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RESEARCH ARTICLE

Grading objective diagnostic components in paroxysmal events: One-year follow-up at a tertiary epilepsy center

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Abstract

Objective: This study was undertaken to develop a model and perform a preliminary internal validation study of the Scale for Objective Diagnostic Components of Paroxysmal Events (STAMP).

Methods: We developed STAMP, which builds on the International League Against Epilepsy task force scale for functional seizures with additional categories for epileptic seizures and syncope. We included 200 consecutive referrals to a Dutch tertiary epilepsy center to evaluate seizurelike events. We recorded demographic and clinical data and collected the clinical evaluation at referral and after 3, 6, 9, and 12 months of follow-up. We ascertained the STAMP at each time point and evaluated factors predicting an improvement in STAMP grade during follow-up.

Results: Of the 200 referrals at baseline, 131 were classified as having epileptic seizures, 17 as functional seizures, and three as syncope, and 49 were unclassifiable. STAMP grade at baseline was 4 (absent) in 56 individuals, 3 (circumstantial) in 78, 2 (clinically established) in six, and 1 (documented) in 11. Over time, 62 cases STAMP grades improved, and 23 remained unclassifiable. A refinement of STAMP grade during follow-up was due to successful event recordings in 34 people (30 video-electroencephalographic [EEG] recordings, four tilt table testing), home videos or clinician-witnessed events in 13, and identification of interictal EEG or magnetic resonance imaging abnormalities in seven. An improved STAMP grade after 12 months of follow-up was significantly more likely in those with higher event frequency, unclassifiable events, longer event duration, and a shorter time since the first event and less likely in those with a history suggestive of seizures.

Significance: This epilepsy service evaluation underscores the crucial role of event recording in improving diagnostic certainty. STAMP may be used to monitor diagnostic performance over time but requires further validation.

KEYWORDS

certainty, classification, diagnosis, functional seizures, syncope

1 | INTRODUCTION

Most seizure-like events are ultimately diagnosed as epileptic, functional, or syncopal. When the initial presentation is uncertain, further evaluation often occurs in a specialized epilepsy service. Providing a more in-depth diagnosis is one of the core services that a specialized center offers. However, the diagnostic performance of specialized services is still underassessed.

History-taking is the cornerstone in evaluating seizure-like events.[1–4] Evaluation of well-documented cases of epilepsy, functional seizures, and syncope has resulted in the identification of distinguishing features and the development of decision tools, for instance, to distinguish epilepsy from vasovagal syncope[4,5] or epilepsy from functional seizures[4,6,7] or to classify seizures.[8,9] Despite this, some cases are inconclusive or mislabeled.[9] The frequency of a false-positive epilepsy diagnosis ranges from 2% to 71%,[10] contributing to an average delay in diagnosis in functional seizures of 7–10 years.[11] Several factors play a role in misdiagnosis. These include lack of clinical expertise, absence of eyewitness accounts, low frequency of events making detailed observations difficult, and recall bias.[12,13] For instance, eyewitness accounts of reflex syncope or tonic–clonic seizures were found to be often incorrect because distinguishing features are overlooked or due to inaccurate recall.[14] Similarly, eyewitness reports of video-recorded semiological signs that could potentially discriminate between epilepsy and functional seizures were unreliable.[15]

Diagnostic accuracy depends on the complex amalgamation of clinical evaluation and the results of investigations. Clinical evaluation is subjective and judgmental and often challenging to evaluate. Monitoring change in investigation-resulting evidence may help quantify the shift in diagnostic certainty over time. This may help assess the efficacy of epilepsy services and identify characteristics of those who benefit from further investigations. One approach is the use of classification scales. These were developed and are used in research and clinical practice for disorders such as Alzheimer dementia,[16] multiple sclerosis,[17] and cerebral amyloid angiopathy.[18] Whereas the International League Against Epilepsy (ILAE) Nonepileptic Seizures Task Force established a grading scale for functional seizures,[19] no such scale is available for other causes of seizure-like events. It is, however, possible to adapt this framework to encompass syncope and epilepsy.

