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Spatiotemporal profiles of focal and generalised spikes in childhood absence epilepsy

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ABSTRACT – The EEG in childhood absence epilepsy (CAE) may contain focal and generalised spike-wave discharges (SWDs) with focal, mainly frontal, "lead-in". The term "frontal absence" has been used to imply fast, secondary, 3-Hz generalisation from occult frontal foci with potential impact on clinical EEG interpretation and syndrome classification. The aim of this study was to investigate the relationship between focal and generalised SWDs. We studied five children with CAE and examined a sufficient number of focal ("interictal") and generalised SWDs in order to obtain reliable analysis. All generalised SWDs with focal lead-in were "decomposed" into their "pre-generalisation" focal and "generalised" constituents, which were studied separately. Two types of focal SWD ("interictal" and "pre-generalisation") and generalised SWD were visually clustered into groups, waveform-averaged, and plotted in the 2D-electrode space. Spatiotemporal analysis demonstrated a variety (mean: 4.2 per child; SD: 2.12) of mainly frontal and occipital locations for pre-generalisation focal SWDs with propagation along the longitudinal axis in either direction and across homologous sites. Interictal focal SWDs demonstrated similar spatiotemporal characteristics. In contrast, the topography and propagation patterns of the first generalised spike of the SWD showed less variability (mean: 2.5 per child; SD: 2.07), mainly involved the fronto-temporal/temporal areas, and correlated poorly (<10%) with that of the pre-generalisation focal SWD. Our findings suggest that the process of generalised epileptogenesis in genetic epilepsies with electrographic "frontal absences" is far more complex than that proposed by the model for occult frontal focus with fast secondary generalisation. (*Published with Supplemental data*)

Key words: childhood absence epilepsy, EEG, focal discharge, generalized discharge

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Idiopathic generalised epilepsies (IGEs) (Commission, 1989), or genetic epilepsies with generalised seizures (Berg *et al*., 2010), comprise a third of the epilepsies. According to the recent ILAE revision of concepts and terminology, generalised seizures are believed to originate from within, and rapidly engage, bilaterally distributed networks which include cortical and subcortical structures, but not necessarily the entire cortex. Although, individually, the onset of seizures may appear to be localised, location and lateralisation are not consistent from one seizure to another, and generalised seizures can be asymmetric (Berg *et al*., 2010). Such "incompleteness" of the established bilateral (thalamo-) cortical ictal process may be expressed clinically by variable disturbance of awareness, responsiveness or cognition during typical absences or by regional/asymmetric myoclonic seizures, as well as electrographically by asymmetric generalised spike-wave discharges (SWDs), frequently with variable focal lead-in.

In contrast to incomplete or even asymmetric (Niedermeyer *et al*., 1979; Velizarova and Genton, 2010) generalised SWDs, a possible mechanism to explain the phenomenon of interictal focal SWDs (Allen and Forster, 1949; Holmes *et al*., 1987; Aliberti *et al*., 1994; Lombroso, 1997) still remains unresolved, and an official ILAE position is awaited. On clinical grounds, such focal graphoelements may shift EEG interpretation towards occult structural (cryptogenic) epileptogenesis with secondary bilateral synchrony (SBS), potentially impacting on patients' management, particularly when "focal" clinical manifestations during frontally-led absences are present (Leutmezer *et al*., 2002). The latter, also referred to as "frontal absences", which are believed to represent fast secondary generalisation from a frontal focus (Lagae *et al*., 2001; Jocić-Jakubi *et al*., 2009), appear to correspond to those with apparently localised onset of the 2010 ILAE revision (Berg *et al*., 2010).

Recent scalp EEG evidence suggests that focal and generalised SWDs not only co-exist, but may be functionally linked, an association already suspected since the mid 1960s (Bray and Wiser, 1965); isolated focal SWDs may appear to be similar to those leading or following generalised SWDs (Williamson *et al*., 2009; Koutroumanidis *et al*., 2009), while their topography correlates with that of the leading spike of generalised SWD (and absences) (Koutroumanidis *et al*., 2012). On visual clinical EEG analysis, the apparent continuity between the leading focal spike(s) and the first generalised burst of the ensuing (lead-in) 3-Hz, repetitive SWD may imply a causal relationship; for example, direct triggering from a cortical focus in some analogy with SBS (Tukel and Jasper, 1952; Blume and Pillay, 1985), or even with the direct generation of a focal seizure from a structural (symptomatic), cortical spike focus. However, IGEs are clinically, electrographically, pharmacologically, and genetically distinct from structural focal epilepsies, including SBS, and how the leading focal SWD can foster spike-wave generalisation is far from clear.

In a previous report (Koutroumanidis *et al*., 2012), we separated epileptic discharges as focal and generalised, and identified a good topographic relationship between *interictal* focal spikes (those occurring distal to generalised discharges and absences) and the leading spikes of generalised spike-wave discharges in all children with childhood absence epilepsy (CAE) and "focal" absences. However, our analysis was based on clinical EEG interpretation. To better understand the relationship between focal and generalised discharges in CAE, we hereby *separately* studied the leading focal spikes (which we previously considered as the "focal" onset of typical absences) and the first generalised spike of the lead-in, 3-Hz, repetitive SWD by averaging clustered spike discharges. In other words, we "decomposed" "frontal" (or "occipital") absences and subclinical generalised SWD into their two electrographic constituents: the focal onset, which we henceforth refer to as "*pre-generalisation focal spikes*", and the generalised spike-wave sequence. A similar spike topography and propagation pattern would imply a direct cortical trigger for the "led-in" absences, and this was the obvious hypothesis to test. To this end, we also compared topography and propagation between interictal and pre-generalisation focal spikes, as well as between single and repetitive generalised SWDs.

Methods

Patients

The 5 children reported here (Patients 1-5) correspond, respectively, to Patients 3, 2, 4, 5, and 1 of a recently reported group of 13 children with CAE (Koutroumanidis *et al*., 2012), diagnosed according to the 1989 classification criteria (Commission, 1989). Of these 13 children, focal EEG discharges were identified in 11, but only the 5 included here demonstrated a sufficiently large number of focal and generalised discharges which could be clustered into large groups for reliable waveform averaging and meaningful analysis. The video-EEG recordings in these 5 children were performed during wakefulness and sleep; the latter was obtained after partial sleep deprivation. For patients with IGE or genetic epilepsies with generalised seizures, we generally aim to record at least 30 to 45 minutes of light sleep (stages 1 and 2) without pursuing prolonged periods of stage 3 or REM sleep; patients are then awakened and subjected to

activation with one or multiple sessions of hyperventilation and photic stimulation. The total duration of a sleep-deprived EEG typically ranges between 60 and 90 minutes. Background information and clinical and EEG characteristics of the 5 children reported here can be found in our previous report.

