# Using phenomenology and semiology to support the differential diagnosis of transient loss of consciousness.

Thesis submitted to the University of Sheffield for the degree of Doctor of Philosophy.

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# Contents

# Acknowledgements

*Man or mouse, oak or orchid, we take a livelihood from our land and our fellows, and give in return an endless succession of acts and thoughts, each of which changes us, our fellows, our land, and its capacity to yield us a further living. Ultimately, we give ourselves.*

*ALDO LEOPOLD, 'ECOLOGY AND POLITICS'*

To Dad, who taught me good.

To Mum, who taught me virtue.

To Anna, who taught me care.

To Lily, Ruaridh, and Billy, who taught me hope.

To Markus, who taught me most of the rest.

# Abstract

**BACKGROUND:** Transient loss of consciousness (TLOC) is a common acute presentation; over 90% are due to either syncope, epilepsy, or functional/dissociative seizures (FDS). Differential diagnosis is challenging. Better clinical criteria to support differential diagnosis – including clinical decision aids (CDAs) – could improve outcomes.

**OBJECTIVES:** This thesis aims to: (1) review barriers to accurate TLOC diagnosis; (2) provide external validation of candidate diagnostic criteria; and (3) develop a CDA for TLOC diagnosis.

**METHODS:** Methods include: (1) narrative review; (2) ethical analysis; (3) thematic analysis of semi-structured interviews with 20 first-presentation TLOC patients; (4) retrospective cohort video study of 189 videos from 50 patients with epilepsy or FDS; (5) retrospective cohort diagnostic accuracy study of 300 patients with syncope, epilepsy, or FDS; and (5) prospective cohort diagnostic accuracy study of 178 first TLOC patients.

**RESULTS:** *Experiences of initial TLOC assessment*: First TLOC can be a disorienting 'biographical disruption'. Communication supports interim self-management. *Individual diagnostic features*: FDS are more likely than epilepsy to show peri-ictal social responsiveness in video review. This is externally validated as predicting FDS in first-presentation TLOC, as are fluctuating course or waxing/waning movements, asynchronous limb movements, younger age at onset, and total non-ictal and peri-ictal symptoms. Other diagnostic features derived from chronic patient cohorts are not validated in first presentations. *CDA development*: A machine learning classifier trained on 36 patient/witness questionnaire responses in the chronic syncope/epilepsy/FDS cohort classified 86.0% of patients correctly. Validation accuracy was worse (75.8%) in the first-presentation TLOC cohort. A classifier trained on first-presentation data identified 9 optimal patient-reported predictors. It correctly identified 80.8% of diagnoses, non-significantly superior to initial clinician assessment (70.5%, $p$=0.192). Patients reported the CDA accessible and acceptable to use.

**CONCLUSIONS:** CDAs could improve outcomes for patients who experience TLOC. Future research needs to be conducted within the first presentation setting to ensure validity.

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# List of abbreviations

| Abbreviation | Definition |
|---|---|
| **A&E** | Accident and Emergency |
| **ACTH** | Adreno-cortico-trophic hormone |
| **AI** | Artificial intelligence |
| **AMU** | Acute Medical Unit |
| **ANOVA** | Analysis of Variance |
| **ASM** | Anti-seizure medication |
| **AUROC or AUC** | Area under ROC |
| **CART** | Classification and Regression Trees (algorithm) |
| **CCG** | Clinical commissioning group |
| **CDA** | Clinical decision aid |
| **CDR** | Clinical decision rule |
| **CDST** | Clinical decision support tool |
| **CI** | Confidence interval |
| **CK** | Creatine kinase |
| **CT** | Computed tomography |
| **DSLS** | Dissociative Seizures Likelihood Score |
| **ECG** | Electrocardiogram |
| **ED** | Emergency Department |
| **EEG** | Electroencephalogram |
| **EMU** | Epilepsy Monitoring Unit |
| **ES** | Epileptic seizure |
| **ESC** | European Society for Cardiology |
| **FDS** | Functional / dissociative seizure |
| **FN** | False negative |
| **FP** | False positive |
| **FWER** | Family-wide error rate |
| **GP** | General Practitioner |
| **HRQoL** | Health-related quality of life |
| **ICS** | Integrated care system |
| **IDCV** | Instrument Development and Construct Validation (framework) |
| **IED** | Interictal epileptiform discharge |
| **ILAE** | International League Against Epilepsy |
| **iPEP** | Initial Paroxysmal Event Profile |
| **IQR** | Interquartile range |
| **LASSO** | Least absolute shrinkage and selection operator |
| **LIME** | Locally intelligible, model-agnostic (explanations) |
| **LLM** | Large language model |
| **LR** | Likelihood ratio |
| **MRI** | Magnetic resonance imaging |
| **NASH** | National Audit of Seizure Management in Hospitals |
| **NASSS** | Nonadoption, Abandonment, and challenges to the Scale-up, Spread, and Sustainability (framework) |
| **NEAD** | Non-epileptic attack disorder |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Care Excellence |

| | |
|---|---|
| **NIHR** | National Institute for Health Research |
| **NPV** | Negative predictive value |
| **OOBE** | Out-of bag error |
| **OR** | Odds ratio |
| **PEO** | Paroxysmal Event Observer questionnaire |
| **PEP** | Paroxysmal Event Profile |
| **PESQ** | Paroxysmal Event Symptoms Questionnaire |
| **PEWQ** | Paroxysmal Event Witness Questionnaire |
| **PNES** | Psychogenic non-epileptic seizure |
| **PPV** | Positive predictive value |
| **RABTC** | Rapid access blackout triage clinic |
| **RF** | Random forest |
| **RfPB** | Research for Patient Benefit |
| **ROC** | Receiver operating (characteristic) curve |
| **ROS** | Review of symptoms |
| **SDEC** | Same Day Emergency Care (Centre) |
| **SRQR** | Standards for Reporting Qualitative Research |
| **TCS** | Tonic-clonic seizure |
| **TIA** | Transient ischaemic attack |
| **TLOC** | Transient loss of consciousness |
| **TN** | True negative |
| **TP** | True positive |
| **vEEG** | Video-electroencephalogram |

# Included publications

2.1. **Wardrope, Alistair**. "The Promises and Pitfalls of Seizure Phenomenology." *Seizure: European Journal of Epilepsy* 113 (2023): 48–53. https://doi.org/10.1016/j.seizure.2023.11.008.

2.2. **Wardrope, Alistair**, and Heather Stewart. "Epistemic Privilege, Phenomenology and Symptomatology in Functional/Dissociative Seizures." *Social Epistemology,* ePub ahead of print (2024). https://doi.org/10.1080/02691728.2024.2400066.

2.3. **Wardrope, Alistair**, Lindsay Blank, Melloney Ferrar, Steve Goodacre, Daniel Habershon, and Markus Reuber. "'It Is Just a Big Question Mark': A Qualitative Interview Study of Patient Experiences of the Initial Assessment of Transient Loss of Consciousness." *BMJ Open,* In press (2025).

3.1. **Wardrope, Alistair**, Siew Wong, Jonathan McLaughlan, Maytal Wolfe, Maria Oto, and Markus Reuber. "Peri-Ictal Responsiveness to the Social Environment Is Greater in Psychogenic Nonepileptic than Epileptic Seizures." *Epilepsia* 61, no. 4 (2020): 758–65. https://doi.org/10.1111/epi.16471.

3.2. **Wardrope, Alistair**, Stephen J Howell, and Markus Reuber. "Diagnostic Features of Functional/ Dissociative Seizures in the First Presentation of Transient Loss of Consciousness." *Epilepsy & Behavior* 164 (2025): 110263. https://doi.org/10.1016/j.yebeh.2025.110263.

4.1. **Wardrope, Alistair**, Jenny Jamnadas-Khoda, Mark Broadhurst, Richard A. Grünewald, Timothy J. Heaton, Stephen J. Howell, Matthias Koepp, Steve W. Parry, Sanjay Sisodiya, Matthew C. Walker, and Markus Reuber. "Machine Learning as a Diagnostic Decision Aid for Patients with Transient Loss of Consciousness." *Neurology Clinical Practice* 10, no. 2 (2020): 96–105. https://doi.org/10.1212/CPJ.0000000000000726.

4.2. **Wardrope, Alistair**, Melloney Ferrar, Steve Goodacre, Daniel Habershon, Timothy J Heaton, Stephen J Howell, and Markus Reuber. "Validation of a Machine Learning Clinical Decision Aid for the Differential Diagnosis of Transient Loss of Consciousness." *Neurology Clinical Practice*, In press (2024).

The final paper, included as a supplementary chapter, remains under review:

4.3. **Wardrope, Alistair**, Lindsay Blank, Melloney Ferrar, Steve Goodacre, Daniel Habershon, Markus Reuber. "Acceptability and utility of an online patient-completed clinical decision aid for the differential diagnosis of transient loss of consciousness: a qualitative interview study". *JMIR Formative Research*, Manuscript under review (2024).

# Section 1 Commentary

## 1.1. Introduction

This thesis focuses on clinical criteria to support the differential diagnosis of transient loss of consciousness (TLOC). Its 8 chapters (7 accepted for publication in peer-reviewed publications, and one supplementary chapter still under review) are organised into three sections: the first discusses some of the difficulties in the clinical assessment and first presentation of TLOC, from clinician and patient perspectives. The second focuses on the external validity of prior research on the differential diagnosis of TLOC. The third, and largest, section comprises the piloting, development, and initial validation of a patient-completed clinical decision aid (CDA) for the differential diagnosis of TLOC in adult patients in emergency and primary care settings.

In this commentary, I discuss the clinical and research background to, and literature surrounding, each of these areas. In §1.2 I introduce the problem of TLOC, and its three main causes: syncope, epileptic seizures (ES), and functional/dissociative seizures (FDS). I then outline the scale of the clinical, social, and health economic problem raised by the misdiagnosis of TLOC.

In §1.3, I discuss why diagnosing the cause of TLOC can be so challenging, reviewing the evidence for different candidate diagnostic criteria to support differential diagnosis, looking in particular at: information from patients about their TLOC; information from witnesses to the TLOC episodes; and biomarkers or other investigations found in the first presentation setting.

§1.4 discusses the limitations of this evidence base, demonstrating that much of the research behind it is subject to significant biases that limit its external validity when applied to the first-presentation context.

§1.5 discusses the role of CDAs in supporting the differential diagnosis of TLOC. After a review of the requirements of CDAs suitable for use in emergency care settings, I provide a summary of existent candidate CDAs to support TLOC diagnosis, and discuss their limitations. I then discuss the piloting, development, and validation of a CDA that forms the bulk of this thesis.

I close in §1.6 with a discussion of future research directions in TLOC diagnosis and management.

## 1.2. Transient loss of consciousness

### 1.2.1. Definition and aetiology

Transient loss of consciousness (TLOC; colloquially known as a ‘blackout’) is defined as spontaneous loss of awareness with complete recovery and without residual neurological deficit, not due to head trauma.[1–3] Over 90% of emergency or primary care TLOC presentations with an identifiable cause are due to either syncope, epileptic seizures (ES), or functional/dissociative seizures (FDS).[4,5]

#### *1.2.1.1. Syncope*

Syncope is TLOC due to cerebral hypoperfusion, characterised by a rapid onset, short duration, and spontaneous complete recovery.[3] The pathophysiological hallmark of syncope is a low

systemic blood pressure resulting in global cerebral hypoperfusion; it can further be subclassified according to three main causes of this fall in blood pressure.[3,5]

The most common type, reflex (or neurally-mediated) syncope, results from inappropriate autonomic reflex activity resulting in either reduced sympathetically-mediated peripheral vasoconstriction (i.e. increased vasodilatation; vasodepressor syncope), or parasympathetically-mediated bradycardia (cardioinhibitory syncope). Reflex syncope may be precipitated by triggers such as pain or emotion, situational factors like micturition or defaecation, postural changes, or direct baroreceptor stimulation (carotid massage).

