jackson, 2014; Blumenfeld, 2005), which can lead to disrupted processing (Goldie and Green, 1961; Carney and Jackson, 2014).

No study to date has deeply investigated oculomotor functions in relation to local brain activation and visual attention in patients with absence seizures. Here, we study neurophysiological readouts and dynamics of network activation during goal-directed eye movements and visual attention in children with absence seizures, both recorded during and in between seizures. We hypothesize that the dissimilarity of symptoms during seizures is reflected in differences in electroencephalographic (EEG) features, functional connectivity, and activation of the frontal eye field. This can also assist in the identification of biomarkers, useful to determine the risk of practicing everyday activities, such as cycling.

2. Methods

2.1. Subjects

We included pediatric patients with absence seizures under treatment. All patients were referred to the Dutch epilepsy clinic Kempenhaeghe in Heeze, the Netherlands, for a 24 h-long video-EEG evaluation. Our study complied with the Declaration of Helsinki and was approved by the local ethics committee (ACE 2020 009). Participants and their tutors - when younger than 16 - provided written informed consent, according to the approved research protocol.

2.2. Task and procedure

The measurement setup comprised a custom-built computerized choice reaction time task (CRT task), synchronized with a 21-channel EEG and a screen-based eye tracker. With this setup, we have available a compact test that allows the quantitative characterization of visual attention during EEG recording (Barone et al., 2022). More details about the CRT task and the measurement setup are shown in Fig. S1 in the Supporting Information. All measurements were performed in the Epilepsy Monitoring Unit (EMU) at Kempenhaeghe in the early morning (7 a.m.), which is a favorable moment for the appearance of spontaneous seizures.

The EEG was recorded at 256 Hz with a portable EEG amplifier (SD LTM 23 PLUS, Micromed S.p.A., Italy), using Ag/AgCl electrodes (10–20 system). Electrode impedance was kept below 20 kΩ and a common average at channel G2 (i.e., halfway between Fz and Cz) was used. Every EEG trace was re-referenced offline to the average of all channels, excluding channels Fp1 and Fp2. Of the 21 channels, 19 were used for further analysis (Fp1, Fp2, F7, F3, Fz, F4, F8, C3, Cz, C4, T7, T8, P7, P3, Pz, P4, P8, O1, O2). Each measurement lasted approximately 45 minutes during which all patients experienced one or more absence seizures (see Table 1). The outcomes of interest were assessed both during the interictal and ictal periods, which could reliably be identified from the EEG recordings. To perform the CRT task, patients were seated in front of a laptop screen and instructed to direct their gaze towards 1) a fixation cross in the center of the screen, 2) a white dot (i.e., cue) at eight, randomized possible positions and 3) the face of a monkey (the target) at eight, randomized possible positions. Patients were instructed to press a button corresponding to the left or right side of the face covered by the hand of the monkey.

2.3. Eye movements and reaction times

The output data from the eye tracker (ET, Tobii Pro Nano, Tobii Technology, Danderyd, Sweden) consists of the x- and y-coordinates of the left and right eye and time stamps. ET data was obtained after performing a fully automated five-point calibration procedure of the ET at the beginning of the task. Eye movement analyses were performed with custom scripts in Python 3.8.3. Details on pre-processing of ET data can be found in (Barone et al., 2022).

Reaction time (RT) was defined as the time between the appearance of the visual target and the correct button press. Errors included either a wrong button press or no button press. From the total RT, we derived three RT subcomponents using ET. First, the saccadic latency (SL), defined as the sampling time between the appearance of target and last sample within the area of interest (AOI) around the fixation cross. Second, the visual reaction time (VRT), defined as the sampling time from the first sample outside the AOI of the fixation cross to the first sample within the target AOI, and, third, the processing speed (PS) i.e., the sum of SL and VRT subtracted from the total RT.