EEG recording

The EEG was derived from 19 Ag/AgCl electrodes placed on the scalp, according to the international 10-20 system. Electrode impedance was kept below 5 kOhms during recordings. The EEGs of Patients 1 and 5 were AC recorded, amplified, band-pass filtered at 0.05-100 Hz, and digitized through a 20-bit resolution A/D converter at 256 Hz by a Nicolet Voyageur system (Nicolet Biomedical Inc., Madison, WI, USA). The EEGs of Patients 2, 3, and 4 were performed using a Nihon-Kohden Neurofax EEG-1100 system (Nihon Kohden Corporation, Tokyo, Japan) with a 512-Hz sampling rate and otherwise similar parameters. The 50-Hz notch filter was not applied during the recordings.

Events

We identified four groups of epileptic EEG activity for analysis after "decomposition" of all generalised SWD that appeared to be led in by focal spikes:

1) **Focal interictal SWDs** that involved a few adjacent electrodes and occurred distal to generalised SWDs with a clear stretch of intervening physiological background activity (*figure 1A and B*);

2) **Focal pre-generalisation SWDs** that appeared as above, but immediately preceded a generalised SWD without any intervening physiological background activity. This *complex* of temporally-related focal pre-generalisation and generalised SWDs corresponds to what is known in the literature as a "generalised SWD with a focal lead-in", or "frontal absence" if the focal lead-in is frontal (*figure 1D; arrows*);

3) **Single generalised interictal SWDs**, characterised by a single spike-wave discharge covering the whole of the cerebrum (*figure 1C*);

4) **Generalised repetitive SWDs with multiple regular 3-4-Hz generalised spike-wave oscillations** (*figure 1D*), irrespective of the presence of behavioural changes (absences) or clinical features.

Groups (3) and (4) included both the "decomposed" generalised SWD and those that occurred without a discernible lead-in.

Analysis

We used signal averaging to increase the resolution of the spikes and demonstrate the time-dependent changes of their topography in space, *i.e.* their propagation patterns. Manual cursor marking provided by the Scan software (Neuroscan Inc., Charlotte, NC, USA) was performed in order to create event channels. The leading spike of the focal or generalised

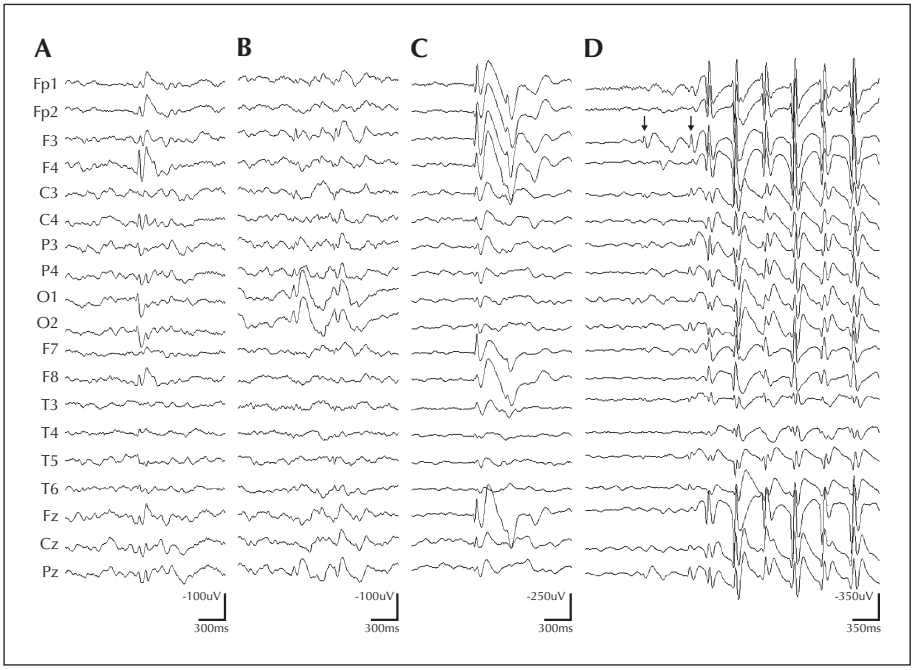

Figure 1. Raw EEG traces of the events analysed in this CAE study. (A) Interictal focal discharge over the right frontal (F4) area. (B) Interictal focal discharge over the occipital (O1, O2) areas. (C) Single generalised interictal discharge. (D) Generalised SWD with focal discharges over the left frontal (F3) region (arrows), immediately before the onset of generalisation (pre-generalisation spikes).

discharge, or the spike of maximal amplitude if a leading spike was not discernible due to high synchrony, was visually selected and a marker was manually placed at the negative peak of the spike. For the repetitive generalised discharges that appeared to be led in by focal pre-generalisation spikes, we marked the earliest spike or the spike with the highest voltage of the first generalised spike-wave, ignoring the focal pre-generalisation spike that was analysed separately. Spike discharges were then clustered into groups according to electrode dominance. Double spikes, polyspike discharges, and spikes in close proximity were identified and excluded from further analysis. Spike marking and clustering was performed visually (Emerson *et al*., 1995) by three of the investigators (VK, DT, and MK) and any difference was resolved by consensus.

Event-related methodology was applied by means of a custom-made Matlab-based (The Mathworks, Natic, MA, USA) software suite, developed at the Neurophysiology Unit at the University of Patras. Waveform averaging was performed for each marked event, after baseline correction, within a time window of ±1 second for each cluster of spikes in each patient. Electrode space mapping was performed using the multiquadric interpolation method based on the Green function and described by Sandwell (1987). The amplitude of the mapped signal was colour-coded in a bipolar linear form; the red band for baseline (zero voltage) values, the blue band for negative values, and a yellow-green-magenta scale for intermediate values. For each cluster of spikes, 5-ms snapshots of topography were derived from onset (where the negative rising deflection of the spike stood out from the baseline) to fade-out (where the negative falling slope of the spike reached the EEG baseline level again) with time 0.00 corresponding to the marked spike.

Results

A total of 320 interictal focal, 110 pre-generalisation focal, 52 single interictal generalised, and 115 generalised repetitive SWDs were identified and spatiotemporally analysed. The topography and propagation pattern of all the different types of each of these four groups of graphoelement in the five children are summarised in *table 1*. Details of the topography and propagation patterns of all types of discharge, with

Table 1. Localisation and propagation patterns of focal and generalised spikes.