Syncope due to orthostatic hypotension results from failure of postural accommodation reflexes that would otherwise maintain cerebral perfusion against gravity when a person moves from sitting or lying to standing. Reduction in blood pressure at the head and neck due to the effect of gravity should stimulate compensatory vasoconstriction and increase in cardiac output. This mechanism most commonly fails due to medications interfering with one or both compensatory mechanisms, such as many antihypertensives. Volume depletion from inadequate fluid intake or excessive loss including haemorrhage also interferes with this mechanism. More rarely, it can be produced by autonomic failure – either primary autonomic failure as seen in synucleinopathies such as Parkinson's disease and Multiple System Atrophy, or as a secondary manifestation of systemic diseases like diabetes or amyloidosis.[3]

The last main type is cardiac syncope, or syncope due to sudden primary impairment of cardiac output. This may be due to arrhythmia, or structural disease of the heart or great vessels (e.g. aortic stenosis, hypertrophic cardiomyopathy, pulmonary embolism). This group poses the highest risk of short-term morbidity and mortality.[6]

#### *1.2.1.2. Epileptic seizures*

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[7] Seizures can be focal – originating in networks confined to one cerebral hemisphere – or generalised – rapidly and invariably involving networks distributed across both cerebral hemispheres.[8] Not all ES result in TLOC, but both generalised (e.g. generalised tonic-clonic and typical absence) and focal (focal impaired awareness and focal to bilateral tonic-clonic) seizures can cause TLOC.[9]

Not everyone who experiences an epileptic seizure has epilepsy. Many brain insults (such as cerebrovascular disease, infection, or trauma), or systemic illnesses affecting brain function (such as toxic or metabolic exposures) can produce acute symptomatic seizures.[10] Even amongst those who experience an 'unprovoked' epileptic seizure, only 27% (95% confidence interval [CI] 24% to 31%) will have a further seizure in the next 6 months, 43% (95% CI 37% to 44%) in two years.[11] Epilepsy is defined conceptually as an enduring predisposition to ES; in practice, this is defined as either: having at least two unprovoked ES more than 24 hours apart; having a single epileptic seizure, and greater than 60% estimated seizure recurrence risk; or having a defined epilepsy syndrome (on the basis of clinical, electrophysiological, and/or imaging data).[7]

#### *1.2.1.3. Functional/dissociative seizures*

Functional/dissociative seizures (FDS), also known *inter alia* as non-epileptic attacks, psychogenic non-epileptic seizures, or conversion disorder with seizures,[12] are episodic disturbances of normal functioning and reduced self-control that typically resemble ES, but are not associated with the abnormal neuronal activity characteristic of that condition.[13] Various

aetiological models of FDS exist;[14] they hold in common that the hallmark alterations in functioning and behaviour are involuntary responses to precipitating situations, sensations, memories, or emotions.

## 1.2.2. Epidemiology

Reliable epidemiological data regarding first TLOC presentations is challenging to obtain; existing studies are influenced heavily by setting (e.g. primary/emergency care presentations[15] compared with secondary care clinic referrals[16,17] or inpatient admissions[18]), inconsistent or ill-defined terminology generating coding difficulties,[5,12] and patient under-reporting due to concerns regarding stigma or social implications.[19]

With these caveats, TLOC accounts for 1.2-2.2% of all adult Emergency Department presentations,[15] and 1-6% of hospital inpatient admissions.[20] Up to half of the UK population will experience TLOC at some point in their lives.[1]

Adults of all ages experience TLOC, though the frequency of different aetiologies varies with age. The incidence of syncope increases markedly in later life, being higher in adults >70 years and with annual incidence as high as 6% in older adults in long-term care settings.[21] ES have a bimodal age distribution, with incidence peaking in early adulthood and a secondary peak at 60-69 years.[22] Incidence of FDS peaks in young adulthood, though there are often delays to diagnosis of many years.[23]

The prevalence of both syncope and epilepsy is overall similar across gender categories,[24,25] though there are gender differences in subtypes and outcomes.[25–27] FDS, meanwhile, are significantly more common in women, with estimated ratios ranging from 1.15 to 4.4 in different populations.[23]

## 1.2.3. The problem of misdiagnosis of the causes of transient loss of consciousness

The initial assessment of patients with a first presentation of TLOC centres on excluding secondary causes, and then differentiating between the three main causes above. This is essential to identify patients at imminent risk of severe morbidity or mortality, identify appropriate investigations, and determining best ongoing management and referral.[1]

Unfortunately, the differential diagnosis of TLOC is challenging, and misdiagnosis common. Estimates of misdiagnosis rates vary from 20-30%;[28,29] in the prospective cohort of unselected adult first TLOC patients included in §4.2, the initial assessing clinician's diagnosis agreed with the expert reference standard in just 67.4% of cases (equivalent to misdiagnosis rate of 32.6%).

### *1.2.3.1. Clinical relevance*

Such misdiagnosis has major implications for patient outcomes. Syncope has a 9.1% 10-day morbidity or mortality (necessitating early identification), while at 1 year the mortality for cardiac syncope lies at over 30%.[30,31] Patients who have early specialist assessment for ES have longer times to seizure recurrence,[32] and increased odds of long-term seizure freedom.[33] For patients with FDS – who have a median time from first presentation to diagnosis of four to seven years,[34] misdiagnosis places them subject to prolonged disability, and risks potentially fatal mistreatment.[35,36]

#### *1.2.3.2. Psychosocial relevance*

Beyond health-related outcomes, delayed or missed TLOC diagnoses have profound psychosocial impacts. Despite being a paroxysmal condition with patients asymptomatic between episodes, people who experience TLOC report lower general health-related quality of life (HRQoL) than healthy comparators, and show significant functional impairments. In one Dutch study, people experiencing TLOC reported mean impairment in 33% of listed functional activities.[37] In the qualitative study of patient experiences of the first assessment of TLOC included in §2.3, TLOC represented a profound "biographical disruption,"[38] altering their experiences in ways more akin to chronic persistent illnesses. A lack of clear diagnosis deprived patients of the tools to navigate this disruption.

More practically, diagnoses like epilepsy also have a range of associated psychological and social implications, such as for employment and driving.[35,39] Patients with uncomplicated vasovagal syncope (who require no further management beyond lifestyle advice) who are misdiagnosed as having an epileptic seizure find themselves unable to drive for at least six months, and in some occupations find themselves unable to work.

#### *1.2.3.3. Health economic and policy relevance*

The need for improved tools and pathways for TLOC assessment and diagnosis is clearly evident from the current treatment gap in TLOC management, and increasing service pressures. The number of patients waiting more than 18 weeks for assessment and treatment for neurological disorders in England and Wales rose to 44% in April 2023 (up from 26% in April 2021), with 5% waiting over a year.[40] Even those with suspected first seizures, who should be seen within two weeks, face a median wait of 48 days in the UK and Ireland.[41]

The annual direct medical costs of epilepsy misdiagnoses in England and Wales were estimated as running to £29 million in 2002; when indirect costs to community services were considered, this figure rose to £138 million.[39] The complete costs to society are likely to be much greater when loss of earnings (of patients and carers) associated with avoidably delayed or inaccurate diagnoses are taken into account.

These costs are avoidable; a recent report commissioned by the Neurological Alliance highlights that epilepsy misdiagnosis is a key driver of the current 'treatment gap' in epilepsy in the UK, and improved diagnosis and treatment could reduce direct and indirect costs of epilepsy by as much as 52%.[40] The NHS RightCare Epilepsy Toolkit estimates that £12.1 million could be saved annually in non-elective care if national variations were reduced to bring all clinical commissioning groups (CCGs; now replaced by Integrated Care Systems [ICSs]) in line with performance of their best-performing peers.[42]

Consequently, the development of improved methods for TLOC diagnosis is widely recognised as a research priority in epilepsy and syncope priority-setting exercises,[43,44] as well as being a priority area for service improvement within the NHS.[42]

## 1.3. The challenges of differential diagnosis of the transient loss of consciousness

The differential diagnosis of TLOC is challenging on initial presentation, accounting for the high rates of missed or delayed diagnosis described above. It is by definition paroxysmal; by the time patients present, the condition has usually resolved. This means that there is a lack of unique distinguishing clinical features,[34,45,46] and inter-ictal investigations do not contribute to diagnosis

in the majority of cases.[47,48] The first section of this thesis focuses on the clinical and ethical challenges of accurate history-taking in TLOC presentations; in this commentary I supplement this discussion with a narrative review of the role of other inter-ictal data (including witness-reported semiology and investigative biomarkers) in the differential diagnosis of TLOC.

## 1.3.1. Ictal phenomenology

The subjective experience of TLOC – its phenomenology – is often the only record of the event clinicians have available from which to make their assessments. Despite this, it has received relatively less attention than either visible signs or investigation results in research into TLOC-causing disorders; for example, only 25% of the most-commonly studied seizure manifestations are subjective.[49]

### *1.3.1.1. Diagnostic yield of subjective features*

Holistic history-taking by expert clinicians has a high diagnostic yield and accuracy for TLOC-causing disorders.[50–52] However, as explored further in the next section of this commentary, evidence surrounding specific clinical features used in such evaluation to support the differential diagnosis of TLOC is challenging because of heterogeneity in setting, definitions of relevant diagnoses, and comparators. Expert guidance emphasises the role of detailed history-taking in the assessment of suspected syncope,[3,50,53] but the European Society of Cardiology notes that insufficient evidence exists to evaluate the diagnostic yield of individual features of the history.[54] Attempts that have been made to evaluate their diagnostic yield do not consider all relevant causes of TLOC, contrasting syncope only with tonic-clonic seizures.[55,56] Meanwhile, research on symptoms in the diagnosis of ES and FDS overwhelmingly focus on differentiating them from each other (and not from syncope), and in populations with chronic seizure disorders.[46,57]

In one of the few studies to explore systematically the diagnostic value of patient-reported symptoms in the differential diagnosis of TLOC across syncope, ES and FDS, Reuber *et al*. found that, in a population of patients with gold-standard diagnoses of chronic (mean duration 23.2 years in the epilepsy group, 15.0 FDS, and 14.1 syncope) TLOC-causing disorders, 57 out of 76 peri-ictal symptoms differed significantly across diagnoses in 3-way ANOVA.[34] Patients with FDS reported more frequent and a broader range of symptoms than either epilepsy or FDS. Diagnostic accuracy of individual symptoms are not reported, but a multinomial logistic regression model based on a 5-factor latent factor analysis correctly classified 91% syncope diagnoses, 66% epilepsy and 78% FDS.

In §4.2, I describe systematic prospective evaluation of the diagnostic yield of these subjective features in the differential diagnosis of TLOC. Out of 35 peri-ictal symptoms included in the Paroxysmal Event Symptoms Questionnaire (PESQ), no individual symptom was over 80% sensitive and specific for any diagnosis, highlighting the limited value of individual clinical features to support differential diagnosis. Table 1.3.1 summarises the diagnostic performance of the most-discriminating symptoms.

| DIAGNOSIS | FEATURE | SENSITIVITY (95% CI) | SPECIFICITY (95% CI) |
|---|---|---|---|
| **Syncope** | Feeling hot or cold during | 0.54 (0.45-0.62) | 0.64 (0.48-0.78) |
| **Epilepsy** | Post-ictal confusion | 0.69 (0.50-0.84) | 0.60 (0.52-0.68) |
| | Unaware of having had attack after | 0.63 (0.44-0.79) | 0.66 (0.57-0.73) |
| **FDS** | Tingling or numbness of skin | 0.58 (0.28-0.85) | 0.75 (0.67-0.81) |

| | | | |
|---|---|---|---|
| | Feeling conscious but unable to react | 0.67 (0.35-0.90) | 0.81 (0.74-0.86) |
| | Drifting in and out of consciousness | 0.67 (0.35-0.90) | 0.70 (0.62-0.77) |
| | Muscles aching after | 0.67 (0.35-0.90) | 0.81 (0.74-0.86) |
| | Post-ictal confusion | 1.00 (0.74-1.00) | 0.59 (0.51-0.67) |

*Table 1.3.1. Diagnostic statistics for individual peri-ictal symptoms in the differential diagnosis of transient loss of consciousness. CI = confidence interval. FDS = functional/dissociative seizure*

In §3.2, I also report confirmation of Reuber *et. al's* previous observation that people with FDS report richer subjective ictal experiences, and this may support differential diagnosis. Patients with FDS endorsed more PESQ symptoms (median 12, interquartile range 6.75) than those with ES (median 6, IQR 4) or syncope (median 4, IQR 5.75). Area under receiver-operating curve (AUC) for total peri-ictal symptoms reported was 0.864 (95% confidence interval 0.781-0.948), with a threshold of 9 or more reported symptoms having sensitivity 0.920 and specificity 0.720 for FDS.