We developed a novel scale for seizure-like events and applied it to monitor diagnostic performance in referrals to a tertiary center.

Key points

- We developed a classification scale (STAMP) to monitor diagnostic performance in referrals to a tertiary center.
- The overall diagnostic yield increased during follow-up from 76% to 89%; rejection of the initial diagnosis was rare.
- Increase in supporting evidence mostly occurred in the first 3 months after referral, mainly due to successful event recordings.
- STAMP grade improvement was associated with higher event frequency, unclassifiable events, shorter disease duration, and longer event duration.
- STAMP grade refinement was less likely in those with a history suggestive of seizures.

2 | MATERIALS AND METHODS

2.1 | Enrollment

We enrolled 200 consecutive referrals to a tertiary epilepsy center in the Netherlands, with their first appointment in 2019. We excluded those aged 15 years and younger. We evaluated the diagnostic evidence within the following year. All had previously been assessed by a neurologist in a general hospital and were referred due to a (suspected) diagnosis of epilepsy, functional seizures, or unexplained seizure-Hisory like events. We collected demographic data (age and sex). We complemented this with potential factors that may help predict increased evidence following referral. These include time since the first event (years), availability of eyewitness accounts (yes/no), presence of triggers (yes/no), event frequency (events/year), duration, and whether events only occurred during sleep (yes/no). In the case of missing data from history taking (e.g., not reporting whether triggers were present), they were recorded as absent. The Medical Ethics Committee of Utrecht University Medical Center approved the study protocol without requiring individual informed consent, as it used anonymous data gathered during routine clinical care.

2.2 | Classification of objective diagnostic components

We developed the Scale for Objective Diagnostic Components of Paroxysmal Events (STAMP) by applying the ILAE scale for functional seizures and adding

categories for epileptic seizures and syncope along similar lines (Table 1). We named it a scale for objective diagnostic components rather than a diagnostic certainty scale, as it only assesses one aspect of diagnostic certainty. STAMP was not developed as a clinical prediction model, but we used TRIPOD recommendations to enhance reporting transparency.[22] The lowest level, "absent," refers to the diagnosis exclusively relying on accounts of the events without further supporting evidence. It requires symptoms and signs of a typical occurrence to be consistent with the semiology of the presumed cause. This category should only be used if the history is consistent with the suspected cause; if symptoms and signs conflict, the case should be labeled as "unclassifiable."

The next level, "circumstantial," is based on adding diagnosis-specific interictal findings. For a diagnosis of epileptic seizures, we considered interictal electroencephalographic (EEG) or magnetic resonance imaging (MRI) abnormalities or genetic mutations, providing that the result is known to increase the risk for epilepsy and the abnormalities fit with the presumed seizure type. Similarly, we included interictal electrocardiographic (ECG) abnormalities, echocardiography abnormalities, or the documentation of orthostatic hypotension without accompanying symptoms as circumstantial evidence for syncope.

We reserved the second-highest level, "clinically established," for well-documented cases evaluated by a specialized clinician but that lacked event recording via EEG or ictal blood pressure and ECG measurement. The "documented" level is reached for epilepsy and functional seizures through ictal video-EEG (vEEG) recording with typical semiology in the absence or presence of EEG changes, for vasovagal syncope through positive tilt table testing with symptom recognition, and for cardiac syncope through ictal ECG recording. This level is labeled as "documented" rather than "definite" (as is customary in other clinical classification scales) due to the risk of incorrectly equating a recorded episode to previous events and misinterpreting vEEG or tilt table testing due to muscle artifacts obscuring EEG changes. We determined the diagnostic category for each case at

TABLE 1 Proposed four-level Scale for Objective Diagnostic Components of Paroxysmal Events for three causes of seizure-like events: epileptic seizures, functional seizures, and syncope.