2.4. EEG features

EEGs were filtered offline using a Hamming windowed FIR band-pass filter between 1 and 30 Hz. For each patient, absence seizures during the total measurement were visually identified in the EEG (i.e., 3 Hz spike-wave discharges > 3 s). For each patient, we extracted 1) the average maximum amplitude of all seizures for anterior (i.e., F7, F3, Fz, F4, F8) and posterior channels (i.e., P7,

Table 1
Overview of patients in the preserved and unpreserved group based on the percentage of trials with upgaze and missed targets during the CRT task. The percentage of trials is intended for trials during seizures only for seven patients (S) and for all the trials for ten patients (T). The asterisk refers to subjects who presented seizures during measurement, but for whom it was not possible to synchronize eye movements and EEG. For these patients, the definition of preserved and unpreserved was based on all the trials of the task (see Section S1 of the Supporting Information). The values of correct responses, upgaze, and missed target refer to the percentage of trials. N-MS: number of absences during total measurement; N-CRT: number of absences during CRT task; Upgaze: percentage of trials with upgaze patterns of eye movements; Missed Target: percentage of trials with no fixation on the target stimulus; Correct responses: percentage of trials where correct button press is given; S: during seizure; T: total number of trials; P: Preserved; U: Unpreserved.

N-MS	N-CRT	Correct responses S	Upgaze S	Missed Target S	Correct responses T	Upgaze T	Missed Target T	Group
2	1	0	0	0	98	3	0	P
4	2	25	75	0	88	4	0	U
2	NA*	NA*	NA*	NA*	100	0	0	P
10	5	43	86	73	80	19	30	U
7	4	0	67	0	85	3	9	U
5	4	100	0	0	86	0	1	P
14	NA*	NA*	NA*	NA*	99	2	2	P
2	2	100	50	100	87	10	13	U
1	NA*	NA*	NA*	NA*	98	1	2	P
7	4	100	50	25	97	6	9	U

P3, Pz, P4, P8, O1, O2); 2) the seizure duration, defined as the time between the first and last spike of a seizure (more details can be found in Fig. S6 of the Supporting Information); 3) the peak frequency during the seizure using Welch's power spectral density (PSD) estimate (MATLAB pwelch).

2.5. EEG source reconstruction

Given the high seizure variability among subjects, we reconstruct EEG sources at each time point during every seizure. For every subject, we considered a 3-layer template headmodel based on the segmentation from BrainWeb: Anatomical Model of Normal Brain, developed in (Oostenveld et al., 2003), and openly available in FieldTrip. The template, expressed in Montreal Neurological Institute (MNI) coordinates, consists of three concentric superficial meshes, separating scalp from air, skull from scalp, and brain from skull. We used the Boundary Element Method (BEM) to simulate the electric potential generated by known sources in the brain (forward problem) and applied a dipole fit (Scherg, 1990) to reconstruct the EEG sources (inverse problem). In particular, we used the dipole fit method that is implemented in FieldTrip, which consists of two steps. First, a grid search is performed giving as outcome a dipole location with the lowest residual variance (RV). Second, a non-linear search is applied to refine the position of the dipole identified in the previous step, with a lowered RV. Since some dipole coordinates were localized outside the brain compartment of the headmodel, we repeated the grid search step for these dipoles, only. For further analyses, we subsequently selected the localized dipoles with a RV within the average RV, plus one standard deviation.

Once all dipole positions and strengths were estimated, we calculated the percentage of dipole sources located in the left and right hemispheres for each patient. Furthermore, we identified the fraction of dipoles in the bilateral FEFs using the FEF coordinates defined by Vernet et al. 2014.

2.6. EEG connectivity and graph analysis

We chose the phase lag index (PLI) to determine phase-based, bivariate, channel connectivity over time during seizures since it accounts for volume conduction. First, we determined the phase angles of each channel via wavelet convolution in the frequency domain. PLI was calculated as follows (Stam et al., 2007):

$$PLI = |\frac{1}{n}\sum_{t=1}^{n} sgn(I(exp^{i(\phi j-\phi k)t}))| \quad (1)$$

where n is the number of channels, ϕ are phase angles, j and k are a pair of EEG channels and t is time. We estimated the PLI at 3 Hz, i.e., the notable EEG frequency during absence seizures. We defined a threshold (median PLI plus one standard deviation) for each subject and binarized the PLI adjacency matrices found for each channel pair (1 if above the threshold, 0 if below). We averaged the binarized PLI adjacency matrices of the patients belonging to the preserved and unpreserved groups, obtaining one matrix per group. The PLI values for each pair of channels above the threshold were counted as connection values to implement unweighted graph analysis. To perform graph analysis, we defined EEG channels as nodes and identified the nodes with a number of connections ≥ 13, which we defined as hubs of the graph. We could then describe the "Hubness" of our connectivity results, describing both long and short-range connectivity, as the total number of connections of each hub.