### *1.3.1.2. Difficulties in history taking*

The discrepancy between the importance of the history to diagnosis in expert hands, and the limited diagnostic utility of individual historical features, belies the challenges inherent in accurately determining TLOC symptoms.

§2.1 explores the nuances of constructing the patient history from subjective experiences of TLOC, with emphasis on ES and FDS. This chapter describes a range of barriers the clinician confronts in attempting to translate an individual person's subjective experience into interpersonally-intelligible symptoms suitable for diagnostic evaluation. Qualitative and philosophical research into the phenomenology of illness finds that many ictal experiences are difficult to describe to the clinician, or others. This might be because they are inarticulable (as the author and person with epilepsy Margiad Evans put it, "language is demanded by epilepsy … that simply does not exist",[58(p172)]) or ineffable (fundamentally and irreducibly first-personal).[59,60] Still others find their experiences unspeakable, due to stigma surrounding their condition, or fears of being labelled mad.[61]

Beyond difficulties of translating experience, patients also have to remember their ictal experiences to share them as symptoms later. However, post-ictal subjective reporting shows poor concordance with ictal assessment,[62] with less than half of intra-ictally reported seizure symptoms recalled post-ictally.[63]

A third complication in defining TLOC histories comes from the interplay between sensory input and prior expectations in shaping recalled experience. There is increasing evidence to show that our reported and recalled experiences are the result of a constant, bidirectional updating of predictions. Our expectations of what things should feel like thus shapes what we think they feel like, modifying experience[64,65] and memory.[66,67] This can obscure certain aspects of ictal phenomenology that can only be rendered more salient by specific interviewing techniques.[68]

The expertise of clinicians experienced in the differential diagnosis of TLOC comes in part from recognising and navigating these barriers to eliciting accurate TLOC histories. However, doing so in an ethical fashion is not straightforward. In §2.2, I describe an analysis of the ethics of testimonial exchange in the eliciting of TLOC histories, with an emphasis on FDS. Due to some of the barriers described above, patients with TLOC in general – and FDS in particular – may provide initial accounts of their TLOC experiences that are contradicted by descriptions reached

by more careful and systematic exploration (or, more prosaically, by witness accounts or direct observation of seizures). In order to arrive at these latter, more reflective, accounts, the clinician must therefore suspend belief in the patient's initial testimony.

This account challenges existing interpretations of the ethics of clinical testimonial exchange, which hold that a clinician's inadequate credence in patients' testimonies about illness experience represent a form of "testimonial injustice" – a kind of injustice where people are harmed by insufficient acknowledgement of their ability to know and share certain kinds of information.[69] Rather than uncritical acceptance or unwarranted dismissal of patient testimonies, in order to elicit accurate TLOC histories clinician and patients must be epistemic peers – engaging in mutual dialogue and exchange of ideas and beliefs.[70(p61)] This requires addressing interpersonal barriers – building trust in clinicians so patients feel empowered to explore their experiences – and structural ones, giving time and resources to clinical consultations to allow for more careful and reflective exploration of TLOC symptoms.

## 1.3.2. Witness-reported semiology

While much can in principle be learned from subjective TLOC experiences, by definition for at least part of their presentation people with TLOC will have impaired awareness, and thus be unable to report all details. Only the minority of TLOC presentations will be directly witnessed by the assessing clinician. For this reason, guidance on differential diagnosis emphasises a collateral history from a TLOC witness as an essential component of clinical assessment.[1]

### *1.3.2.1. Diagnostic yield of witness-reported semiology*

As with patient symptoms, heterogeneity of setting, patient population, and diagnostic comparators limit utility and generalisability of research on witness-reported semiology. Again, many putative features discriminate between syncope and particular types of ES, though largely these have not been systematically studied or reported.[54] Diagnostic scores to distinguish syncope from ES have previously found witness features such as head turning, unusual posturing or motor activity, or tongue laceration (favouring ES), or diaphoresis (favouring syncope) as having discriminatory value.[55,56,71] Subsequent research on tongue lacerations have shown that not all lacerations, but lateral lacerations, are predictive of ES.[72]

The literature on features distinguishing ES from FDS is more extensive, largely drawing from the chronic population, many studies being conducted in epilepsy monitoring units (EMUs) with video-EEG (vEEG)-confirmed diagnoses (and, as such, videos of events available for review). More reliable features supportive of ES include post-ictal stertor (specific but insensitive) and shorter episode duration < 2 minutes, while FDS is favoured by side-side head movements (specific but insensitive) and ictal eye closure (relatively specific, with highly discrepant results for sensitivity).[46]

Few studies evaluate the diagnostic yield of witness-reported semiology in differentiating between all three diagnoses. Chen *et al.* explored the diagnostic yield of systematic witness interrogation regarding 31 semiological features in differentiating between syncope, ES, and FDS in patients with chronic (mean duration 23.7 years for ES, 15.1 for FDS, and 14.8 for syncope) TLOC-causing disorders.[73] Witnesses reported that syncope displayed fewer semiological features and a narrower range of features than either ES or FDS. 24/31 items differed significantly in reporting frequencies between diagnoses. A multinomial logistic regression model trained on both witness data and patient-reported symptoms[34] accurately classified 92% of syncope, 80% ES, and 79% FDS.

§4.2 describes a prospective validation of witness-reported features in the differential diagnosis of ES from syncope in the first-presentation TLOC setting. Low witness response rates for participants with FDS in this study precluded tripartite classification. Using 45 witness reports on the 18-item Paroxysmal Event Witness Questionnaire (PEWQ), 3 items had sensitivity and specificity > 0.5 for syncope, 4 items for ES. These are summarised in Table 1.3.2.

In order to reflect better the role of witness reports in the differential diagnosis of FDS, I supplemented PEWQ responses with reports extracted from notes review of participants in the previous study. §3.2 reports the value of these diagnostic features in the diagnosis of FDS. Only 3 features – fluctuating course, asynchronous limb movements, and preserved awareness or social responsiveness – differed significantly at Holm-Bonferroni corrected $p < 0.05$. Diagnostic statistics for these features are summarised in Table 1.3.2.

| DIAGNOSIS | FEATURE | SENSITIVITY (95% CI) | SPECIFICITY (95% CI) |
|---|---|---|---|
| **Syncope** | Limp during | 0.82 (0.65-0.93) | 0.73 (0.39-0.94) |
| | Pale during | 0.85 (0.69-0.95) | 0.64 (0.31-0.89) |
| | Shallow breathing after | 0.65 (0.46-0.80) | 0.55 (0.23-0.83) |
| **Epilepsy** | Violent shaking of arms or legs | 0.55 (0.23-0.83) | 0.91 (0.76-0.98) |
| | Arms and legs rigid | 0.55 (0.23-0.83) | 0.88 (0.73-0.97) |
| | Shaking > 1 minute | 0.55 (0.23-0.83) | 0.88 (0.73-0.97) |
| | Snoring after | 0.64 (0.31-0.89) | 0.74 (0.56-0.87) |
| **FDS** | Fluctuating course | 1.00 (0.29-1.00) | 0.88 (0.75-0.96) |
| | Asynchronous limb movements | 0.75 (0.19-0.99) | 0.95 (0.84-0.99) |
| | Preserved awareness or social responsiveness | 0.67 (0.22-0.96) | 0.94 (0.83-0.99) |

*Table 1.3.2. Diagnostic statistics for witness-reported semiology in the differential diagnosis of transient loss of consciousness. CI = confidence interval. FDS = functional/dissociative seizures.*

### *1.3.2.2. Difficulties in obtaining accurate semiology*

Despite the diagnostic utility of accurate ictal semiology, inferring it from witness reports is not straightforward, especially in the context of a first presentation of TLOC. The biggest barrier is a witness being available to give a collateral history. In the prospective cohort of first presentation TLOC patients described in §4.2, out of 178 participants, only 46 (25.8%) were able to identify a witness able to complete the PEWQ. Even after prolonged (at least 6 months') follow-up, often with multiple healthcare contacts, the PEWQ combined with notes review in §3.2 only identified witness reports for 65 (36.5%) of participants. This is unsurprising as first events often occur unwitnessed, or else only witnessed by bystanders in public environments, whom the patient has no means of contacting by time of presentation. The National Institute for Health and Care Excellence (NICE) therefore prioritises development of systems for promoting good-quality information from a witnessed TLOC as one of its research recommendations for management of TLOC.[1]

Even when witness counts are captured, they do not reliably indicate the presence or absence of individual semiological features. Syed *et al*. reviewed videos of 120 seizures from 35 patients with ES and FDS for presence or absence of 48 features of reported diagnostic value. Separately, they asked family and carers to identify a 'best witness' of these patients' seizures to report on the presence or absence of these features. These witnesses had seen a median 18 (IQR 8-100) of the participants' seizures. Even these frequent witnesses incorrectly reported

signs in 6-79% of subjects; of the 6 most-discriminating semiological features, witness reliability was not statistically significantly different from guessing.[74] For witnesses at first presentation, who may only have seen a single event (and also for this not to be an unexpected and often frightening event for them), reports are likely to be less reliable still.

#### *1.3.2.3. Role of smartphone/home video recordings*

The more widespread prevalence of readily-accessible home video, in the form of smartphone recordings, has provided a novel means of addressing difficulties with the reliability of witness reports. Several studies have investigated the utility of smartphones in the differential diagnosis of seizures in the chronic population.[75,76] In a recent prospective masked study, expert interpretation of videos predicted ES in 89.1% (95% CI 84.2-92.9), with specificity 93.3% (88.3-96.6); use of smartphone video significantly improved diagnostic accuracy of expert assessment over clinical assessment alone, with odds ratio for correct diagnosis (OR) 5.45 (1.01-54.3).[75] While syncope research has focussed on other smartphone applications – most notably non-invasive ECG monitoring[77,78] – videos are also recommended in the differential diagnosis of syncope.[79]

However, this use too comes with caveats. In the same study, non-expert (US resident) clinicians were less accurate in their assessment of smartphone videos, despite greater confidence in their diagnoses. Witnesses must receive careful instruction on recording, and confirmation be sought that the recording represents a typical event, as otherwise recordings may represent atypical attacks, or less-relevant parts of the attack (e.g. post-ictal period) that can result in misdiagnosis.[80] Moreover, their use is again limited in the first-presentation TLOC setting, as videos typically are captured only in people with frequent events, whose friends or carers have been instructed by a clinician to record their TLOC.

### 1.3.3. Biomarkers and investigations

Capture of a TLOC event during investigative monitoring (vEEG for FDS or ES, ECG and/or continuous blood pressure monitoring for syncope) permits making a definitive diagnosis; but only the minority of patients will have these events captured. Extensive research on inter-ictal investigations has, however, only shown them to have modest diagnostic value and to be highly time-sensitive, hence the emphasis of this thesis on other data sources.

#### *1.3.3.1. Yield of peri-ictal investigations*

There is significant variability in the performance and diagnostic yield of investigations in the first presentation of TLOC.[48,81] In most patients, most investigations are normal or do not contribute to differential diagnosis. In unselected ED cohorts, the highest-yield tests are those for orthostatic hypotension or cardiac syncope – 12-lead ECG and lying and standing blood pressure.[48,82] Other, more expensive investigations (such as advanced neuroimaging) are increasingly used (rates in the USA increasing from 21% to 45% of syncope presentations),[83] despite their low diagnostic yield in absence of other clinical suspicion for intracranial abnormality (in the absence of recent head trauma or new neurological signs or symptoms, in older adults such imaging has negligible effect on diagnosis or management).[82] Furthermore, the role of many investigations is not to differentiate between ES, FDS, and syncope, but to determine what type of ES or syncope a patient has, once the cause of their TLOC is already determined.