Level of supporting accurate diagnostic components	Epileptic seizure	Functional seizures	Syncope
1. Documented	Recording of typical event[a] Video-EEG		Recording of typical event Blood pressure (reflex syncope/OH) or ECG (cardiac)[b]
2. Clinically established	Video recording of the event with semiology typical of diagnosis by a clinician specialized in seizure-like events[a] Alternatively, the event witnessed by a clinician specialized in seizure-like events[a]		
3. Circumstantial	Epileptiform activity on interictal EEG, mutation, or MRI abnormality known to cause epilepsy	Video recording[a] Alternatively, event witnessed by a clinician not specialized in seizure-like events	Interictal ECG abnormalities, echocardiography abnormalities (cardiac), asymptomatic orthostatic hypotension on active standing test (OH), or daytime drops of systolic blood pressure on 24-h ambulatory blood pressure recording (reflex syncope/OH)[c]
4. Absent	History[d] Symptoms and signs of typical event consistent with semiology of the presumed cause		
5. Unclassifiable	History Symptoms and signs insufficiently typical to distinguish between diagnoses		

Abbreviations: ECG, electrocardiography; EEG, electroencephalography; MRI, magnetic resonance imaging; OH, orthostatic hypotension.

[a]Additional requirement for functional seizures: no epileptiform activity on routine interictal EEG.[19]

[b]A documented diagnosis of provoked syncope (e.g., tilt table testing) requires complaint recognition. Tilt table test should include continuous blood pressure measurements and ECG; video and EEG are optional. In the case of OH, active standing test suffices.

[c]A wide range of findings could suggest or support a diagnosis of cardiac syncope including certain ECG or echocardiography abnormalities.[20] Similarly, an active standing test with documented OH but without symptoms supports a diagnosis of OH.[20] OH and reflex syncope are also more likely, with documented daytime systolic blood pressure drops during 24-h blood pressure monitoring.[20,21]

[d]History alone is sometimes sufficient to establish a definite diagnosis. For instance, a definite diagnosis of vasovagal syncope can be established on clinical grounds.[20]

baseline according to the judgment of the treating neurologist. We added a category of "unclassifiable events" to include those evaluated for seizure-like events. We collected data on objective diagnostic components for epileptic seizures, functional seizures, and syncope at referral and after 3, 6, 9, and 12 months of follow-up (Box 1). When there was a change in supporting evidence, a second observer (R.D.T.) evaluated its relevance (e.g., whether the MRI abnormality supported a diagnosis of epilepsy).

BOX 1 Case: A 29-year-old woman with unexplained seizures

A 29-year-old woman was referred by her general practitioner after she had suffered six unexplained events with loss of consciousness and limb shaking in the previous year. A neurologist previously evaluated her in a regional hospital and performed electroencephalography (EEG) and brain magnetic resonance imaging; both were noninformative, and no diagnosis was reached. After the initial clinical assessment, given several atypical semiological features, a putative diagnosis of functional seizures was made. Her companions agreed to record a home video of her events. At 3 months, an evaluation of a home video confirmed the diagnosis of functional seizures, and a referral to psychology was made for therapy. Events persisted, and at 9 months, she was admitted for a prolonged video-EEG recording to exclude any remaining diagnostic uncertainty and to offer reassurance. This proved successful, and the finding encouraged her to take up psychological treatment.

In this case, the level of supporting evidence changed twice during the 12-month follow-up. At the initial evaluation, the Scale for Objective Diagnostic Components of Paroxysmal Events was graded 4 (absent), increasing to "clinically established" at 3 months and "documented" at the end of the follow-up. As individuals infrequently visit the emergency department of a regional hospital after a seizure, a clear description of her diagnosis—functional seizures, documented by video-EEG registration—may help to deliver appropriate care and avoid unnecessary ancillary tests.