EEG analysis was performed with MATLAB (version R2018b) and the freely available EEGlab (version 2021.0) and FieldTrip (version 20220714) toolboxes (Delorme and Makeig, 2004; Oostenveld et al., 2011).

2.7. Statistics

We used a two-sampled Mann-Whitney U test to compare the medians of our task outcomes and EEG features across the two groups. The choice of a non-parametric test was based on sample size (i.e., smaller than 30) and the non-normality of the variables included in our analysis. We applied Spearman's correlation to compare the relationship between age and task outcomes (Section S6 of the Supporting Information, Figs. S7 and S8). If $p < 0.05$ we considered the results statistically significant. Correction for multiple comparisons for non-parametric tests was computed with Benjamini-Hochberg procedure (Q = 10%). Statistical analysis was performed using the module *statistics* in Python 3.8.

3. Results

3.1. Preserved and unpreserved eye movements

Ten patients (7–18 years old, mean age = 13 ± 3.7; 5 females) had absences during the measurement. Patients' demographics are summarized in Table S1 of the Supporting Information. Five patients showed impaired eye movements during absences. We defined this impairment as either not being able to correctly reach the target of the CRT task with the eyes (here referred to as "missed target") or showing a sudden upgaze towards the top side of the laptop screen (here referred to as "upgaze"). Subsequently, we

divided our sample into two groups: five patients with unpreserved eye movements (i.e., ≥50% of trials with missed targets during seizures or ≥50% of trials with upgaze during seizures) and five patients with preserved eye movements (cf Table 1). Examples of patients from the preserved and unpreserved group are shown in Fig. 1.

For three patients we could not determine the exact synchronicity of eye movements and EEG. We included them in the preserved group as the total number of trials during the task with missed targets and upgaze was ≤2%. Both groups had a mean age of 13 y, with three males and two females in the unpreserved group and two males and three females in the preserved group. Three out of five patients in the unpreserved group and one out of five in the preserved group showed a deficiency in the button-press response to the target.

3.2. Correct responses, reaction times, and subcomponents

The mean difference in correct responses was significant between the two groups. RT and its subcomponents determined with the eye tracker (i.e., SL, VRT, PS) show a trend of longer RTs for the unpreserved group, but no significant difference was found. For further details, please see Section S3 of the Supporting Information (Figs. S2 and S3). Furthermore, we tested the effect of age on RT and the percentage of correct responses (Section S6 of the Supporting Information) and we found no significant correlation.

3.3. EEG features

EEG analyses included all absences in the EEG recordings during the entire measurement for all patients, i.e., also absences that occurred during the pauses from the CRT task (*cf* N-MS in Table 1). Peak frequency during absences differed for the two groups, with the unpreserved group showing a mean peak frequency 0.3 Hz lower than the patients with preserved eye movements, Fig. 2, left. In Section S4 of the Supporting Information, we report more details about the temporal dynamics of the peak frequency during the absences for each group. Seizure duration was not significantly different between the two groups (Fig. S6 of Section S5 of the Supporting Information).

The averaged maximum EEG amplitude per seizure of the two groups, both for all channels and anterior or posterior channels, only, is shown in Fig. 2, right. The average amplitude of posterior channels was significantly different for the two groups (mean difference: 193 μV, $p < 0.05$), while no significant difference was found for the maximum amplitude of anterior channels or when averaged over all channels.

3.4. EEG source reconstruction

EEG source reconstruction with dipole fitting revealed a consistent pattern of source locations during seizures within subjects. In Fig. 3, fitted dipoles of two seizures for four different patients of the two groups are shown. The similarity in the positions of the dipoles reflects the consistency of the EEG time series for the same subject, as revealed by the great resemblance of the EEG signals (channel F4) of two absences per subject.

Independently from the group, a trend of clustered dipoles is visible in fronto-central regions of the right hemisphere. We estimated differences in dipoles in the left and right hemispheres using fractions of all the dipoles of the two groups in the two hemispheres. We found that the mean difference of the percentage of