The only investigations that NICE guidelines for TLOC in adult patients recommend at initial assessment are 12-lead ECG, and lying and standing blood pressure "if clinically appropriate."[1]

These tests are relatively quick to perform, and have a low cost per test affecting diagnosis or management.[82] Both tests require evaluation in the context of the clinical presentation; ECG abnormalities are often non-specific and only suggestive of a syncopal presentation in tandem with clinical features,[3,50] while orthostatic hypotension is very common (over 20% in older adults[84]) and so may be comorbid with unrelated causes of TLOC.

Various serum investigations have been investigated as biomarkers for the cause of TLOC, though evidence for their use chiefly comes in the differentiation of ES from FDS.[85,86] Prolactin, the most widely studied, peaks rapidly after bilateral tonic-clonic seizures (TCS), reaching maximum elevations by 20 minutes,[87] returning to normal by 2-24h.[88] However, it has very low sensitivity for focal seizures.[88] Similarly, serum lactate is significantly higher after bilateral TCS than either focal seizures or FDS if tested within 3 hours of seizure.[89] However, lactate again differentiates poorly between focal seizures and FDS, and furthermore is non-specific; in a population of healthy controls asked to simulate seizures, serum lactate measured immediately afterwards was mean 9.1mmol/L higher than pre-simulated seizure.[90] Creatine kinase rises from 12-24h after bilateral TCS, peaking in 48-72h.[85,87] It differentiates TCS from syncope and FDS at 48h, but not 24h, post-ictally.[91] However, it is non-sensitive (estimated 14.6-62.5% sensitivity).[91] Other serum biomarkers include metabolites (ammonia), hormones related to acute stress response (cortisol, ACTH), and markers of neuronal injury (neuron-specific enolase, S100-B), but none has established value in supporting differential diagnosis between syncope, ES, and FDS.[85,92]

For other investigations, including EEG, prolonged cardiac rhythm monitoring (either with wearable ECG or implantable loop recorders), structural cardiac testing (e.g. echocardiography or coronary angiography), and neuroimaging, patient selection is crucial to avoid over-investigation, low-yield testing, and identification of incidental abnormalities. For example, 4.3% of high-resolution brain MRIs demonstrate incidental findings unrelated to presentation,[93] 0.5-2.5% of routine EEGs of healthy controls display interictal epileptiform discharges (IEDs),[94] and continuous cardiac monitoring only identifies a cause in 9.6% of hospitalised syncope patients,[95] but produces many more alarms requiring health worker response (in low-risk patients with chest pain, only 0.2% of such alarms change management.[96])

#### *1.3.3.2. Pre- and post-test probabilities*

The issue of incidental findings is a specific demonstration of a larger issue in how to interpret investigation findings in diagnostic reasoning. That larger issue is of the role of prior probabilities in determining the significance of abnormal results. Much of the work in this thesis (especially that of Section 4) is motivated by the identification of a need for principled prior clinical probabilities of different diagnoses, not just to decide which investigations to perform, but how to interpret their results.

Probabilistic reasoning in differential diagnosis can be understood using a simple Bayesian model. In terms of diagnosis, we are most interested in determining to what extent our evidence, $E$, supports a given diagnostic hypothesis, $H$. The probability of $H$, given that we know $E$, is written: $p(H|E)$. Bayes' rule tells us how to determine this ('posterior' or 'post-test') probability:

$$p(H|E) = \frac{p(E|H)}{p(E)} p(H) \quad (1)$$

That is, the post-test probability depends upon: the pre-test probability (how likely did we think $H$ was before doing the test?); the probability of the test result (how likely is it we would get this

test result on an unselected member of the population?); and the likelihood of the evidence (when people have *H*, how likely is it that they will get test result *E*?). Intuitively, *p*(*H*) states how likely the diagnosis was based on all information available to us before performing the test. *p*(*E*) tells us about how surprising the test result is. *P*(*E*|*H*) tells us the likelihood of a positive test result when our hypothesis is true.

Contingency tables used to assess diagnostic performance divide populations into those with ($D_+$) and without ($D_-$) a diagnosis, and with ($T_+$) and without ($T_-$) a positive test result. This produces the fourfold subdivision of our test population:

| | $T_+$ | $T_-$ |
|---|---|---|
| $D_+$ | *a* | *b* |
| $D_-$ | *c* | *d* |

*Table 1.3.3. Diagnostic contingency table.*

From this, we can calculate sensitivity and specificity, and positive and negative predictive values:

(2) $$\text{sensitivity} = \frac{a}{a+b} = p(E|H)$$

(3) $$\text{specificity} = \frac{c}{c+d} = p(\neg E|\neg H)$$

(4) $$p(H|E) = p(D_+|T_+) = \frac{a}{a+c} = \text{PPV}$$

(5) $$p(H|\neg E) = p(D_+|T_-) = \frac{b}{b+d}$$

(6) $$p(\neg H|E) = p(D_-|T_+) = \frac{d}{b+d}$$

(7) $$p(\neg H|\neg E) = p(D_-|T_-) = \frac{b}{b+d} = \text{NPV}$$

To make this mathematical apparatus more amenable to clinical application requires one last step. In equation (1), the post-test probability depends upon the *likelihood* of evidence if the diagnostic hypothesis were true, *p*(*E*|*H*) (which is equal to the sensitivity – see equation (2)), *pre-test probability p*(*H*), and the *probability of the evidence p*(*E*). Probability of the evidence *p*(*E*) can be hard to justify empirically. However, the comparison of two hypotheses, *H* and *H'*, does not require determining *p*(*E*):

(8) $$\frac{p(H|E)}{p(H'|E)} = \frac{p(E|H)}{p(E|H')} \times \frac{p(H)}{p(H')}$$

In the case of whether a patient has a single diagnosis (*H*) or not (¬*H*), this reduces to:

(9) $$\frac{p(H|E)}{p(\neg H|E)} = \frac{p(E|H)}{p(E|\neg H)} \times \frac{p(H)}{p(\neg H)}$$

This is further simplified by observing that *p*(*E*|*H*) is the sensitivity; and *p*(*E*|¬*H*) = 1 – *p*(¬*E*|¬*H*) = 1 – specificity; thus the ratio of posterior probabilities is the product of the ratio of prior probabilities, and the *positive likelihood ratio* ($LR_+$):

(10) $$\text{LR}_+ = \frac{p(E|H)}{p(E|\neg H)} = \frac{\text{sensitivity}}{1-\text{specificity}}$$

We can also simplify this for cases when the test is negative, using the *negative likelihood ratio* ($LR_-$):

(11) $$\text{LR}_- = \frac{p(\neg E|H)}{p(\neg E|\neg H)} = \frac{\text{1- sensitivity}}{\text{specificity}}$$

This can be illustrated in considering the role of EEG in the differentiation of ES and FDS. Table 1.3.4 gives the percentages of people with ES and FDS who will show the corresponding findings on a single routine interictal EEG (figures for FDS are from a large study of first routine EEG in FDS;[97] the figures for epilepsy use a meta-analysis for frequency of IEDs,[98] while the frequency of focal non-epileptiform abnormalities is calculated from those reported by Doppelbauer *et al.*[99])

| EEG finding | Epilepsy | FDS |
|---|---|---|
| **IEDs** | 17% | 2% |
| **Focal non-epileptiform abnormalities alone** | 18.2% | 16% |
| **Normal** | 64.8% | 82% |

*Table 1.3.4. Prevalence of inter-ictal EEG changes in epilepsy and FDS. EEG = electro-encephalogram. FDS = functional/dissociative seizure. IED = interictal epileptiform discharge.*

The percentages in this table are equivalent to the likelihoods of the different investigation findings, given the corresponding diagnosis, *p*(EEG finding|diagnosis). Using these and equation (8), determines post-test probabilities of epilepsy for a range of pre-test probabilities – graphed in Figure 1.3.1.

The figure demonstrates that, while nonspecific changes make ES somewhat more likely, they do not add much more than does a normal EEG. If, before doing the EEG, there is a high pre-test probability of FDS, nonspecific abnormalities should not change the presumptive diagnosis.

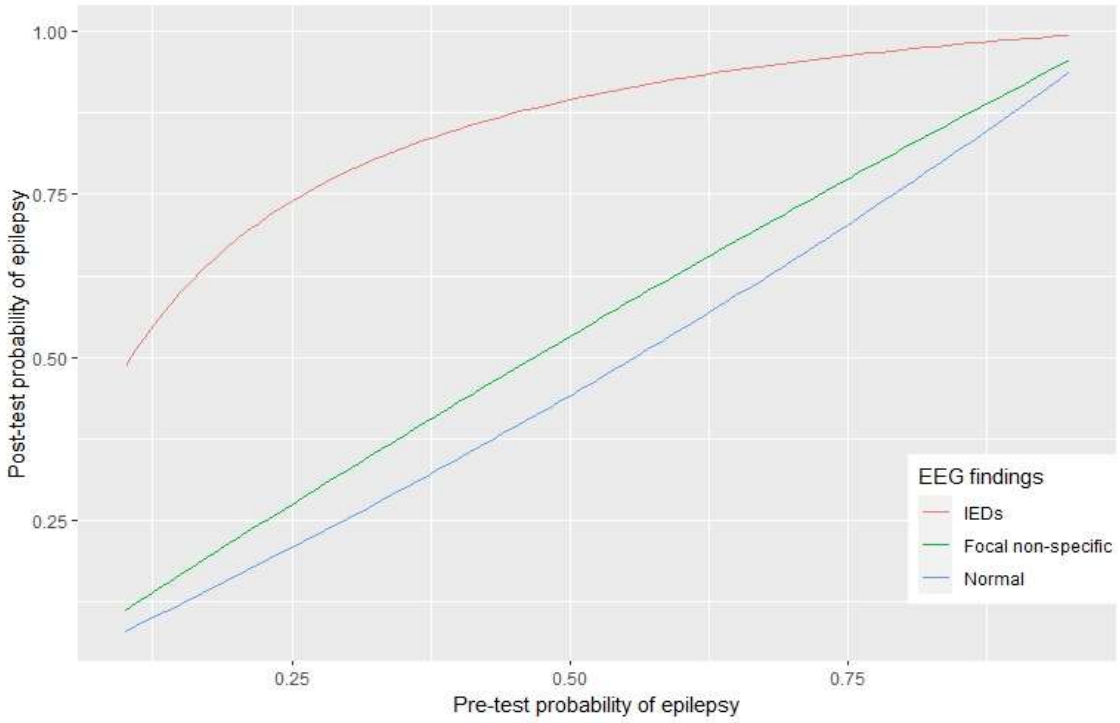


*Figure 1.3.1. Dependence of post-test probability of epilepsy against FDS depending on interictal EEG findings: epileptiform discharges (red), non-specific focal slowing (green), and normal EEG (blue). FDS = functional/dissociative seizures. IED = interictal epileptiform discharge.*

## 1.4. External validity of diagnostic accuracy studies in the differential diagnosis of transient loss of consciousness

In the application of diagnostic accuracy research to clinical practice, it is essential to consider the external validity of the research; that is, the extent to which the context in which the study is performed is representative of the setting to which its results will be applied.[100,101] Several biases can affect external validity of diagnostic accuracy studies. Spectrum bias describes the variation in diagnostic test performance across patient subgroups.[102] Ecological validity describes the extent to which the study setting and environment translates to the real world, or whether the artificial setting affects the subject of inquiry.[103] Existing research in the differential diagnosis of TLOC has significant problems with both spectrum bias and ecological validity.