2.3 | Statistical analysis

We evaluated factors predicting a change in STAMP grade after 12 months compared to baseline by using the Mann–Whitney *U*-test for continuous variables (age, time since first event, event duration, event frequency) and the 2×2 χ^2 test for categorical variables (all other). We applied the Bonferroni correction to adjust for multiple testing (cutoff *p*-value .05/12 = .0042).

3 | RESULTS

3.1 | Case characteristics

We evaluated 200 cases, including 107 females (53.5%). The age ranged from 16 to 84 years, with a median of 37 years. Time since the first event ranged from <1 year to 73 years, with a median of 8 years. Most ($n = 147$, 73.5%) were referred by a neurologist, whereas 53 (26.5%) were by their general practitioner following a previous neurological evaluation. Eyewitness accounts were available for 156 individuals, and 34 reported event triggers. Event frequency ranged from singular events to >30 daily events (median = 11 per year). Event duration ranged between 2 s and 3 h, with a median of 3 min. Ten reported having only sleep-related events. Eighteen (9%) were lost to follow-up, including nine after the initial consultation.

3.2 | Change in objective diagnostic components and diagnosis

One-hundred thirty-two individuals were classified as having epileptic seizures at baseline, 17 as functional seizures, two as syncope, and 49 as unclassifiable. The STAMP grade of those with a presumed diagnosis at baseline was 4 in 56 cases, 3 in 78, 2 in six, and 1 in 11. In 62 STAMP grades, they were improved during follow-up, in 48 cases at 3 months, in 10 cases at 6 months, in two at 9 months, and in four at 12 months (Figure 1). In two instances, the STAMP grade improved twice during follow-up. The final STAMP grade at 12 months was 4 in 39 cases, 3 in 74, 2 in 19, and 1 in 45, whereas 23 cases remained unclassifiable.

The overall diagnostic yield increased during follow-up from 76% to 89%. In eight cases, the initial diagnosis of epileptic seizures changed to functional seizures (five cases), syncope, sleep disorder, or paroxysmal movement disorder (one case each). Of the 48 cases with unclassifiable events at baseline, 16 were eventually diagnosed with functional seizures, four with syncope, four with epilepsy, and one with gastric disorder (Figure 2). In most cases, this was due to an improvement in objective diagnostic