	Focal interictal	Focal pre-generalised	Single generalised interictal	First generalised
Patient 1	F3 (36; 26.0%) O2→F3 (30; 21.7%) F4 (23; 16.7%) O1 (21; 15.3%) F4→F3 (15; 10.8%) O1→F4 (7; 5.1%) F3→F4 (6; 4.4%)	O2→F3 (17; 54.8%) F4→F3 (5; 16.2%) F3 (5; 16.2%) O→F4 (3; 9.6%) F3→F4 (1; 3.2%)	F8→F4,F3 (16; 47.1%) T4→F4,F3 (12; 35.3%) F7,F3→F (6; 17.6%)	T→F (21; 72.4%) T3,F3→F4 (8; 27.6%)
Patient 2	P3,O1 (22; 53.6%) F4 (13; 31.7%) F (5; 12.3%) F3 (1; 2.4%)	P (5; 41.6%) F4 (4; 33.4%) O2→F (2; 16.7%) F3 (1; 8.3%)	F4→F (5; 100%)	F4→F (11; 55,0%) T3,F3→F4 (9; 45,0%)
Patient 3	F4→T6,O2 (36; 84.7%) F3→P4 (7; 15.3%)	F4→T6 (5; 55.5%) F3→T6 (4; 44.5%)	O2→P4 (13; 100%)	O1,O2→F4 (5; 83.3%) F4→P,O (1; 16.7%)
Patient 4	Fz (27; 37.5%) Cz→F3 (16; 22.3%) Fp→F4 (12; 16.6%) F4→F3 (8; 11.1%) F3→F4 (7; 9.7%) Fp (2; 2.8%)	F4 (24; 47.1%) F3→P3 (10; 19.7%) F3→F4 (7; 13.7%) F4→F3 (6; 11.7%) Fp (2; 3.9%) O,P (2; 3.9%)	N/A	O,P→F3,F4 (16; 53.3%) O1,P3→F3,F4 (14; 46.7%)
Patient 5	F4max→F3 (24; 88.8%) F4→F3max (3; 11.2%)	F3→F (5; 71.4%) F8→F (2; 28.6%)	N/A	F3→F (3; 100%)

F: bilateral frontal; T: bilateral temporal; P: bilateral parietal; O: bilateral occipital; Fp: bilateral fronto-polar.

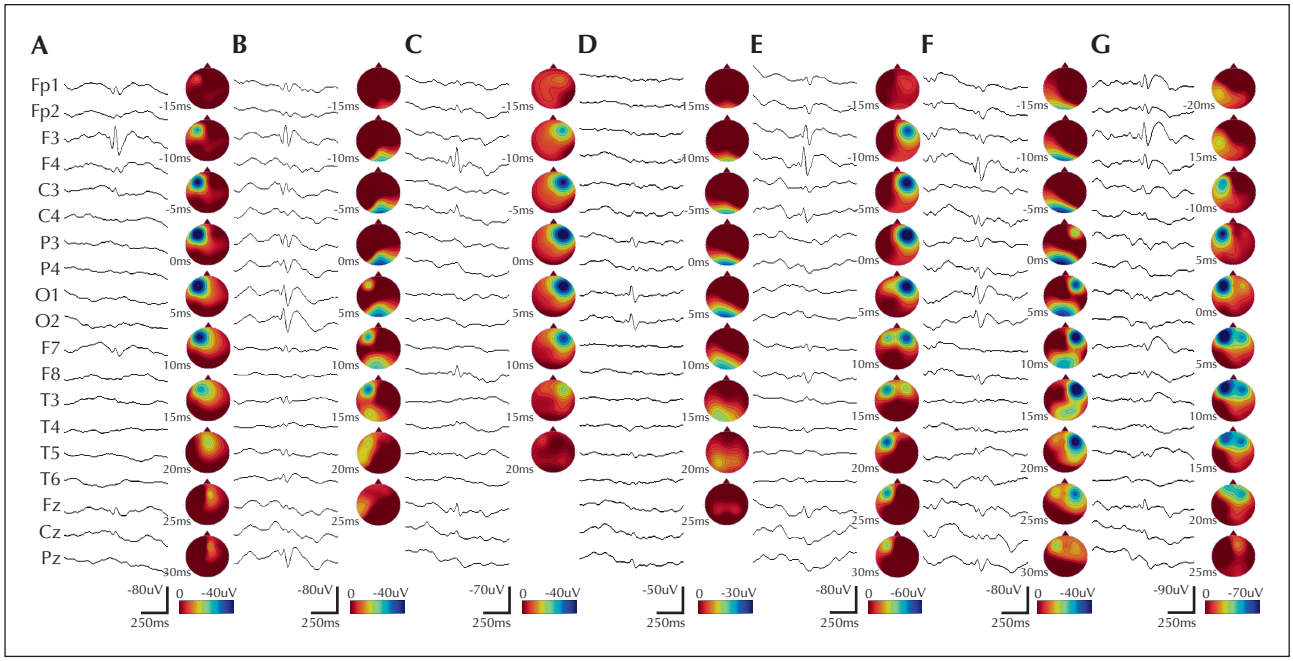

Figure 2. EEG waveform averages and spatiotemporal profiles in Patient 1.
The seven distinct types of discharge (A-G) are represented in order of abundance, with (A) the most abundant.

relevant illustrations, are presented for Patient 1 in *figures 2-4* and for other patients in *figures S1-6* in the on-line supplementary material (click on the download button). The relationship between pre-generalisation focal SWDs and the first generalised spike of the following repetitive SWDs in the five patients is illustrated in *figure 5*.