### 1.4.1. Spectrum bias

As discussed already, the paroxysmal nature of TLOC-causing disorders is such that inter-ictal investigations are often normal, and diagnoses can remain persistently uncertain; the majority of patients do not receive gold-standard diagnoses.[104] This creates a challenge for diagnostic accuracy studies, in that it can be difficult to define an independent reference standard for diagnoses.[105] One solution to this used in many diagnostic accuracy studies is to recruit samples only of patients who have received gold-standard diagnoses. This provides an independent reference standard against which to evaluate diagnostic accuracy. However, it also assumes that the patients who undergo such testing are representative of the population as a whole. Furthermore, since gold standard investigations such as vEEG or cardiac electrophysiology are expensive and labour-intensive, they are not used in unselected patient cohorts; for example, where syncope is the likely diagnosis, a patient is unlikely to undergo vEEG. Studies recruiting such patients will therefore often focus only on a restricted diagnostic question; for example, differentiation of ES from FDS. In a recent systematic review of diagnostic criteria to support the differential diagnosis of TLOC, not one study was identified that studied diagnostic accuracy across ES, FDS, and syncope in a sample of patients with gold-standard diagnoses (vEEG confirmed diagnoses of ES or FDS, or syncope confirmed on tilt table, electrophysiological, or other cardiac physiological testing).[46]

Reviews of relevant literature demonstrate the extent of spectrum bias present in research on the differential diagnosis of TLOC. Reviewing the primary studies cited in the NICE evidence review on differential diagnosis of TLOC,[1] as well as the aforementioned recent systematic review[46] and 2018 ESC guidelines on syncope,[54] only one study (4.3%) recruited a sample of participants with syncope, ES, and FDS at their first TLOC presentation. Only four studies (17.4%) included syncope, ES, and FDS groups; only two (8.7%) were recruited at the point of first TLOC presentation. All others recruited from established patient cohorts with chronic disorders, 21 (91.3%) from specialist tertiary Cardiology or Neurology centres. Of the average duration of TLOC-causing disorder since onset reported across all studies, the median reported value was 15.6 years (inter-quartile range 14.325-20.05).

§3.2 demonstrates the real-world implications of this spectrum bias on the external validity of diagnostic criteria to support the differential diagnosis of TLOC. It reports external validation of a range of diagnostic features in a prospectively-recruited sample of 178 patients with a first presentation of TLOC. In this study, rather than investigation-confirmed gold-standard diagnoses, we used multiple expert rater consensus diagnoses at end of follow up as the reference standard, following established practice in the field[50,106] on the basis that clinical

diagnoses of TLOC-causing disorders by multiple experts are highly robust.[107,108] Of 13 categorical features extracted from the literature, only three were significantly more likely in FDS than the other diagnoses after controlling for multiple comparisons. Of six continuous or interval features, three differed significantly between FDS, ES, and syncope. However, contrary to the existing literature,[109,110] patients with FDS were younger at onset than comparators (median age at onset 22.5, compared with 41.5 in the ES group, and 64 in the syncope group). This is a direct reflection of the spectrum bias of previous studies; recruiting from patients with established seizure disorders, these studies include patients with childhood-onset epilepsies (who would be unlikely to have a first TLOC presentation as an adult); and recruiting largely from tertiary Neurology settings, syncope (which is more prevalent in older adults) is under-represented. Two classifiers developed and validated in cohorts with chronic seizure disorders recruited from tertiary care settings, the Dissociative Seizures Likelihood Score (DSLS),[111] and the Initial Paroxysmal Event Profile (iPEP) classifier described in §4.1, also performed worse in this cohort.

### 1.4.2. Ecological validity

Semiology studies in the differential diagnosis of TLOC largely take advantage of the abundance of high-quality video available from inpatient vEEG recordings. However, research conducted solely in such settings – or similar ones, like tertiary Cardiology syncope units – not only faces the problems of spectrum bias surveyed above, but also presents the problem that identified signs have only been found to occur in the artificial hospital environment. The hospital environment is "a form of environmental manipulation" that does not recreate the settings in which TLOC may otherwise occur; the fact of admission alone can change a person's TLOC disorder, e.g. reducing frequency of ES,[112] making FDS more likely to occur,[113] or last longer when they do occur.[114] In the review of studies listed above, the majority (73.9%) were performed in inpatient tertiary Neurology or Cardiology services.

One potential means of addressing this problem is the use of smartphone videos, which provide TLOC recordings from more naturalistic environments. However, these videos face the challenges of quality, representativeness, and reference standard diagnosis discussed above. §3.1 describes an attempt find a *via media* between these two alternatives, studying ictal semiology to support differentiation of FDS from ES in a vEEG equipped, non-hospital setting. In this study, we recorded videos and simultaneous EEG of 193 seizures from 50 patients with ES or FDS recorded in the William Quarrier Scottish Epilepsy Centre. This unit differs from hospital Epilepsy Monitoring Units (EMUs), in that all patients inhabit a communal residence – with separate bedrooms, and shared cooking, relaxation, and recreation areas – laid out in an environment designed to replicate a normal communal home environment. Rather than being confined to their bed space, they can move around this space freely, as time-locked video recording is available throughout the building. This allows study of semiology in a more natural environment, as well as permitting study of how semiology changes according to the patient's social environment. As an inpatient tertiary Neurology setting, however, this study is limited by the spectrum biases described previously, and featured no syncope group.

Of 18 studied semiological features, 14 were identified with at least fair inter-rater reliability between non-expert clinician raters. Of these, the most highly-discriminating features were those indicating responsiveness to the social environment in FDS; people with FDS were more likely to have seizures with intensity affected by the presence of others (odds ratio [OR] = 199.4 [95% CI 12.0-3309.9]), and to display post-ictal behaviour affected by the presence of others (OR = 91.1 [17.2-482.1]). These semiological features would be more challenging to study in the

traditional EMU setting. Supporting the ecological validity of these results, the two features most strongly diagnostic of FDS in this study (fluctuating intensity and socially-responsive intensity) were also two of only three categorical features supporting FDS diagnosis validated in the first-presentation TLOC cohort in §3.2.

Future semiological studies may be able to develop this approach further with the increasing availability of home vEEG; this will not only allow recording of seizures in patients' home environments where they are exposed to typical stressors and physical activities that may influence seizure occurrence,[115] but also support the inclusion in research of populations who might otherwise be excluded (such as those with intellectual disability or neurodivergence that makes hospital inpatient admission intolerable).[114]

## 1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

The challenges of making prompt and accurate diagnoses for patients presenting with TLOC discussed in the previous sections make a powerful *prima facie* case for the development of a clinical decision aid (CDA) or clinical decision support tool (CDST) to support expert generalists in their first assessment of TLOC presentations. CDAs are algorithmic decision tools intended to support clinicians in identifying important clinical outcomes (e.g. diagnosis or prognosis) using a manageable number of clinically available predictor variables.[116] The increasing availability of large databases of healthcare electronic data, and development of sophisticated analytic tools to exploit it, has resulted in increased interest in the use of machine learning and artificial intelligence (AI) in the construction of CDAs.[117] Making best use of such data and technology is a policy priority in the UK healthcare context, emphasised in both the 2019 NHS Long-Term Plan,[118] and Lord Darzi's 2024 Independent Investigation of the NHS.[119] However, overall computerised decision aids have achieved only modest if any significant improvements in healthcare outcomes.[120] In part this may relate to lack of consideration of how best to design and implement CDAs; the five core principles of CDA design dictate that they must provide the right information, to the right person, in the right format, through the right channel, at the right time.[121,122]

The papers in Section 3 of this thesis describe the development and validation of a CDA for the differential diagnosis of TLOC. §4.1 outlines the initial development of a pilot CDA from secondary analysis of an existing dataset of patients with chronic, gold-standard diagnoses of TLOC-causing disorders. §4.2 reports the development and validation of a tool based on the results of the pilot study in a population of patients with a first presentation of TLOC, while supplementary chapter §4.3 provides qualitative data on participants' experiences of the acceptability and utility of interacting with the CDA.

### 1.5.1. Use of clinical decision aids in emergency care

Given the wide range of presentations, limited information available, and need to manage large patient volumes safely and effectively, CDAs are widely recommended to support clinicians' diagnostic and management decisions in emergency care settings.[123] These range from simple flow charts like the Ottawa Ankle Rules,[124] to more complex multivariate prediction scores like the National Emergency Laparotomy Audit (NELA) score.[125]

Well-designed and implemented CDAs help clinicians' practice to align with guideline-directed standards.[126] This can improve clinician performance, including in differential diagnosis.[127]

CDAs can also support clinicians to achieve this more efficiently, reducing use of unnecessary and high-cost investigations.[128] However, evidence of CDAs' performance in trial settings is not sufficient to ensure their outcomes translate to clinical benefit; subsequent implementation research shows that some CDAs fail to change practice significantly, largely due to clinician non-concordance.[129] In order to develop CDAs fit for supporting emergency and primary care practice, it is therefore important to understand not just how the CDA performs in ideal conditions, but also how it will perform in the 'real world' and how clinicians will use it in practice;[130,131] in particular, what are the barriers to and facilitators of physician uptake of a new CDA.

Not all factors affecting uptake of CDAs depend on the design of the CDA itself; from a thematic analysis of semi-structured interviews with emergency clinicians in the UK, Hayes identified that, along with the design of the CDA itself, factors concerning the care providers, the environment of their practice, and the institutions within which they worked might enable or impede widespread use of CDAs.[117] The Ottawa Acceptability of Decision Rules Instrument (OADRI),[116] a validated scale for measuring the likely clinical acceptability of new candidate CDAs for emergency care use, similarly considers factors both related to the CDA itself, and the context in which it is to be used. The tool-related factors that affect uptake of CDAs can broadly be divided into three main areas of concern: how *useful* the CDA is; how *accessible* it is to apply in the working context; and how *justifiable* its decisions are – whether to patients, other clinicians, or in legal contexts.

#### *1.5.1.1. Utility*

To gain broad uptake, a CDA should address an important problem that clinicians regularly confront in their practice, and do not already have satisfactory means to address. Utility could be measured in terms of clinical outcomes (e.g. patient benefit or reduced patient harm),[116,117] or in terms of efficiency – whether time, resource use (e.g. of high-cost investigations),[128] or economic costs of patient management.

#### *1.5.1.2. Accessibility*

Beyond utility, CDAs must be easy and accessible to use in the clinical environment within which they are designed to be applied. For simple CDAs, this might be as basic as a short set of rules that are easy for the clinician to remember;[116] however, for computer-based CDAs (as with those employing machine learning techniques) this will involve a range of considerations. From a pure software design perspective, the CDA must have an interface that is easy to learn to use, easy to interact with, and does not interrupt other workflows.[117] If drawing from multiple data sources, it should integrate with existing health IT systems (e.g. electronic health records). It must also use only hardware available in the relevant clinical context, so its outputs are available at the point of decision making.

#### *1.5.1.3. Justifiability*

Lastly, acceptable CDAs should support clinical decision-making in ways that are justifiable – to patients, to other clinicians, and ultimately in a medico-legal setting. For CDA use to be considered justifiable, it is necessary but insufficient for there to be a good evidence base. The outputs of the CDA should be *explainable*, such that the clinician can understand why the CDA produces the output it does, and ideally can use its outputs as data to share with patients to support shared decision-making. This implies that the CDA should support, but not supplant, the clinician; its outputs "should be perceived as recommendations, not mandatory edicts."[117]

#### *1.5.1.4. Patient-completed clinical decision aids*

The majority of CDAs are designed to be completed and utilised by clinicians, but attending to the core principles of CDA design shows that the right information, right person, right format, and right time for information provision could also come through patients. Patient completion of CDAs prior to clinician assessment could empower patients to participate in their care and support shared decision-making,[121] while reducing the time burden on clinicians and so improving the utility and accessibility of the CDA. Computerised CDAs already exist for management of chronic conditions such as hypertension and multiple sclerosis;[132,133] patient-facing checklists have also been employed successfully in ED settings to support patient-centred care.[134] Given that around 9 in 10 patients attending EDs in England in 2018-19 spent over an hour in the department,[135] typical ED attendances provide ample opportunity for self-administration of such a tool. Implementation within now-commonplace smartphone or browser-based applications could ensure user-friendliness.

### 1.5.2. Candidate clinical decision aids for the differential diagnosis of transient loss of consciousness

The piloting, development, and validation of a CDA for the differential diagnosis of TLOC comprises the focus of §4 of this thesis. This work was motivated by a lack of well-validated tools to support this clinical challenge. However, a range of different CDAs have been developed that address related clinical questions. In this section I briefly survey these different instruments.

#### *1.5.2.1. Search strategy*

A 2018 systematic review identified relevant papers from a systematic search of clinical criteria to support the differential diagnosis of TLOC.[46] To update this, I used CDAs included in this prior review, as well as the review itself, as starting references for citation searching following a pearl-growing strategy, with iterative citation searching of subsequently identified papers. I include newly-identified CDAs, or new prospective validation of previously-developed CDAs. I have excluded reviews of individual diagnostic criteria, CDAs for paediatric populations, or for differentiating between subtypes of TLOC-causing disorders (e.g. syncope risk stratification, or differentiating between generalised and focal epilepsies).