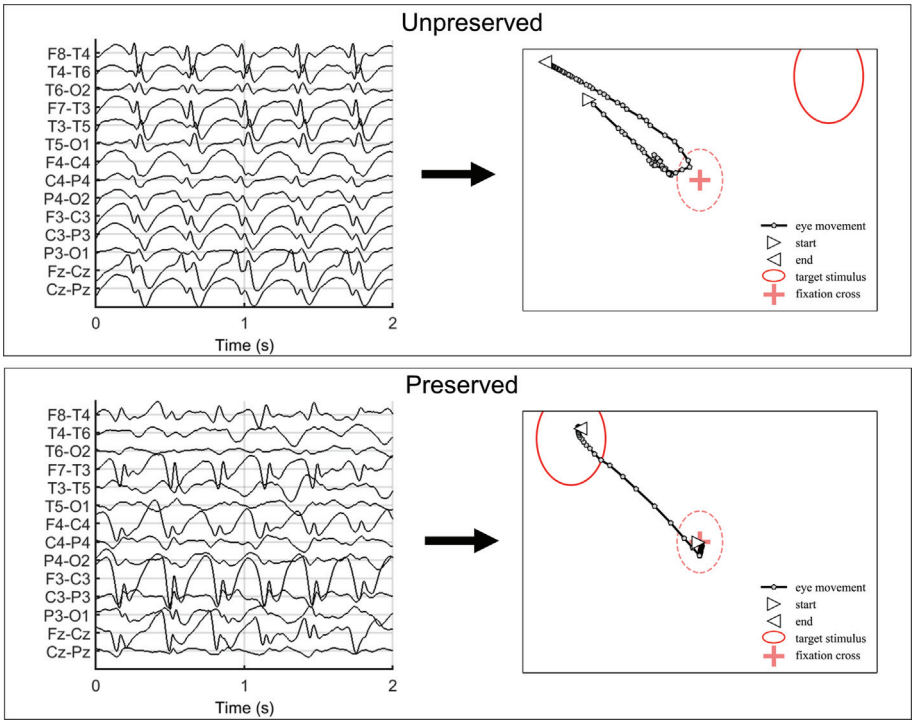

Fig. 1. An example of synchronous EEG activity and eye patterns during the choice reaction time (CRT) task in a patient from the unpreserved (top) and preserved group (bottom). Left panels: 2-s-long EEG epochs during a characteristic 3 Hz absence seizure. Right panels: eye movements during target presentation of the CRT task. The two triangles represent the beginning and the end of the eye movement, and its direction. The red, continuous ellipse corresponds to the visual target stimulus, and the cross in the middle of the screen mimics the fixation cross the patients need to stare at during the beginning of each trial. The grey pentagons throughout the black line of the eye trajectory represent fixation points. The patient of the unpreserved group (top panel) was experiencing an absence seizure already at the beginning of the trial, and the gaze was positioned away from the fixation cross. During the seizure, the ability to perceive the fixation cross and move the eyes accordingly seems preserved. Thereafter, an upgaze towards the top-left side of the screen is visible, preventing the patient from reaching the target stimulus with the eyes. The patient of the preserved group (bottom panel), instead, was able to start the trial in the correct position (i.e., the fixation cross) and thereafter directs the gaze to the correct target position.

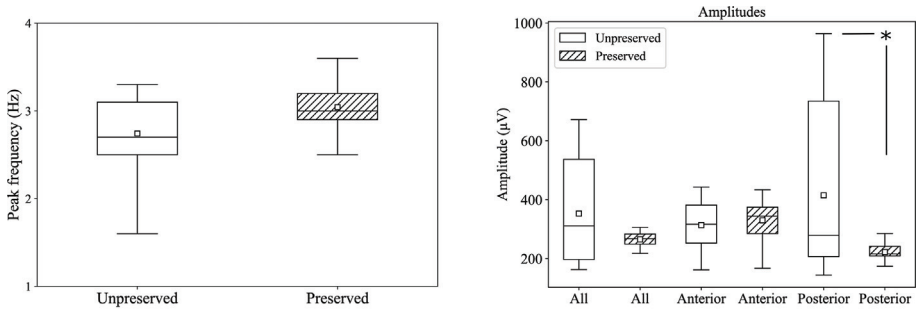

Fig. 2. Left: Peak frequency of all the absences for the two groups. The mean peak frequency in the unpreserved group fp = 2.7 ± 0.4 Hz and fp = 3 ± 0.3 Hz in the preserved group; this was statistically significant ($p < 0.05$). Right: Averaged maximum EEG amplitude during absences. Left boxes: amplitude of all EEG channels; central boxes: anterior channels (i.e., F7, F3, Fz, F4, F8); right boxes: posterior channels (i.e., P7, P3, Pz, P4, P8, O1, O2). The differences are significant for the posterior channels ($p < 0.05$).

dipoles lying in the two hemispheres is significantly different for both groups (right: 84%, left: 14% for the unpreserved group; right: 86%, left: 13% for the preserved group; $p < 0.05$).