The following associations were observed between the four groups of discharge:

1) With only a few exceptions (such as the pre-generalisation focal SWD F3 to F of Patient 5), the topography at onset (interictal and pre-generalisation) and pattern of propagation of the focal spikes were similar in each patient (*table 1*). In particular, 88 of the 110 pre-generalisation focal spikes (80%) also occurred interictally, distal to repetitive generalised SWD;

2) The topography at onset and pattern of propagation of the first spike of the "decomposed" and spontaneously synchronous generalised SWD were also similar (Patients 1-3; *table 1*). Topography and propagation were remarkably similar between single generalised spikes and the first generalised spike of the repetitive SWD in each patient with both types of discharge, indicating that the former was an initial subset of the latter for each patient; all 39 generalised single spikes of Patient 1 (n=34) and Patient 2 (n=5) were similar to the first spikes of the generalised prolonged SWD, while the 13 single generalised spikes of Patient 3 showed the same occipital-to-frontal propagation as the first spikes of the repetitive generalised SWD, although with an earlier onset from the contralateral occipital area;

3) In sharp contrast, topography at onset and propagation correlated poorly between focal and generalised discharges; of the 110 pre-generalisation focal SWDs, only 9 (8.2%) showed the topography and propagation of the first spike of repetitive generalised SWDs (4 from F3 to T6 in Patient 3 and 5 from F3 to F in Patient 5; *table 1*). On the other hand, only 4 of the 115 generalised SWDs (3.5%; F4 to P,O of Patient 3 and F3 to F of Patient 5) showed similar initial propagation to pre-generalisation spikes (*table 1*).

The mean topographic variability (number of distinguishable clusters per patient) of focal SWDs was almost two times greater than that of generalised SWDs (focal interictal: mean=4.20, SD=±2.20; focal pre-generalised: mean=4.20, SD=±2.12; single generalised: mean=3.33, SD=±3.21; repetitive generalised: mean=2.00, SD=±1.22; collectively, focal: mean=4.20, SD=±1.98; and generalised: mean=2.5, SD=±2.07).

Patient 1

Seven types of focal interictal SWD (n=138) were identified during an EEG recording of one hour and 15 minutes. The first (n=36; 26.0%) demonstrated onset with maximum signal over the left frontal area and drifted towards the midline (*figure 2A*). The second (n=30; 21.7%) originated bilaterally in the occipital lobe (O2>O1), propagated to the left frontal lobe with a

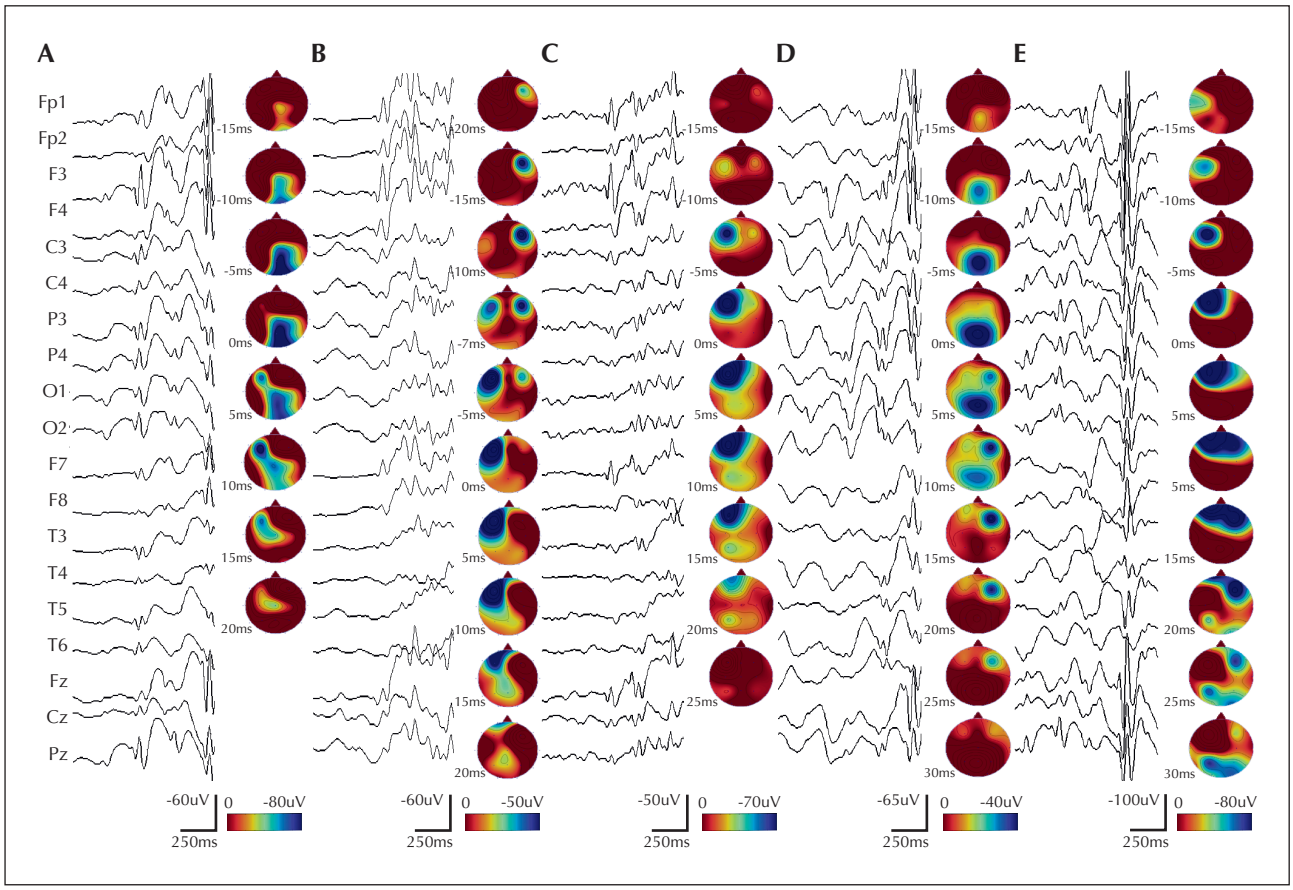

Figure 3. EEG waveform averages and spatiotemporal profiles of focal discharges before generalised SWDs in Patient 1. The five distinct types of discharge (A-E) are represented in order of abundance, with (A) the most abundant.

mean latency of ≈15 ms without apparent involvement of the intervening cortical areas, and drifted over the left temporal region (*figure 2B*). The third (*n*=23; 16.7%) demonstrated onset and maximum signal over the right frontal area and drifted locally (*figure 2C*). The fourth (*n*=21; 15.3%) originated with maximum signal over both occipital areas, drifting slightly over the left parietal region (*figure 2D*). The fifth (*n*=15; 10.8%) demonstrated onset and maximum signal over the right frontal region and propagated to the left frontal region (*figure 2E*). The sixth (*n*=7; 5.1%) originated over both occipital areas (O1>O2) and propagated to the right frontal region with a mean latency of ≈15 ms without apparent involvement of the intervening cortical areas, drifting frontally (*figure 2F*). The seventh (*n*=6; 4.4%) demonstrated onset and maximum signal in the left frontal region, propagating to the right frontal region (*figure 2G*).