#### *1.5.2.2. Differentiating seizures from syncope*

Two CDAs address the question of differentiating syncope from ES. The best-validated of these is the 9-point score reported by Sheldon *et al*.[55] Drawing on a sample comprising patients recruited from Cardiology and Neurology outpatients and inpatient cardiology wards, all of whom had supportive investigative evidence of their diagnoses (electrocardiography or tilt-table testing for syncope, or EEG supportive of either a focal or genetic generalised epilepsy for ES), they derived a 9-feature score for classification into like ES or syncope. The score items comprise 3 witness-reported semiological features (abnormal behaviour [defined as amnesia, unresponsiveness, unusual posturing, or limb jerking]; post-ictal confusion; and unilateral head-turn), and 6 patient-reported symptoms (waking with a cut tongue; association with emotional stress; prodromal déja or jamais vu; presyncopal symptoms; pre-episodal diaphoresis; or association with prolonged standing or sitting). The original paper reported sensitivity and specificity for ES of 94% in a separate validation sample. A subsequent validation in a prospectively-recruited cohort of 159 patients in a first-presentation TLOC setting reported overall classification accuracy of 72.3%; this was improved to 81.5% by incorporating age and gender into the model.[136]

An earlier score developed by Hoefnagels et al used just four features to distinguish ES from syncope “or other causes”; one demographic (age), one witness-reported (post-ictal disorientation), and two symptoms (pre-ictal nausea, and tongue biting). However, they do not report overall diagnostic performance and the score has not undergone subsequent validation.

Table 1.5.1 summarises characteristics of these two CDAs.

1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

| REFERENCE | SETTING | POPULATION | TYPE | INPUT VARIABLES | SENSITIVITY (%) for ES | SPECIFICITY (%) for ES | EXTERNAL VALIDATION |
|---|---|---|---|---|---|---|---|
| **Sheldon et al 2002**[55] | Neurology and cardiology clinics; cardiology wards | 538 patients with at least one TLOC and diagnostic evidential support (tilt table, electrophysiology, EEG) | Regression-based score | 3 witness-reported semiology; 6 phenomenology | 94 | 94 | In prospective first-presentation cohort 159 patients: accuracy 72.3%, improved to 81.5% with incorporation of age and gender[136] |
| **Hoefnagels et al 1991**[56] | Neurology referrals | 94 patients with at least one TLOC | Regression-based score | 1 demographic; 1 witness-reported semiology; 2 phenomenology | NR | NR | None |

*Table 1.5.1. Summary of clinical decision aids for the differentiation of seizures from syncope. ES = epileptic seizures. TLOC = transient loss of consciousness. EEG = electro-encephalogram. NR = not reported.*

#### *1.5.2.3. Differentiating epilepsy from FDS*

By contrast, there is a far more extensive literature on CDAs to distinguish ES from FDS; a recent structured narrative review identified 55 different reports of questionnaires for the differential diagnosis of FDS.[57] The vast majority of these CDAs were developed in tertiary Neurology settings, using patients with chronic ES or FDS with video-EEG confirmed diagnoses. Many depend on information not usually available at first presentation (e.g. EEG findings or video-documented semiology). Few have undergone external validation. In this section, I confine the discussion to tailored CDAs designed specifically for the differential diagnosis of ES and FDS (rather than e.g. the diagnostic value of single clinical criteria, or scores on standardised questionnaires like personality inventories).

Of these CDAs, the most developed are the family of classifiers produced by Wesley Kerr and colleagues that contributed to the development of the Dissociative Seizures Likelihood Score (DSLS). They performed retrospective analysis of demographic, historical, phenomenological and semiological questionnaires given to patients with video-EEG confirmed diagnoses of ES or FDS (and in some studies also including those with dual diagnoses, or those with physiologic seizure-like episodes including syncope) recruited from a tertiary Epilepsy Monitoring Unit (EMU). They used both regression-based and non-linear classifiers (decision forests and support vector machines) to develop classifiers that could predict FDS on the basis of history,[137] comorbidities,[138] peri-ictal phenomenology and semiology,[109] and a combination of the above.[111] This latter score, the DSLS, identified likely FDS in initial validation with a sensitivity of 84% (95% CI 80-89%) and specificity 74% (70-77%). The positive predictive value for FDS was 51% (47-55%). The DSLS is the only one of the CDAs identified to have undergone external validation. Single-centre external validation in another EMU in the USA reported similar performance to that found in initial validation;[139] however, in a similar patient population (established diagnoses recruited from EMUs) in Iran, performance was significantly worse (sensitivity for FDS 76%, specificity 69%).[140]

In §3.2, I report external validation of the DSLS in a first-presentation TLOC cohort. Evaluation was limited by missing data concerning some aspects of witness-reported semiology, but with the assumption that non-reported semiology was not present, of 44 patients (32 ES, 12 FDS) the DSLS classified 65.9% accurately. Sensitivity and specificity for FDS were 83% and 59% respectively.

Other CDAs to differentiate epilepsy from FDS were also developed in the EMU setting from patients with chronic TLOC-causing disorders. The spectrum bias generated by this emphasis is evident down to the individual variables used as inputs for various CDAs. Many of these (e.g. number of current[138] or previous[111,138] anti-seizure medications, or duration of seizure disorder[111,141,142]) assume a chronic disorder, while others (e.g. results of inter-ictal EEG[142] or video available for expert review[143]) are unlikely to be available until after a person experiencing TLOC has undergone specialist assessment, limiting their utility (since specialist assessment outperforms any TLOC CDA.[111]).

The different CDAs reviewed utilise a wide array of variables to predict likely diagnoses of FDS or ES; these are summarised in Table 1.5.2. It is of particular importance for application to the first presentation setting that far fewer patient-reportable phenomenological variables are included than witness-reported semiology, given the low frequency with which witnesses are identified at a first presentation. The studies themselves are summarised in Table 1.5.3.

1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

| VARIABLE TYPE | FAVOURS ES | FAVOURS FDS |
|---|---|---|
| **Demographic** | • Older age[144,145]<br>• Longer delay to assessment[111,137]<br>• Employed or in full time education[137] | • Female gender[109,111,138,140,144,145]<br>• Older age at seizure onset[140] |
| **History and comorbidities** | • Shorter duration of seizure disorder[111,142]<br>• Number of current ASMs[138]<br>• Number of previous ASMs[111,138]<br>• More frequent seizure-related injuries[141]<br>• Childhood febrile seizures[137]<br>• Previous head injury[111,137]<br>• Diabetes mellitus[138]<br>• Cancer[138] | • Shorter duration of seizure disorder[141]<br>• Greater seizure frequency[111,141,142]<br>• More frequent seizure-related ED visits[141]<br>• Number of comorbidities[111,138,142]<br>• Number of non-seizure physical symptoms[141]<br>• Number of medications[111,138,141,142]<br>• Poor ASM concordance[142]<br>• Previous concussion[137]<br>• Psychological trauma or abuse[111,137,141,142]<br>• Psychological or psychiatric comorbidity[140,141]<br>• Migraine or headaches[111,138,144]<br>• Asthma[111,138]<br>• Light-headedness[144]<br>• Chest pain[144]<br>• Globus[144]<br>• Fatigue[144]<br>• Chronic pain[138]<br>• Fear of passing out[144]<br>• Worry about being alone[144]<br>• Thoughts of physically harming someone[144]<br>• Bothersome sexual thoughts[144]<br>• Scary thoughts or visions[144]<br>• Caregiver relationship difficulties[141]<br>• Family history of psychiatric disorder[141] |
| **Phenomenology** | • Sleep deprivation triggers[109,111]<br>• Incontinence[109,111,142]<br>• Tongue bite[142]<br>• Post-ictal confusion[109,145] | • Emotional stress triggers[141]<br>• Ictal hallucinations[109,111] |
| **Semiology (witness report)** | • Prolonged unresponsiveness[142]<br>• Eye deviation[146]<br>• Limb automatisms[109,111,141]<br>• Repetitive movements[140,141] | • Greater number of different seizure types[111]<br>• Longer seizure duration[109,111,140–142,145,146]<br>• Prolonged unresponsiveness[141] |

| | | |
|---|---|---|
| | • Tonic-clonic movements[109,111]<br>• Loud post-ictal breathing[146]<br>• Post-ictal snoring[146] | • Eye closure[109,111,142]<br>• Side-side head movements[146]<br>• Evolution of movements[140]<br>• Hip thrusting[111]<br>• Back arching[142]<br>• Muscle twitching[109]<br>• Shallow post-ictal breathing[146]<br>• Rapid post-ictal recovery[142] |
| **Semiology (video review)** | • Stereotyped movements[143] | • Patient awake[143]<br>• Bizarre movements[143]<br>• Brief asynchronous muscle jerks[143]<br>• Asynchronous limb movements beyond the seizure[143]<br>• Eye closure[143] |
| **Investigations** | | • Normal inter-ictal EEG[142] |

*Table 1.5.2. Summary of variables used as predictors in clinical decision aids for the differential diagnosis of epileptic and functional/dissociative seizures. ES = epileptic seizures. FDS = dissociative seizures. ASM = anti-seizure medication. EEG = electro-encephalogram. Items appearing in both columns have conflicting predictive value in different studies.*

### *1.5.2.4. Diagnosing epilepsy against other non-epilepsy diagnoses*

Two recent papers present candidate CDAs for differentiating ES from all other non-seizure diagnoses, including syncope and FDS (as well as other diagnoses, such as migraine and transient ischaemic attack, that are not commonly causes of TLOC, but may cause other paroxysmal events). Both use convenience samples, one considering all patients referred for routine EEG,[147] the other from outpatient Cardiology and Neurology clinics.[145]

The model developed by McInnis *et al* aims to predict epilepsy diagnosis on the basis of 6 predictors identified from a larger list of candidate predictors through a penalised (LASSO) regression model.[147] They identified 6 groups of predictors used as input for the final model; syncope signs (including prodromal visual blackout, sweating, presyncope, or provoking sit-stand transition); witness-reported generalised tonic-clonic movements or forced head turn to one side; past medical history associated with epilepsy (including developmental delay, autism, focal deficit on neurological examination, previous brain injury, or history of neurodegenerative disease); presence of post-ictal confusion; number of prior spells; and a past medical history associated with cardiac disease (abnormal ECG, history of atrial fibrillation/flutter, chest pain or angina, dyspnoea, or 'heart disease'). They do not validate their model on a separate sample, but report an AUROC of 0.86 and ES sensitivity of 0.836 and a specificity of 0.716 from 10-fold cross-validation.

Beyond the specifics of the CDA, McInnis' model is of particular interest for efforts to streamline the assessment of TLOC in that it combines use of a CDA with another clinician-independent tool to facilitate diagnostic triage – artificial intelligence (AI) interpretation of investigation findings, in this case EEG. As would be expected from the sensitivity and specificity of routine EEG for inter-ictal epileptiform changes (reviewed in §1.3.3 above), they report that negative EEG does not significantly effect post-test probability, but that a positive EEG markedly shifted post-test probabilities for those who had an indeterminate pre-test probability from their CDA.

They do not report the details of their AI EEG interpretation, or whether combining their CDA with the AI EEG ultimately improved diagnostic accuracy.

Details of the two studies reporting CDAs to differentiate epilepsy from non-epilepsy diagnoses are summarised in Table 1.5.4.