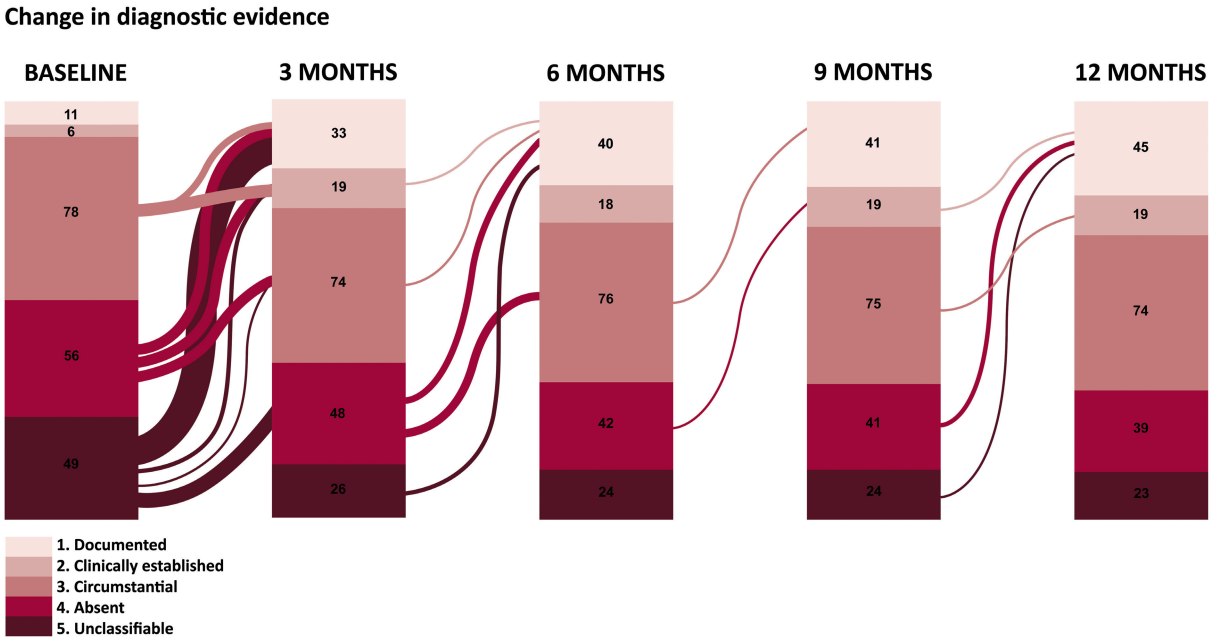

FIGURE 1 Sankey plot visualizing the change in Scale for Objective Diagnostic Components of Paroxysmal Events grade at each time point: baseline (i.e., clinical evaluation at referral) and after 3, 6, 9, and 12 months of follow-up.

components, in seven due to additional historical information (e.g., description of new events).

STAMP grade improved due to successful event recordings in 34 (30 vEEG, four tilt table testing), home video-recorded or clinician-witnessed (e.g., consultation room) events in 13, and identification of interictal EEG or MRI abnormalities in eight. Improvement of STAMP grade after 12 months was more likely in those with higher event frequency, unclassifiable events, a shorter disease duration, and a more prolonged event duration and less likely for those with a diagnosis suggestive of epilepsy upon referral (Table 2). Other clinical parameters were not associated with the refinement of STAMP grade following referral.

4 | DISCUSSION

We developed a classification scale for objective diagnostic components to monitor the diagnostic performance of a tertiary epilepsy center. STAMP grade increased in approximately one third of cases, mainly within the first 3 months, predominantly due to successful event recording (vEEG or tilt table testing). In only a minority, the initial diagnostic category was rejected. A better STAMP grade after 12 months of follow-up was more likely in those with higher event frequency, shorter disease duration, and a more extended event, whereas STAMP grade refinement was less likely in those with a history suggestive of seizures.

There are limitations to our approach. We received referrals from district hospitals covering approximately 70% of the total Dutch population. Nonetheless, our cases are from a single tertiary center; thus, some selection bias remains. Further studies in other health systems are needed to confirm the added diagnostic value of specialized epilepsy services. As we focused on the change in objective diagnostic components (i.e. the level of support of investigations), our scale needs to consider the quality of the history taking. As ancillary testing constitutes only one aspect of diagnostic certainty, we could not evaluate the quality of the diagnosis. Specific presentations can be diagnosed based on history alone and do not necessarily require clinical documentation. Vasovagal syncope is a good example. Similarly, cardiac syncope is considered highly likely/definite if the account is supported by specific prespecified interictal ECG or echo abnormalities.[20] Therefore, STAMP was not designed as a prediction model for individual diagnosis. Implementing STAMP requires further validation to establish sensitivity and specificity, ideally in a cohort of classifiable cases with blinding of previous assessments. Notably, validating a syncope diagnosis would be critical, as we have only studied a few cases. Some characteristics were present in only a few cases (e.g., events being solely nocturnal). This could result in identifying further predictors of an increase in STAMP level. Lastly, although STAMP contains mainly objective components, subjective elements remain. A correct interpretation of the results of ancillary testing requires clinical expertise. For instance, identifying and classifying interictal EEG[23] and