Five distinct types of focal pre-generalisation SWD (*n*=31) were identified. The first (*n*=17; 54.8%) originated over the right occipital region and propagated to the central areas (through P4), crossing to the left frontal region and drifting locally (*figure 3A*). The second (*n*=5; 16.2%) demonstrated right frontal onset, crossed with maximum signal over the left frontal region, and drifted to the left fronto-polar and parietal areas (*figure 3B*). The third (*n*=5; 16.2%) demonstrated left frontal onset and propagated to the ipsilateral parietal areas (*figure 3C*). The fourth (*n*=3; 9.6%) demonstrated bilateral occipital onset and propagated to the right frontal area (*figure 3*D). The fifth (*n*=1; 3.2%) originated over the left frontal region and crossed the midline towards the right frontal area (*figure 3E*).

Three types of single generalised SWD (*n*=34) were identified. The first (*n*=16; 47.1%) originated over the right fronto-temporal region, rapidly crossed with maximum signal over the left frontal region, and drifted over the left fronto-polar and parietal areas (*figure 4A*). The second (*n*=12; 35.3%) demonstrated right temporal onset, propagated to both frontal areas with maximum signal on the left, and drifted over the left fronto-polar and temporal areas, slightly over the parietal cortex (*figure 4B*). The third (*n*=6; 17.6%)

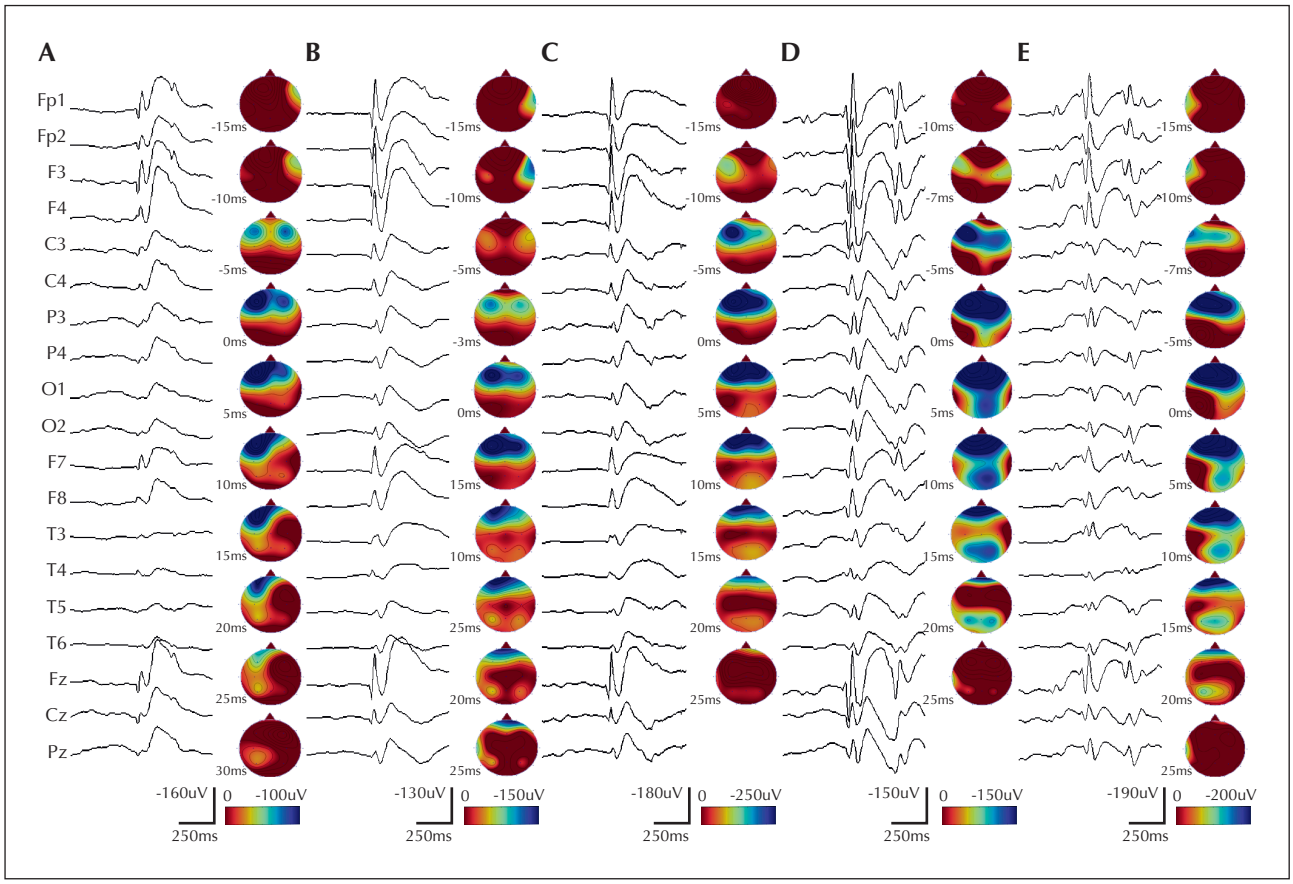

Figure 4. EEG waveform averages and spatiotemporal profiles of single generalised interictal discharges (A-C) and first generalised spike of the SWD sequence (D and E) in Patient 1.
The three distinct types of discharge (A-C) are represented in order of abundance, with (A) the most abundant. For (D) and (E), the discharge in (D) was more abundant than that in (E).

demonstrated left fronto-temporal onset, with maximum signal over the frontal region, and drifted to both fronto-polar areas and slightly towards the posterior regions (*figure 4C*).
Two distinct types of generalised repetitive SWD (*n*=29) were identified. The first (*n*=21; 72.4%) demonstrated bilateral fronto-temporal onset, spreading frontally and drifting over the fronto-polar and parietal/occipital regions (*figure 4D*). The second (*n*=8; 27.6%) demonstrated left temporal onset, propagated with maximum signal over both frontal regions, and drifted over both fronto-polar regions, the right parietal region, and left posterior temporal regions (*figure 4E*).
In summary, the topography (frontal and occipital) and propagation patterns of interictal and pre-generalisation focal SWDs were similar; the extent of propagation patterns was minimal (local frontal or occipital) and complex (occipital to frontal and from one frontal area to the contralateral homologous region) (*table 1*). The temporal/fronto-temporal onset and complex propagation of the single generalised interictal SWD and first spike of the generalised repetitive SWD were also similar, but distinct from the focal interictal and pre-generalisation SWD. In particular, none of the 31 pre-generalisation spikes demonstrated the same onset location or propagation as the first spikes of the two types of lead-in, repetitive, generalised SWDs (*table 1*).