1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

| REFERENCE | SETTING | POPULATION | TYPE | INPUT VARIABLES | Sensitivity (%) for FDS | Specificity (%) for FDS | EXTERNAL VALIDATION |
|---|---|---|---|---|---|---|---|
| **Syed et al 2009**[148] | EMU; two centre | Chronic with vEEG-confirmed diagnoses | Hybrid neural-Bayesian classifier | 53 patient-reported demographic, clinical, seizure-related and psychosocial variables | 85 | 85 | None |
| **Azar et al 2010 (SIPQ)**[146] | EMU; single-centre | Chronic with vEEG confirmed diagnosis | Logistic regression model | 6 witness-reported semiology | NR | NR | None; overall accuracy 84.4% in leave-one-out cross-validation |
| **Kerr et al 2017**[138] | EMU; single-centre | Chronic with vEEG confirmed diagnoses of epilepsy, FDS, mixed disorder, and physiologic non-seizure episodes inc syncope | Logistic regression model | 1 demographic, 9 historical | 55 | 90 | None |
| **Kerr et al 2018**[137] | EMU; single centre | Chronic with vEEG confirmed diagnoses of epilepsy, FDS, mixed disorder, and physiologic non-seizure episodes inc syncope | Logistic regression model | 3 demographic, 6 historical | 71 | 74 | None |
| **Kerr et al 2019**[109] | EMU; single centre | Chronic with vEEG | Decision forest | 6 witness-reported semiology, 3 phenomenology, 1 | 56 | 39 | None |

1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | confirmed diagnoses | | demographic (10 others included in derivation but with no more than chance contribution to model | | | |
| **Kerr et al 2020 (DSLS)[111]** | EMU; single-centre | Chronic with vEEG confirmed diagnoses; mixed FDS and ES excluded | Support vector machine with recursive feature elimination | 1 demographic, 11 historical, 3 phenomenology, 4 witness-reported semiology | 84 | 74 | In chronic EMU populations: in Iran sensitivity 76%, specificity 69%[140]; in USA sensitivity 82%, specificity 81%[139]<br><br>In first presentation: sensitivity 83%, specificity 59% |
| **Trainor et al 2020 (AASQ)[144]** | EMU; single-centre | Chronic with vEEG-confirmed diagnoses; mixed FDS and ES excluded | Univariate feature selection; logistic regression model | 2 demographic; 23 historical | 93 | 75 | None |
| **Janocko et al 2021 (DDESVSFS)[142]** | EMU; two centre | Chronic with vEEG confirmed diagnoses; mixed FDS and ES excluded | LASSO regularised regression feature selection; integer coefficient model | 1 investigation (EEG), 6 historical variables, 1 recorded semiology | 95.2 | 86 | None |
| **Baroni et al 2021 (SS-PNES)[141]** | EMU ; single-centre | Chronic with vEEG-confirmed diagnoses | Rasch rating scale model | 13 historical, 2 semiology | 89 | 85 | None |
| **Dashtkoohi et al 2023 (CFSS)[140]** | EMU; single-centre | Chronic with vEEG-confirmed diagnoses | Regression-based integer coefficient model | 3 demographic, 3 semiology | 86.96 | 73.81 | None |

1.5. Clinical decision aids for the differential diagnosis of transient loss of consciousness

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sobregrau et al 2024 (PNES-DSC)[143]** | EMU ; single-centre | Chronic with vEEG-confirmed diagnoses; mixed FDS and ES excluded | Feature selection based on exhaustive comparison of all possible feature combinations | 6 clinician-identified semiology from video recordings | 45.2 (single video)<br><br>69.6 (multiple videos) | 97.6 (single video)<br><br>97.2 (multiple videos) | None |

*Table 1.5.3. Summary of clinical decision aids for the differential diagnosis of epileptic seizures and functional/dissociative seizures. ES = epileptic seizures. FDS = functional/dissociative seizures. PNES = psychogenic non-epileptic seizures (aka FDS). (v)EEG = (video-)electro-encephalography. EMU = epilepsy monitoring unit. AUROC = area under receiver-operating characteristic curve. SIPQ = short ictal/post-ictal questionnaire. DSLS = dissociative seizures likelihood score. CFSS = clinical functional seizure score. SS-PNES = scale for the suspicion of PNES. PNES-DSC = PNES diagnostic suspicion checklist. AASQ = anxiety, abuse, and somatisation questionnaire. DDESVSFS = differential diagnosis of epileptic seizures vs functional seizures.*

| REFERENCE | SETTING | POPULATION | TYPE | INPUT VARIABLES | Sensitivity (%) for ES | Specificity (%) for ES | EXTERNAL VALIDATION |
|---|---|---|---|---|---|---|---|
| **McInnis et al 2023[147]** | Patients referred for routine EEG; single centre | Chronic with chart review based diagnoses of epilepsy, or other* | LASSO-regularised logistic regression model | 3 historical, 3 semiology extracted from chart review | 83.6 | 71.6 | None |
| **Snyder et al 2024[145]** | Outpatient Neurology and Cardiology clinics; single centre | Chronic with clinician-confirmed diagnoses of epilepsy, FDS, migraine, or syncope | Weighted score of items obtained from univariate analysis; fitted to logistic regression model | 2 demographic; 8 phenomenology | NR; AUROC 0.80 | NR | None |

*Table 1.5.4. Summary of clinical decision aids for the differential diagnosis of epileptic seizures and other non-epilepsy diagnoses. ES = epileptic seizures. FDS = functional/dissociative seizures. EEG = electro-encephalography. LASSO = least absolute shrinkage and selection operator (aka L1 regularisation). AUROC = area under receiver-operating characteristic curve. NR = Not reported. *'Other' diagnoses include syncope, migraine, TIA, single unprovoked seizure, FDS, provoked seizure, autonomic disorder, or undetermined or miscellaneous diagnosis.*

#### *1.5.2.5. Tripartite classification*

It is of particular note that the CDAs reviewed above are all designed for binary classification problems, i.e. distinguishing between two candidate diagnoses (or determining whether a given individual does or does not have a single target diagnosis). This contrasts with the decision problem posed by TLOC in the introduction: whether a patient with primary TLOC has one of three common candidate diagnoses (or indeed one of the rarer causes, or a secondary TLOC).

This poses several limitations, which may compromise the performance of candidate CDAs in a real-world setting. Firstly, and most obviously, there are issues of external validity surveyed in §1.4 above. Criteria that distinguish well between two conditions may perform poorly when a third is introduced; for example, the 'abnormal behaviour' cited in Sheldon et al's syncope diagnostic score is uncommon in syncope, but frequently found in both ES and FDS.

Secondly, the range of application is restricted. In order even to apply a binary classifier, one of the candidate diagnoses needs to have been excluded by the assessing clinician.

Thirdly, estimates of classification performance are likely to be significant over-estimations of real-world performance when based only on binary classification. To see this, look at the performance of a naïve classifier. In a binary classification problem in a balanced population (where all diagnoses are equally prevalent), the naïve classifier that assumes all patients have one diagnosis will be correct 50% of the time. However, in a ternary classification problem, that classifier would only have an accuracy of 33.3%. Obviously, the naïve classifiers would perform differently in unbalanced (real-world) populations where one diagnosis is commoner than the others; however, developing CDAs in settings including only a subset of the relevant diagnoses will distort the relative proportions of patients with different diagnoses, so these classifiers cannot take advantage of that either.

### 1.5.3. Development of a clinical decision aid for the differential diagnosis of transient loss of consciousness

Computerised diagnostic CDAs comprise interventions in complex systems – that is, systems with variable or unstable boundaries (e.g. lines between primary, emergency, and specialist care), that may be structured in different ways at different times (with e.g. different patient pathways), and in which barriers and facilitators to implementation are often emergent and unpredictable.[149–151] Various frameworks have been developed to support the design of scalable and sustainable CDAs to be incorporated within complex systems.[121,122,151,152] In the work described in this thesis, the Nonadoption, Abandonment, and challenges to the Scale-up, Spread, and Sustainability (NASSS) framework[151] provides principles for guiding the development of a CDA that will be resilient to the challenges of wider implementation in primary and emergency care, while the Instrument Development and Construct Validation framework[152] structures the process of CDA development.

The widely-utilised NASSS framework for understanding barriers to and facilitators of implementation of technological innovations in healthcare looks at those interventions through 13 questions across 7 domains in terms of whether the intervention is simple (involving few components interacting predictably), complicated (involving a wider range of entities and processes, but still with analytically soluble or otherwise predictable outcomes), or complex (dynamic, inherently unpredictable, with emergent properties).[151] The greater the simplicity of an intervention across more of these questions, the more likely it is to be sustainably adopted and implemented. The nature of the target condition(s) and the systems within which the CDA

are to be embedded impose answers on some of these; others are open to influence by the design of the CDA. Table 1.5.5 outlines application of the relevant components of the NASSS framework to the problem of differential diagnosis of TLOC, and highlights opportunities for reducing complication and complexity through CDA design.

| DOMAIN/QUESTION | CURRENT COMPLEXITY | OPPORTUNITIES FOR CDA DESIGN |
|---|---|---|
| **Domain 1: Condition or illness** | | |
| **1A. What is the nature of the condition or illness?** | Simple: The different diagnoses causing TLOC are well-characterised and well-understood with established management | |
| **1B. What are the relevant sociocultural factors and comorbidities?** | Complex: Epilepsy and FDS remain stigmatised conditions in many cultures and communities. Learning or communication disabilities can interfere with knowledge sharing in the clinical context. | Patient and community facing outputs could work to increase understanding. Pilot testing with groups of different sociocultural backgrounds could identify and address barriers to implementation |
| **Domain 2: The technology** | | |
| **2A. What are the key features of the technology?** | CDA-dependent | Addressing the CDA to the targeted question of differential diagnosis keeps the intervention simpler |
| **2B. What kind of knowledge does the technology bring into play?** | CDA-dependent | CDAs should minimise inputs requiring expert resources (such as specialist investigations) or skill (such as identification of semiology not reliably reported by lay witnesses) |
| **2C. What knowledge and/or support is required to use the technology?** | CDA-dependent | The interface should be intuitive and accessible to intended end users |
| **2D. What is the technology supply model?** | CDA-dependent | A generic, 'plug and play' interface readily accessible in any contexts (e.g. browser-based) |
| **Domain 3: The value proposition** | | |
| **3A. What is the developer's business case for the technology (supply-side value)?** | Simple: Misdiagnosis has high direct and indirect costs | External validation should include full health economic assessment of implementation |
| **3B. What is its desirability, efficacy, safety, and cost effectiveness (demand-side value)?** | Complicated: Improved diagnosis is in patient interests, but this has to be demonstrated in a way acceptable to patients | External validation prior to implementation is required to confirm CDA efficacy and safety |
| **Domain 4: The adopter system** | | |

| | | |
|---|---|---|
| **4A. What changes in staff roles, practices, and identities are implied?** | CDA-dependent | CDAs as decision support rather than supplanting clinicians maintains existing roles and identities |
| **4B. What is expected of the patient (and/or immediate caregiver)—and is this achievable by, and acceptable to, them?** | CDA-dependent | Assessment of acceptability and utility to patient necessary in CDA development, especially if patient-completed |
| **4C. What is assumed about the extended network of lay caregivers?** | Simple: no assumptions are made | |
| **Domain 7: Embedding and adaptation over time** | | |
| **7A. How much scope is there for adapting and co-evolving the technology and the service over time?** | CDA-dependent | CDA development should be agile and open to change in response to emergent implementation barriers |

*Table 1.5.5. Application of the Nonadoption, Abandonment, and challenges to Scale-up, Spread, and Sustainability (NASSS) framework to the differential diagnosis of transient loss of consciousness. Domains 5 and 6, and question 7B, are omitted as they cover individual organisations rather than a clinical problem, tool, or general care context. CDA = clinical decision aid.*

Consideration of CDA development in light of the NASSS framework demonstrates that simply designing a classifier that is proficient at differential diagnosis of TLOC is insufficient for widespread implementation. Considering the niche it will occupy in the care system, relevant stakeholders, and technology-rated barriers to implementation improve likelihood of subsequent uptake.

The IDCV framework uses a mixed-methods approach to structure quantitative instrument development in a way that is sensitive to these concerns. It conceptualises development and validation in a 10-phase process: (1) conceptualising the construct of interest; (2) identifying and describing behaviours underlying the construct; (3) developing the initial instrument; (4) field-testing the initial instrument; (5) designing and field-testing a revised instrument; (6) quantitative validation of the revised instrument; (7) qualitative validation of the revised instrument; (8) qualitative-dominant crossover validation; (9) quantitative-dominant crossover analysis of the revised instrument; and (10) evaluating the process and product.[152] The work of identifying relevant diagnostic criteria through systematic review and content analysis of expert opinions required in phases (1) and (2) took place prior to the work documented in this thesis.[34,46,73] This thesis describes the developing (3) and piloting (4) of an initial CDA for differential diagnosis of TLOC, the initial Paroxysmal Event Profile (iPEP) classifier; and design (5) and quantitative (6), and partial qualitative validation (7) of a revised CDA, the Paroxysmal Event Symptoms Questionnaire (PESQ) classifier.