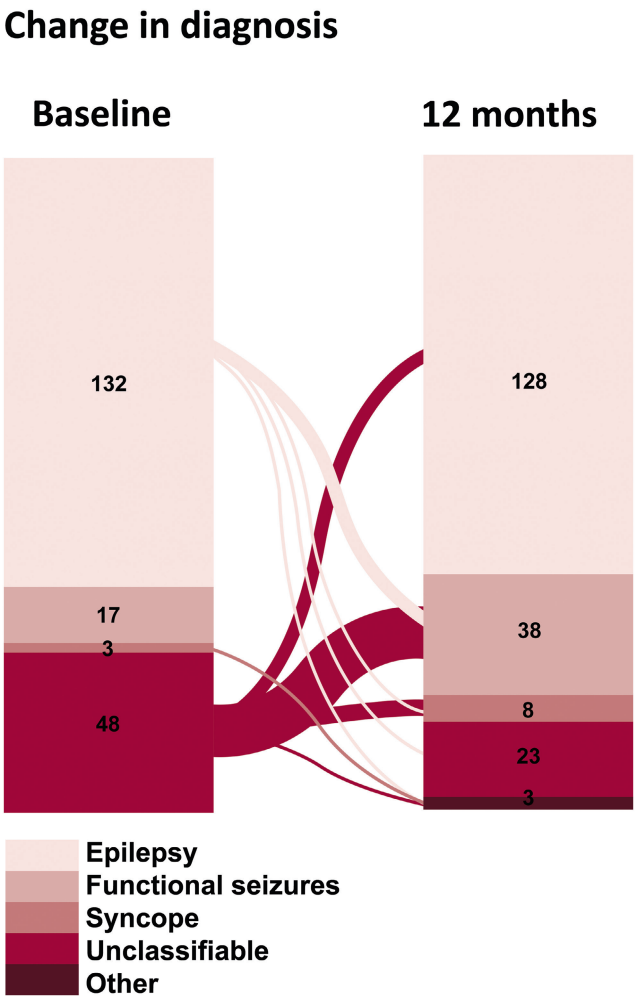

FIGURE 2 Sankey plot visualizing the change in the main diagnostic groups between two points: baseline (ie, clinical evaluation at referral) and after 12 months of follow-up.

MRI abnormalities[24] or interpreting home videos[25] is subjective. This accounts for the ILAE classification scale for functional seizures crediting a greater level of certainty to an expert video assessment versus a nonexpert.[19] Further studies are needed to determine the interrater consistency of STAMP. As we monitored only objective diagnostic components, we did not evaluate other important aspects of the role of an epilepsy center, such as counseling and timely correct treatment.

The added value of specialized epilepsy services is underassessed. Recent evidence suggests that specialist-level referral was associated with an incremental reduction in premature mortality, with the most significant benefit to those referred to a specialized epilepsy program.[26] Besides access to treatment options not available outside of specialist care, improved diagnostic performance was suggested as a potential driver of this benefit.[26] Most changes in diagnostic evidence occurred in the first 3 months after referral despite a median duration of 8 years. This finding suggests that epilepsy clinics are essential in obtaining early diagnostic certainty. Home video and long-term vEEG recordings were crucial in increasing diagnostic objective components. This may also explain why longer event duration was associated with improved STAMP grades, facilitating home video recordings. A recent survey found that the overall quality of home videos of events acquired after explicit instruction was sufficient for clinical interpretation in most individuals with seizurelike events.[27] Tilt table testing also improves diagnostic certainty provided the individual or the witness recognizes the provoked events as similar to the spontaneous ones.[28] In our cohort, in eight cases (4%), syncope was confirmed through tilt table testing, including

TABLE 2 Clinical characteristics at baseline, expressed as *n* (%) or median (interquartile range).