The relative distribution of the dipoles in the FEF is shown in (Fig. 4). During absences the number of dipoles located in the right FEF was significantly larger than on the left side. In addition, the right (1.02% unpreserved vs 0.34% preserved) and bilateral FEF (1.01% unpreserved vs 0.37% preserved) of the two groups have significantly different fractions of dipoles.

3.5. Connectivity and graph analysis

Phase connectivity analysis revealed a statistically significant difference for the PLI values of channel C4, only. Graph analysis for long-range connectivity (Fig. 5, top) displayed one hub (a node with the highest number of connections to other nodes) in the preserved group (channel Cz, N = 13 connections) and three hubs for the unpreserved group (channel C4 and T7 N = 15 connections, channel Fz N = 13 connections). The connections of the hubs are directed both to neighboring and distant nodes (Fig. 5, bottom).

4. Discussion

We report between-subjects differences in eye movements and visual attention in pediatric patients with absence seizures, employing advanced neurophysiological measures. We show that visual attention and eye movements are affected variably during absences: half of our patients had impaired patterns of goal-directed eye movements during absences, while the oculomotor responses were preserved in the other patients (Fig. 1). These differences are reflected in characteristic EEG features, neural sources, and network activation, including differential involvement of the FEFs.

To our knowledge, this is the first study to specifically focus on visual attention during absence seizures, quantitatively exploring the oculomotor symptoms of absences. This consolidates previous