Discussion

Despite their appearance at specific electrode positions in clinical scalp EEG, focal spikes may reflect a series of events that occur sequentially at neighbouring or distal electrode positions, rather than single stationary cortical generators, as revealed by clustering and signal averaging methods. Increased resolution allows the identification and study of distinct propagating patterns of interictal spikes that cannot be fully appreciated by clinical EEG

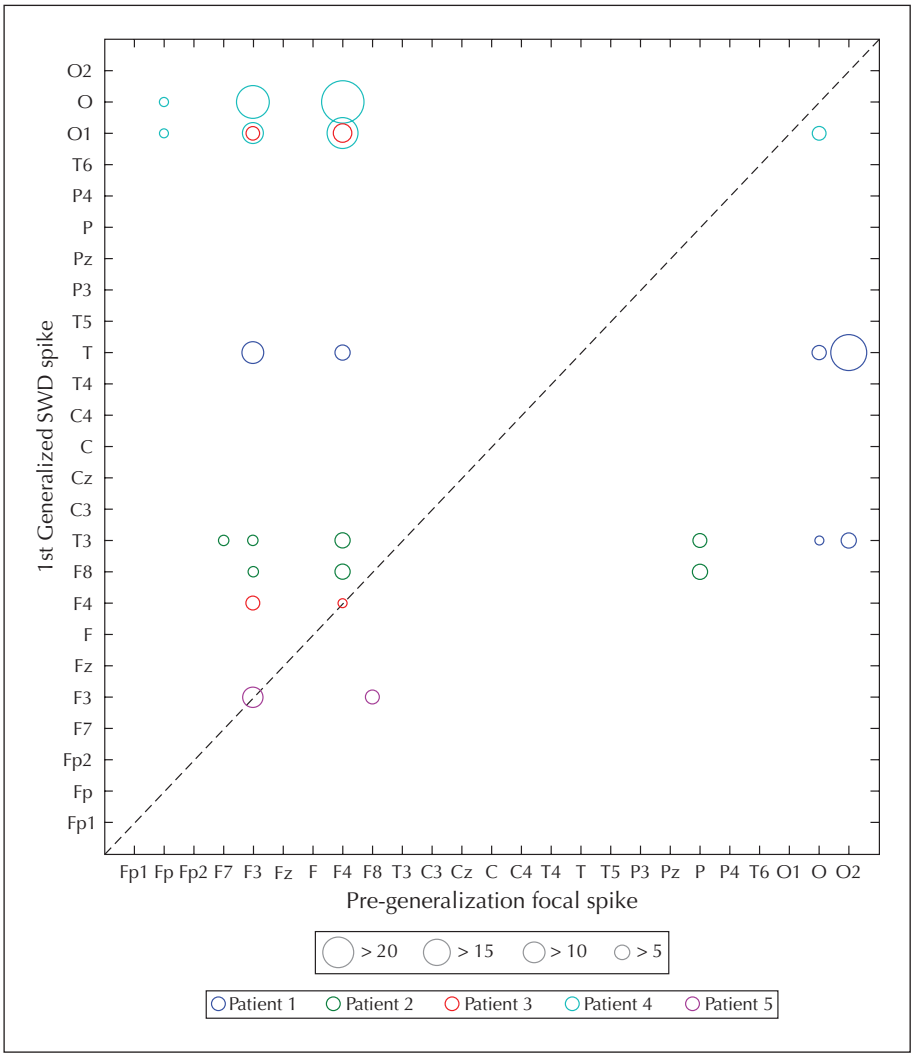

Figure 5. 2D diagram relating pre-generalisation focal SWDs to the first generalised spike of the "led-in", sustained, 3-Hz SWD. The diameters of the circles are proportional to the number of discharges.

interpretation (Emerson *et al.*, 1995). In temporal lobe epilepsy (TLE), for example, the composite scalp recorded signal (temporal spike) is formed by the sequential activation of multiple generators within the epileptogenic zone (Stefan *et al.*, 1991). We studied the sequential spatiotemporal progression of focal and generalised spikes over 2D-electrode space in CAE, focusing on the focally-led, generalised SWD (the so-called "frontal" or "occipital" absences). Our principal finding was the lack of correlation between the leading focal (pre-generalisation) SWD and the first spike of the ensuing generalised SWD (*figure 5*); less than 10% of pre-generalisation focal SWDs demonstrated similar topography and propagation to the first generalised spike of sustained 3-Hz SWDs (*table 1*). In general, focal SWDs were frontal or occipital and spread in both directions along the anterior-posterior axis, while a substantial part of generalised SWDs initially involved the fronto-temporal or temporal areas (*table 1*). To our knowledge, this is the first study of focal spike propagation patterns in IGE (or genetic epilepsies with generalised seizures).

In accordance with our previous observations that were based on visual EEG analysis (Koutroumanidis *et al.*, 2012), we found that the topography and propagation patterns of interictal focal SWDs (those occurring distal to the sustained 3-Hz generalised discharges) and pre-generalisation focal SWDs were similar (*table 1*). Hence, based on scalp EEG, interictal spike foci would appear to signal to cortical areas of (focally-led) absence onset, in some analogy with the ictogenic process in TLE where both interictal foci and the focal seizure onset are recorded over the same temporal lobe (Alarcon *et al.*, 2001). Based on visual EEG

interpretation, the debate on the nature of "frontal" absences (*i.e*. whether they are cryptogenic or idiopathic) would appear to be justified.