Clinical characteristic	Improvement in STAMP grade, $n = 62/200$	No improvement in STAMP grade, $n = 138/200$	Significance[a]
Female	42 (68%)	65 (47%)	OR = 2.36 (1.26–4.42) $p = .007$
Age	39 (23–54)[a]	37 (27–53)[a]	$p = .54$
Years since the first event	4 (1–15)[a]	10 (3–21)[a]	$p = .001$*
Eyewitness observation available	53 (85%)	103 (75%)	OR = 2.00 (.90–4.47) $p = .09$
Event triggers reported	10 (16%)	24 (17%)	OR = .91 (.41–2.05) $p = .83$
Event frequency per year	28 (6–200)[a]	3 (<1–40)[a]	$p < .001$*
Event duration in minutes	5 (2–16)[a]	2 (1–5)[a]	$p = .004$*
Sleep-related events only	3 (5%)	7 (5%)	OR = .95 (.24–3.81) $p = .95$
Events classified as epileptic seizures at referral	27 (44%)	105 (76%)	OR = .24 (.13–.46) $p < .001$*
Events classified as functional seizures at referral	9 (15%)	8 (6%)	OR = 2.76 (1.01–7.54) $p = .041$
Events classified as syncope at referral	1 (2%)	1 (1%)	-
Unclassifiable events at referral	25 (40%)	24 (17%)	OR = 3.34 (1.72–6.65) $p < .001$*

Abbreviations: OR = odds ratio; STAMP = Scale for Objective Diagnostic Components of Paroxysmal Events.

[a]Threshold for significance was set at .0042 to correct for multiple testing (Bonferroni correction; .05/12); significant *p*-values are marked with an asterisk.

one with a previous diagnosis of epilepsy. This diagnostic yield is comparable with the 3% syncope prevalence among tertiary epilepsy referrals in a previous German study.[29]

The results of investigations should only be considered in their clinical context. For instance, five neurologists reviewed vEEG recordings in one study, and diagnostic accuracy was approximately one third.[30] A second study reported a much higher precision of neurologists reviewing home videos and a summary of the clinical presentation.[25] The importance of investigations relative to clinical assessment also depends on the diagnosis, as reflected by the current diagnostic criteria of the different paroxysmal disorders. For instance, clinical reasoning is sufficient for a definite vasovagal syncope diagnosis,[20] whereas a confident diagnosis of functional seizures relies on event recording.[19,31] In contrast, a diagnosis of epilepsy is defined by two unprovoked events at least 24 h apart. Still, depending on the investigation, it can be made after a single event.[32] The need for objective diagnostic components to diagnose epilepsy depends on the prior clinical probability.[33] Event recording may be recommended in more complex presentations, including frontal lobe epilepsy.[34]

As our scale provides insight into the objective diagnostic components of a paroxysmal disorder diagnosis, the clinical context determines whether event recording is required to assign a diagnosis. A major shortcoming in diagnosing epilepsy is the frequent unavailability of a gold standard. Even with long-term follow-up, it is often impractical to document a habitual seizure, particularly in those with infrequent events. The value of STAMP increases in cases of higher complexity as it provides structured, standardized reporting on investigations, improving clarity in communication. Implementing a lexicon of diagnostic certainty for radiologists dramatically reduced the number of expressions used to indicate their diagnostic confidence.[35] Similarly, clinical research could benefit from such a scale comparing cohort results. It is often unclear which criteria were used to establish a diagnosis, with the risk of selection bias as a possible confounder. The European Study on the Burden and Care of Epilepsy suggested considerable variability in the degree of certainty of the epilepsy diagnosis, thus underscoring the need for standardized criteria for documenting diagnosis.[36] Explicit self-rating of diagnostic evidence may also be helpful for clinical practice, for instance, in handover cases between providers.[37] The scale, however, only covers one aspect of diagnostic evaluation and does not grade the medical history's quality and reliability.

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CONFLICT OF INTEREST STATEMENT

J.W.S. reports personal fees from Eisai, UCB, and Angelini Pharma, as well as grants from Eisai, UCB, and Angelini Pharma, outside the submitted work. R.D.T. reports personal fees from UCB, Eisai, Theravarance, LivAssured, Novartis, Xenon, and Angelini, as well as grants from Medtronic and NewLife Wearables, outside the submitted work. None of the other authors has any conflict of interest to disclose. 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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