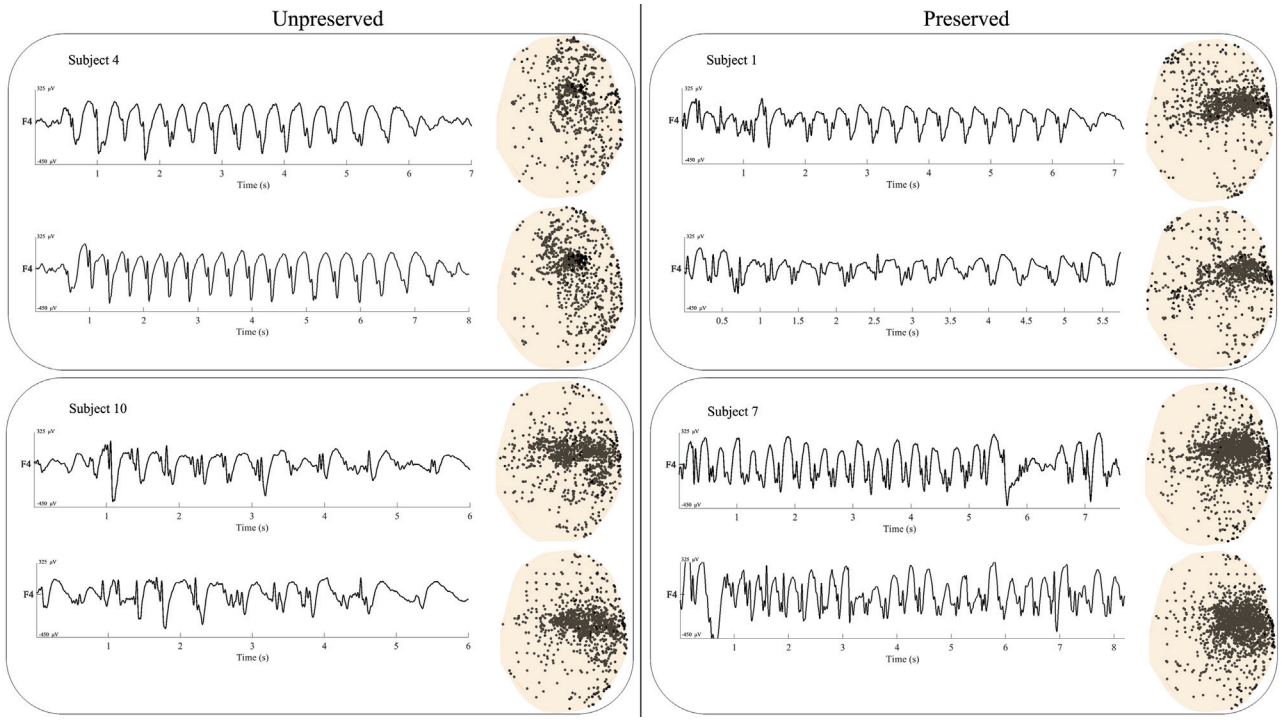

Fig. 3. Shown are absence seizures (channel F4) with the distribution of fitted dipoles, from four different patients. Each dipole corresponds to one time point of the EEG signal presented on the left side of each headmodel. The dipoles are plotted on the BEM headmodel, shown with a horizontal view of the brain from above. Each patient shows characteristic electrographic seizures and a similar distribution of dipoles. Left: patients 4 and 10 from the unpreserved group. Right: patients 1 and 7 from the preserved group.

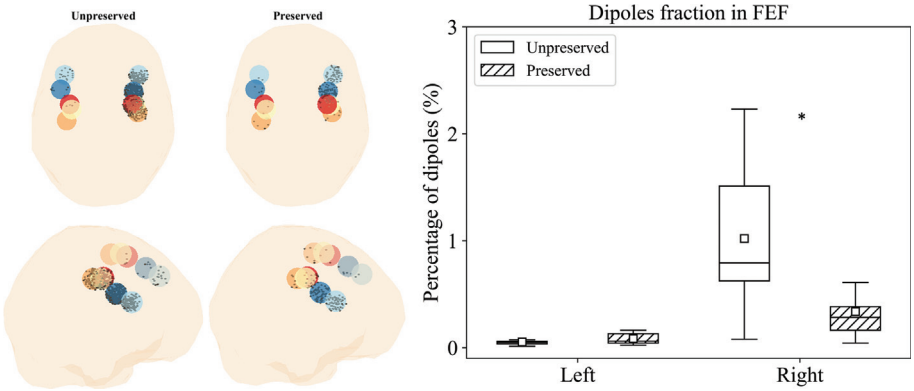

Fig. 4. Left: Dipoles in the frontal eye field, using the coordinates in Vernet et al. 2014. The coordinates are the center of five spheres (radius = 1 cm), defined by different colors. View from above (upper headmodel), and lateral view from the right side (lower headmodel). Right: Percentage of dipoles in the left and right frontal eye field (FEF), showing significant differences for the unpreserved and preserved group in the mean percentage of dipoles in the right FEF (1.02% vs 0.34%, $p < 0.05$).

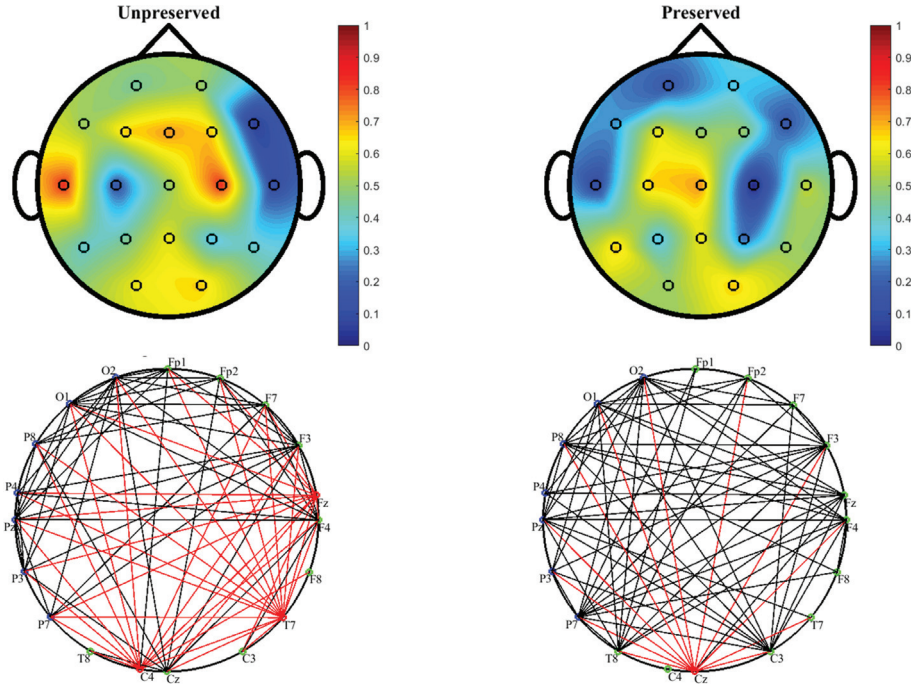

Fig. 5. Hubness of the two groups, defined as the proportion of supra-threshold connections. Top left: the unpreserved group has 3 hubs (C4 and T7 with 15 connections (0.83), and channel Fz with 13 connections (0.72)). Top right: the preserved group has one hub (Cz, 13 connections (0.72)). Bottom: Connections of the hubs of both groups are shown in red while the remaining connections of other sensors are shown in black. Connections of the hubs are both to neighboring and long-distance electrodes for both groups.