However, the overall discordance between pre-generalisation spikes and the onset of generalised SWDs suggests that focally-led absences follow a far more complex process. Although the intimate temporal association between focal leading-in and the ensuing ("led-in") generalised SWD would suggest a causal relationship, the topography and propagation pattern of the former do not appear to determine the leading cortical area of the "ignited" generalised SWD, at least for the vast majority of these composite EEG events. Conceivably, active triggering of thalamo-cortical, 3-Hz, spike-wave oscillations by such interictal/pre-generalisation, cortical, spike-wave foci would require a powerful effect (top-down drive) on the thalamic nuclei, which should exceed a critical level. Such powerful drive is not suggested by the effect of focal SWDs on arousal-related thalamic centres. Recent work has shown that focal spikes in juvenile myoclonic epilepsy (Bonakis and Koutroumanidis, 2008) and CAE (Koutroumanidis *et al*., 2012) tend to occur during sleep periods of reduced vigilance (cyclic alternating pattern [CAP] phase B) and are capable, only occasionally, of enhancing the level of vigilance through thalamic activation (by introducing CAP A phases). Without negating the concept of cortical triggering mechanisms for absences (Tucker *et al*., 2007; Amor *et al*., 2009), the aforementioned evidence would suggest that the role of the pre-generalisation (leading) focal SWD in generalised epileptogenesis may be contributory (by virtue of the close temporal relationship), but is rather unlikely to be directly causal. After all, the vast majority of children with CAE have a mixture of lead-in absences (frontal and occipital) and absences with apparently bilateral synchronous onset (Yoshinaga *et al*., 2004; Sadleir *et al*., 2006; Koutroumanidis *et al*., 2012), showing that pre-generalisation spikes are by no means necessary for the occurrence of absences. Based on our present study, it is not possible to extract any further information regarding these focally-led absences; magneto-encephalography (MEG)-EEG studies may provide further information about the role of the focal pre-generalisation spikes in IGE (or genetic epilepsies with generalised seizures).

The interictal and pre-generalised focal SWDs demonstrated a wealth of different topography and propagation patterns that, on average, gave rise to more than four distinct patterns per patient (*table 1*). Spikes were mostly frontal but also occipital on either side, and propagated in the posterior or anterior longitudinal direction respectively, ipsilaterally or, on occasions, contralaterally. For example, from an occipital region to the contralateral frontal lobe (*e.g*. O2 to F3 and O1 to F4 in Patient 1; *table 1*), raising the question of a possible relationship with the default network. Frontal and occipital spikes also swiftly crossed over to the contralateral homologous area (*table 1 and figure 4C*). In general, propagation patterns displayed a variable interplay between adjacent cortical areas (remaining fairly regional), but also between non-adjacent cortical areas, transcending lobes either through apparent cortico-cortical spread (implied by continuous changes in the 2D maps as in *figure S3A*) or presumably via subcortical pathways when the spread appeared discontinuous, as in *figure 2G*.

This array of interictal focal topography and propagation patterns appears to differ significantly from that exhibited by the interictal spikes in structural (symptomatic) focal epilepsies. Using signal averaging in TLE, Emerson *et al*. (1995) found only three stereotyped propagation patterns for focal (temporal) spikes. The most frequent were to the ipsilateral fronto-polar area (frequently with contralateral fronto-polar spikes concurrent with or following the ipsilateral fronto-polar ones) and within the same temporal lobe (anterior to posterior, and less frequently, posterior to anterior). Contralateral temporal propagation was noted for only 12% of the temporal spikes within 25-55 ms, without further propagation between the contralateral temporal electrode sites. In addition, all patterns of focal seizure onset showed evolution of epileptic activity in time and space, clearly distinct from the pattern observed in "focal" generalised SWDs in this study. Although the sampling rate reported by Emerson *et al*. (1995) was lower than that reported here (200 Hz *vs* 256/512 Hz), limiting their ability to detect finer inter-electrode latency differences, the results are fairly comparable, at least with regards to the number of different spike propagation patterns and their variability and extent.

In contrast to symptomatic epilepsies, spike foci in idiopathic focal epilepsies of childhood may display more complex propagation patterns that can be similar to those observed here in CAE. When compared to a methodologically identical study of interictal spikes in children with Panayiotopoulos syndrome (Kokkinos *et al*., 2010), we noted the following features in common with those described here: a) multifocal occipital and frontal (but also often temporal) topography; b) fast propagating patterns along the longitudinal axis (occipital to frontal and *vice versa*) over the same hemisphere, but also switching between sides; and c) crossing-over from either frontal or occipital lobe to the contralateral homologous area. In the memorable study of Bray and Wiser (1965), it was proposed that central-temporal spikes may have a genetic aetiology (Bray and Wiser, 1965). Our observations of CAE in this study, and recently of Panayiotopoulos

syndrome (Kokkinos *et al*., 2010), suggest that frontal and occipital spikes can also be considered as EEG markers of genetic aetiology, reflecting similar states of interictal cortical excitability for both focal and generalised idiopathic epilepsies.

In conclusion, our findings indicate that, for CAE, focal interictal and pre-generalisation spikes share common topography and propagation patterns, and therefore appear to reflect the same bioelectrical condition; a systemic, genetic cortical hyperexcitability which is much wider, and more complex and versatile than the network of "structural" temporal epileptogenesis. Despite their close temporal relationship with the generalised spike-wave, their role in the generation of the latter remains elusive. Pre-generalisation spikes do not appear to directly trigger cortico-thalamic discharges (and absences), at least not by conventional temporo-spatial evolution, through which structural cortical foci generate focal or secondary generalised seizures. A spatial relationship is conspicuously lacking, thus clinical EEG interpretation in children with otherwise typical CAE should take into account the fact that "frontal" and "occipital" absences do not parallel secondary generalised frontal or occipital seizures. □

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Legends for supplementary results

(*figures S1-6 can be visualized on line from the journal website by clicking on the download button*)

Patient 2

Four types of interictal focal SWD (*n*=41) were identified during a recording of 1 hour and 25 minutes. The first (*n*=22; 53.6%) demonstrated onset and maximum signal over the left posterior region and drift (*figure S1A*). The second (*n*=13; 31.7%) demonstrated onset and maximum signal over the right frontal region, drifting symmetrically over the fronto-polar region (*figure S1B*). The third (*n*=5; 12.3%) originated with maximum signal over both frontal regions, drifting symmetrically to both fronto-polar areas (*figure S1C*). The fourth type (*n*=1; 2.4%) was a left frontal spike.

Four types of pre-generalisation focal SWD (*n*=12) were identified. The first (*n*=5; 41.6%) demonstrated onset and maximum signal over the bilateral parietal region, drifting locally, but also over the frontal-fronto-polar regions, mainly on the right (*figure S1D*). The second (*n*=4; 33.4%) demonstrated onset and maximum signal over the right frontal region and drift (*figure S1E*). The third (*n*=2; 16.7%) demonstrated left fronto-temporal onset and propagated to the right frontal and occipital areas (*figure S1F*). The fourth (*n*=1; 8.3%) was a left frontal spike.

One type of single generalised SWD (*n*=5) was identified. The spike originated over the right frontal area and propagated to the left frontal region and spread locally, drifting over the fronto-polar and slightly over the right posterior areas (*figure S2A*).