descriptive studies that were mainly focused on the phenomenology of staring, upgaze, and oculomotor defects as characteristic signs of absences (Asato et al., 2011; Lunn et al., 2016; Unterberger et al., 2018) or reported on cognitive impairment during seizures via standardized behavioral measures, focusing mostly on the ability to drive (Touloumes et al., 2016; Nirkko et al., 2016; Cohen et al., 2020), which has been proven to be affected by interictal epileptiform discharges, too (Nirkko et al., 2016; Touloumes et al., 2016).

Absence seizures are also an attractive model system for studying consciousness because of the selective, dynamic, and rapidly reversible changes in consciousness associated with altered function in specific brain networks (Blumenfeld, 2005). Our findings of the mechanisms underlying attentional and eye-related deficits during seizures can be beneficial for further insights into the intricate concept of consciousness and cognition. In particular, our results indicate how a selective and reversible involvement of frontal areas can momentarily impair consciousness and awareness in a patient-specific way, i.e., by being able to look and react to an external stimulus or not. This indicates that some aspects of consciousness and cognition are disrupted when a specific network involvement is present during seizures, which here corresponds to more activity in the right FEF and a larger long and short-distance connectivity of the right frontal areas. More research approaches, including neurological disorders not traditionally linked to a strong defect of consciousness, need to address the mechanisms underlying the impairment of cognition and consciousness (Laureys, 2005).

We show that it is possible to individually assess how absence seizures may affect attention. This can enrich our understanding of possible complications due to absence seizures and allows monitoring of progression. Further, our personalized approach can over-

come the high inter-subject variability, resulting from, e.g., age, medication intake, or etiology of the disease.

4.1. Reaction times

Deficits of the oculomotor system affect the reaction to external stimuli in the environment in our sample. We measured the behavioral reaction to visual stimuli by a button press, assessing RTs as well. Three out of five patients in the unpreserved group had difficulties pressing the correct button during absences, while only one patient showed the same deficits in the preserved group. Moreover, even if not statistically significant, the trend of slower RTs found in the unpreserved group (Fig. S2 of the Supporting Information), suggests that generalized seizures affect RTs (Tian et al., 2010; Mitchell et al., 1992). This result suggests that impaired oculomotor functions influence high-level cognition in some patients, who are not able to rapidly and correctly process visual information and react to it accordingly.

4.2. EEG features

We observed that the mean frontal amplitude during absences is higher than the mean posterior amplitude, as reported in other studies, too (Blumenfeld, 2005). Further, EEG amplitudes of the posterior channels during absences were significantly different between the two groups (*cf* Fig. 2, left). This is in partial agreement with (Cohen et al., 2020; Springer et al., 2022), where it was shown that EEG amplitudes during absence seizures are related to a larger behavioral impairment, but no details about amplitude gradients between different cortical areas were reported. In our study, the posterior, higher EEG amplitude of the unpreserved group seems to derive from a greater variance in amplitude of the seizures included. This is mostly due to patient four, who presents an amplitude on average 400 μV higher in posterior compared to anterior channels. In fact, the median values the two groups are not significantly different.

At group level, the peak frequencies during the seizures were statistically significantly different by 0.3 Hz between groups (*cf* Fig. 2, right). Even if on average lower than 3 Hz, the total peak frequency during absences of the unpreserved group is not in the 1.5–2.5 Hz range (i.e., the definition of atypical absences, see Section S4 of the Supporting Information) (Vuilleumier and Jallon, 2000). At present, we can only speculate about the biological significance of this (small) difference in peak frequency, which may indicate a sign of divergent activation during absences. A deeper exploration is needed to use this characteristic as a reliable metric.

4.3. EEG sources and the frontal eye field

The deficits of visual attention and oculomotor functions in our sample suggest differential involvement of cortical networks, and several studies report on the involvement of frontal areas in absence seizures (Rodin et al., 1994;; Vuilleumier and Jallon, 2000; Holmes et al., 2004; Bai et al., 2010; Carney and Jackson, 2014; Blumenfeld, 2005; Goldie and Green, 1961). We reconstructed the sources of the EEG activity during seizures for each patient using dipole fitting. The distribution of the positions of dipoles was very consistent within subjects, reflecting the similarity of the EEG time-series of absences for each patient (*cf* Fig. 3), with clusters of dipoles strongly lateralized to the fronto-central right hemisphere in both groups (84% right vs 14% left for the unpreserved group, 86% right vs 13% left for the preserved group). To our knowledge, this right lateralization of EEG sources during absences has not been previously reported. We argue that this may explain the peculiar cognitive symptoms of absences. The right hemispheric dorsolateral and ventral networks are known to contribute the most to attention, and the larger number of sources of ictal activity in the fronto-central areas of the right hemisphere suggests a major involvement of these networks during absences (Posner, 1990; Vossel et al., 2014; Corbetta and Shulman, 2002).

We additionally focused on the FEF, a relevant brain area for oculomotor functions and attention (Vernet et al., 2014; Chen et al., 2018). We used the available MNI coordinates of the human FEF (Vernet et al., 2014), to determine the dipoles located within the left and right FEF. The MNI coordinates we employed are part of a template and therefore the spatial resolution we used is not millimetric, but sufficiently adequate to approximate the location of the FEF. We showed that the right FEF presents extensively more dipoles than the left FEF in both groups (1.02% vs 0.05% unpreserved; 0.34% vs 0.08% preserved). Furthermore, the average fraction of dipoles in the FEF for the two groups differs significantly for the right FEF (Fig. 4). The larger involvement of the right FEF during seizures in the unpreserved group may account for the differences in oculomotor function and attention as the right FEF has been reported to be especially involved in visual attention and transmission of visual information to posterior areas (Chen et al., 2018).

4.4. EEG networks and connectivity

Network connectivity is affected during absences (Blumenfeld, 2005; Vuilleumier and Jallon, 2000; Goldie and Green, 1961; Elshahabi et al., 2015). We show that the averaged PLI for the two groups revealed a significant difference for channel C4, only, which partially corresponds to the position of the right FEF (Chen et al. 2018) in line with our results of EEG source reconstruction. Further, graph analysis revealed three hubs for the unpreserved group (C4, T7, Fz) and one hub for the preserved group (Cz), indicating a higher complexity of connections for the unpreserved group. The observation that the connections of the hubs are both local and distant may imply a"poor" state of the brain during absences (Ponten et al., 2009). As we aimed to explore if differences in network activation relate to changes in visual attention during the seizures we did not compare differences in connectivity between ictal and interictal states.

4.5. Limitations

Our study has some limitations. First, the number of subjects included is small, although common in the literature (Cohen et al., 2020). Second, our patients were not drug-naïve, and the administered drugs varied per patient (see Table S1 of the Supporting Information). Another limitation is the length of the trials used in the CRT game (800 to 4000 ms), which does not leave room for studying in detail the precise timing of the attentive impairment, which may vary during seizures (H. Blumenfeld 2005). Furthermore, for our source reconstruction, we opted for a standard BEM headmodel and aimed at a resolution of centimeters instead of millimeters. We are aware that anatomically personalized models would lead to more accurate source reconstructions, nevertheless with no MRI scan, and 19 EEG channels only our choice was sufficient to show differential involvement of the frontal eye fields.

5. Conclusion

We found characteristic electrophysiological signatures in patients with unpreserved and preserved visual attention or eye movements during absence seizures. In particular, the right-sided fronto-central brain areas, including the frontal eye field, are more affected during absences in patients with unpreserved eye move-

ments. Our findings extend our understanding of symptomatology and semiology of absence seizures and may further assist to provide tailored advice for risk assessment in participating in daily activities, including cycling (Barone et al., 2020; Springer et al., 2022).

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Data Availability Statement

We are not allowed to share patients' data.

The code of the visual attention task is publicly available at: https://github.com/Valeebarons/Visual_attention_task.

The code of data analyzes for EEG and eye-tracking data is publicly available at: https://github.com/Valeebarons/Analyses_eye-movements_absences.

Declaration of conflicting interests

Michel J.A.M. van Putten is a co-founder of Clinical Science Systems, a manufacturer of clinical EEG software. The remaining authors have no confiicts of interest.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.05.007.

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