Two types of generalised repetitive SWD (*n*=20) were identified. One type (*n*=11; 55.0%) originated from the right fronto-temporal region, spread to the left frontal region, converging with maximum signal over the frontal areas, and drifted towards the fronto-polar and posterior regions along the midline (*figure S2B*). The second type (*n*=9; 45.0%) originated over the left temporal area, spread to the left frontal area, with maximum signal over the frontal area, and drifted in the frontal midline (*figure S2C*).

Spatiotemporal analysis showed that focal interictal and pre-generalisation SWDs shared common topography (frontal and posterior) and propagation patterns (in the majority of cases). On the other hand, generalised single and repetitive SWDs shared frontal or fronto-temporal onset and anterior and posterior propagation. Similar anterior-to-posterior propagation was noted in only 2 of the 12 pre-generalisation focal SWDs (type 3).

Patient 3

Two types of interictal focal SWD (*n*=42) were identified during a recording of 1 hour and 20 minutes. The first (*n*=36; 84.7%) demonstrated onset and maximum signal over the right frontal region, drifted over the right fronto-polar region and propagated to the right occipito-temporal regions (*figure S3A*). The second (*n*=7; 15.3%) originated with maximum signal over the left frontal area and propagated broadly towards the posterior areas, drifting over the right parietal region (*figure S3B*).

Two types of pre-generalisation focal SWD (*n*=9) were identified. The first (*n*=5; 55.5%) originated over the frontal midline with maximum signal over the right frontal region and propagated towards the right posterior temporal area (*figure S3C*). The second (*n*=4; 44.5%) originated with maximum signal over the left frontal area and then displayed complex propagation, first towards the contralateral posterior temporal area, then over the right frontal/fronto-polar region and to the left occipital region (*figure S3D*).

One type of single generalised SWD (*n*=13) was identified. The spike component demonstrated right posterior onset, with maximum signal over the right parietal area, and propagated briefly towards the left occipital area and also ipsilaterally through the temporal areas towards the right frontal and fronto-temporal areas (*figure S3E*).

Of the 33 generalised SWDs recorded, 27 initiated with polyspikes and were rejected and not analysed; the remaining 6 corresponded to two types. The first (*n*=5; 83.3%) demonstrated left occipital onset, crossed to the right occipital region, and propagated through the temporal areas to the right frontal region with maximum signal, drifting over the right fronto-polar region (*figure S3F*). The second type (*n*=1; 16.7%) occurred in the right frontal region with posterior propagation.

The localisation and propagation patterns of the interictal and pre-generalisation focal SWDs were identical (frontal on either side with posterior propagation). Common patterns were also found between single interictal generalised SWDs and the first generalised spike of the repetitive generalised SWDs (occipital on either side, with frontal propagation on the right) with the exception of a single generalised SWD that followed the pre-generalisation pattern.

Patient 4

Six types of interictal focal SDW (*n*=72) were identified. The first (*n*=27; 37.5%) drifted with maximum signal over the frontal midline (*figure S4A*). The second (*n*=16; 22.3%) demonstrated mid-parietal/central onset, propagated to the left frontal region with maximum signal, and drifted over the left fronto-polar area (*figure S4B*). The third (*n*=12; 16.6%) demonstrated bilateral fronto-polar onset, with maximum signal over the right frontal region, and drifted locally (*figure S4C*). The fourth (*n*=8; 11.1%) demonstrated right frontal onset, crossed the midline with maximum signal over the left frontal region, drifting to the left fronto-polar area (*figure S4D*). The fifth (*n*=7; 9.7%) demonstrated left frontal onset, crossed the midline to the right frontal region, and drifted to the right fronto-polar area (*figure S4E*). The sixth (*n*=2; 2.8%) was a fronto-polar spike.
Six types of focal pre-generalisation SWD (*n*=51) were identified. The first (*n*=24; 47.1%) originated with maximum signal over the right frontal region, drifting over the frontal midline to the left frontal area (*figure S5A*). The second (*n*=10; 19.7%) originated with maximum signal over the left frontal region, drifting over the frontal midline and the left parietal area (*figure S5B*). The third (*n*=7; 13.7%) originated with maximum signal over the left frontal area, propagating into two distinct directions; the right frontal and left parietal regions (*figure S5C*). The fourth (*n*=6; 11.7%) initiated with maximum signal over the right frontal region and then crossed the midline to the left frontal area, drifting locally (*figure S5*D). The fifth (*n*=2; 3.9%) was a local fronto-polar spike and the sixth (*n*=2; 3.9%) a local occipito-parietal spike.
No single generalised discharges were identified in this patient's EEG. Two rather similar types were identified in the 30 repetitive generalised SWDs. The first (*n*=16; 53.3%) appeared bilaterally over the occipital-parietal areas, propagated fast and equally over both frontal areas with maximum signal, then drifted over the fronto-polar and left temporal area (*figure S5E*). The second (*n*=14; 46.7%) appeared over the left occipito-parietal area and propagated rapidly to the right and left frontal regions with maximum signal, and drifted over both fronto-polar areas (*figure S5F*).
Again, the location and propagation patterns of the multiple focal interictal and pre-generalisation SWDs were identical (frontal with variable spread) while they differed in topography and propagation relative to the first generalised spike of the repetitive generalised SWDs, which was occipital with anterior spread.

Patient 5

Two rather similar types of interictal focal SWD (*n*=27) were identified during this patient's 25-minute EEG recording. The first (*n*=2; 88.8%) originated with maximum signal over the right frontal region, then crossed the midline and drifted over the left frontal region (*figure S6A*). The second (*n*=3; 11.2%) also demonstrated right frontal onset, but maximum signal was achieved after crossing to the left frontal region (*figure S6B*).
Two types of focal pre-generalisation SWD (*n*=7) were identified. The first (*n*=5; 71.4%) demonstrated onset and maximum signal over the left frontal region, drifting towards both frontal and fronto-polar regions (*figure S6C*). The second (*n*=2; 28.6%) originated over the right fronto-temporal region, spread to both frontal areas with maximum signal, and finally drifted over the left fronto-polar region (*figure S6D*).
No single generalised SWDs were identified. All three generalised repetitive SWDs recorded were identical to the first generalised spike, showing left frontal onset, maximum signal at the left-midline, and symmetrical drift over the frontal and fronto-polar regions (*figure S6E*).
The location and propagation patterns of the focal interictal and pre-generalisation SWDs were again similar (frontal with contralateral spread). On this occasion, the topography and propagation of the first generalised spike of the repetitive generalised SWDs coincided with that of the more frequent pre-generalisation focal SWDs.