### *1.5.3.1. Preliminary work*

The first stages in CDA development, once the clinical question has been adequately posed, is to identify suitable sources of information as inputs to the CDA, and demonstrate their ability in principle to address the decision problem to which the CDA is targeted. To do this, Reuber *et al* developed two extensive questionnaires concerning subjective phenomenology (the 86-item Paroxysmal Event Profile [PEP]) and observer-witnessed semiology (the 31-item Paroxysmal Event Observer questionnaire [PEO]) of TLOC presentations, based on literature review and expert consensus of potentially diagnostic features in TLOC.[34,73] In a large (n=300) sample of

patients with 'gold standard' (physiologically proven) diagnoses of epilepsy, syncope, or FDS, Reuber et al. showed that the PEP could distinguish syncope from epilepsy with a sensitivity of 92% and specificity of 91%, and syncope from FDS with sensitivity of 95% and specificity of 93%. The instrument also was successful in distinguishing between epilepsy and FDS, but with lower sensitivity and specificity (of 80% and 74% respectively).[34] Supplementing subjective experiences with the accounts of a witness to participants' TLOC recorded in the PEO, they were able to differentiate between syncope and epilepsy with an accuracy of 100%, and between FDS and epilepsy with 83% accuracy.[73]

Complementary to this, I conducted a systematic review of candidate clinical criteria to support the differential diagnosis of transient loss of consciousness.[46] This review, discussed further in previous sections, highlighted several candidate criteria to support differential diagnosis, though found most studies at high risk of bias and no well-evidenced criteria adequate for reliable discrimination between ES, FDS, and syncope.

#### *1.5.3.2. Pilot*

For the development of the pilot CDA, reported in §4.1, I used the existing dataset from the PEP and PEO studies. While the PEP and PEO themselves had demonstrated ability to discriminate between TLOC diagnoses, there would be significant barriers to implementing them in their original form in the first presentation context. In total, the PEP and PEO alongside the demographic and ROS questionnaires participants were asked to complete had 134 items, a prohibitively long list for primary or emergency care settings. Secondly, given they were addressed to patients recruited from specialist care settings with chronic TLOC-causing disorders, the PEP and PEO asked respondents to report symptoms and signs on a 5-point Likert scale (ranging from "always" to "never"); after a first presentation with usually a single event, this would be less appropriate.

To develop the pilot CDA, I first re-coded the existing dataset by simplifying answers to "ever"/"never" responses, and divided the dataset randomly into training and validation samples in a 2:1 ratio. I then identified optimal questionnaire items using a random forest based machine learning algorithm. Random forests (RFs) are bootstrap-aggregated ensembles of decision trees that are well-suited to classification problems (such as diagnosis) for low-*n* high-*p* problems (where number of candidate discriminating features *p* is large relative to subjects *n*).[153,154] They also have the advantage of non-linearity, naturally reflecting that clusters of features may have a diagnostic importance that is more than the sum of their parts.

Feature selection reduced the 134 PEP, PEO, and demographic items to 36 features (6 historical/ROS, 20 peri-ictal symptoms, and 18 witness-reported signs), the initial Paroxysmal Event Profile (iPEP). An RF trained on iPEP items identified diagnoses in the validation sample with accuracy of 86.0% (95% CI 76.9–92.6%). Sensitivity for syncope was 100%, for epilepsy 85.7% and for FDS 75.0%. To allow for the possibility of a witness not being available, I repeated this process using only PEP and ROS/demographic questionnaires. This resulted in a 34-feature (8 historical and 26 peri-ictal) model that identified the correct diagnosis with 78.3% (68.4-86.2%) accuracy.

This study demonstrated the feasibility of using an RF classifier as a CDA for the differential diagnosis of TLOC. Using only basic clinical information available at the initial presentation (demographics, ROS, phenomenology, and semiology), a high classification accuracy for TLOC diagnosis could be achieved with a manageable number of questionnaire items. However, this pilot instrument would require extensive revision before clinical use as a CDA. Most notably, the

pilot dataset came from a population with long-standing diagnoses recruited from specialist settings, and as such was subject to all the limitations on external validity in the first presentation setting described in §1.4 above. The original PEP and PEO study also did not seek any data on acceptability and utility of the questionnaires to users, which might constrain their implementation in practice (see Table 1.5.5 above).

#### *1.5.3.3. Development and validation*

Having developed a pilot CDA, it required further development and validation in the target clinical context. I describe this in §4.2**.** We recruited a sample of patients with a first presentation of TLOC from the Emergency Department, Acute Medical Unit, and Neurology and Cardiology outpatient referrals, to a study refining and validating the pilot iPEP classifier. Recruited participants were asked to complete at time of acute attendance or afterwards an online questionnaire, the Paroxysmal Event Symptoms Questionnaire (PESQ), comprising items from the iPEP plus additional items identified in subsequent systematic reviews[46,57] not included in the original PEP. The were also asked to identify a witness to complete an online Paroxysmal Event Witness Questionnaire (PEWQ), developed from the iPEP and PEO via the same method.

As these participants were recruited after their first TLOC presentation, the gold-standard reference diagnoses used in the pilot study – and widely in the TLOC diagnosis literature discussed above – could not be used, as many patients will not have sufficiently frequent (or indeed, any more) TLOC presentations to ensure capture during EEG or cardiac physiological monitoring, and such investigations would not be appropriate for all patients. However, for reasons of external validity discussed above, it was necessary to conduct this study in this patient population. Therefore as reference standard diagnosis, we used two independent expert rater evaluation of all clinical information (except PESQ and PEWQ responses, to which they were blinded) at end of follow-up, at least 6 months after initial presentation. Consensus clinical diagnosis of TLOC-causing disorders by multiple experts is highly reliable,[108,155] and has established use as a reference standard in TLOC research.[51]

We recruited 179 participants out of a target 205. A consensus diagnosis could not be reached for one, so 178 patients were included in final analysis. Only 46 participants identified a witness able to complete the PEWQ, so only demographic and PESQ questionnaires were used as input. I used the first 100 participants to select most-discriminatory features and train a new classifier on responses, following the same approach as used in developing the pilot. The remaining 78 served for evaluation of classifier performance in validation.

The optimal PESQ classifier used 9 variables to classify patients into likely diagnoses: age; onset from sleep; sleep deprivation triggering; waking with a cut tongue; déjà vu; feeling confused after; feeling hot or cold during; skin tingling during; and muscles aching after. The PESQ classifier correctly identified 63/78 (80.8%; 95% CI 70.0-88.5) of diagnoses. Sensitivity for syncope was 96.6% (87.0–99.4). The classifier did not differ significantly from our pre-specified target sensitivity for syncope of 97.5% ($p$ = 0.644). We also performed a post-hoc analysis comparing classifier diagnosis to the initial assessing clinician's diagnosis, and referral or discharge diagnosis. The classifier accuracy was numerically, but not statistically significantly, superior to initial diagnosis (accuracy 70.5%; $p$ = 0.192) and referrer diagnosis (accuracy 75.6%; $p$ = 0.561).

Through this development and quantitative validation of a revised CDA (stages 5 and 6 of the IDCV framework) we were able to demonstrate that a patient-completed CDA trained only on a

small number of datapoints readily reportable at the initial presentation of TLOC performed numerically (though not statistically) significantly better at diagnosis than the initial assessing clinical team's diagnosis at discharge. However, we could not demonstrate that the CDA statistically significantly outperformed the standard of care, and further external validation work would have to assess the impact of clinician-supported decision-making using such a CDA (rather than the classification performance of the CDA in isolation) prior to any consideration of more widespread implementation.

#### *1.5.3.4. Acceptability and utility*

In addition to this quantitative validation, we sought qualitative validation to ensure acceptability and utility of the CDA to the patients completing it (stage (7) of the IDCV framework, addressing questions 1B, 2C, 3B, and 4B of the NASSS framework). This study is described in §4.3. We conducted semi-structured interviews with a purposive sample of participants who completed the PESQ, interrogating the acceptability and utility of the content of the PESQ and the format of its online delivery. We found that participants largely found a simple patient-completed CDA interface based on yes/no questions to be easy and acceptable to use, even for those not usually familiar with using computers. However, they found that the use of medical language could be a barrier to use or understanding. Some also expressed a desire to be able to give more fine-grained answers than permitted by the CDA. Participants were less unanimous on the utility of the CDA; in particular, many were concerned that its classification being based on their own reports was less "*objective*" than medical assessment or investigations. They also felt that, while it may be of use to researchers or clinicians, the benefit was less clear to patients; some participants offered suggestions of how a CDA could be made useful to patients as well, for example by providing them with information on the causes of TLOC and assessment or self-management, or by making their answers available to them to refer to later.

#### *1.5.3.5. Further work*

The work contained in this thesis demonstrates proof of principle of the potential of a CDA to support the differential diagnosis of TLOC at first presentation, but that such a tool would need refinement prior to implementation. This would not only involve refinement of the CDA to improve diagnostic performance; it would also require further qualitative validation, addressing some of the concerns raised by patient participants above, as well as working with clinician users to explore barriers to and facilitators of utilisation from their perspective.

## 1.6. Future research challenges for the differential diagnosis of transient loss of consciousness

This commentary has laid out some of the challenges arising in the differential diagnosis of transient loss of consciousness, and the research contained within this thesis outlines some attempts to address these challenges. In conclusion, I address some ongoing work covering some of the priorities for TLOC research highlighted throughout this thesis.

### 1.6.1. Improved use of artificial intelligence

The CDA developed in this thesis made use of well-established machine learning tools. The advantage of the approach used was that it could use non-linear combinations of simple features that are readily identifiable through patient-completed questionnaires to support the diagnostic decision problem. However, advances in artificial intelligence (AI) provide means for

making use of finer-grained features of the patient's history and experience to support differential diagnosis.

It is now well-established and validated across cultures that the differential diagnosis of seizure disorders can be supported not just by what people say about their experiences, but how they say it.[156–159] The patient narratives of people with ES are characterised by a high degree of formulation effort, with patients putting extensive attempts into articulating difficult-to-describe experiences. They also use passive expressions to describe their experiences.[156,160] People with FDS, meanwhile, often describe a subjectively-barren 'gap', but use more active metaphors to articulate their going into these conditions.[159] These linguistic features can reliably support differential diagnosis between ES and FDS;[156] previous work in cognitive neurology has also shown that identification of similar linguistic features can be performed through automated speech recognition, providing AI-supported diagnostic triage.[161,162]

In work building upon that reported in this thesis, Nathan Pevy and colleagues demonstrated the feasibility of combining a CDA like that described here with automated analysis of speech gained through patient interaction with a 'digital doctor'. They invited a sample of 61 (20 ES, 29 FDS, 12 syncope) patients to complete the pilot iPEP classifier online, and also to interact with a virtual agent. The iPEP classifier identified 65.8% of diagnoses correctly; when the classifier predictions were supported with automated speech analysis, classification accuracy improved to 85.5%.[163]

An alternative – or complementary – approach to AI-supported linguistic analysis in the differential diagnosis of TLOC is offered by the increased availability and abilities of large language models (LLMs). However, results so far have shown limited diagnostic abilities: in a task diagnosing FDS or epilepsy on the basis of short subjective seizure descriptions, ChatGPT-4 did not significantly outperform the 'no information rate'; however, performance did improve with training on examples of seizure descriptions, and on more informative descriptions on which expert neurologist raters agreed more highly.[164]

### 1.6.2. Witness reporting

§4.1, as well as the prior research supporting it,[73] provides a clear quantitative demonstration of the long-established good practice point that – despite the low reliability of reporting of individual semiological features by lay witnesses[74] – witness reports substantially improve the quality of diagnoses in TLOC presentations. This is further evidenced by the fact that the only individual categorical features validated as supporting diagnoses of FDS in the first presentation in §3.2 were witness-reported semiology. It is therefore of significant concern that such witness reports can only be secured in a minority of presentations.

In the prospective first-presentation TLOC study reported in §4.2, only 46/178 (25.8%) of participants were able to identify a witness able to complete the PEWQ. Even by reviewing case notes to extract witness reports from others not known to the participants (e.g. bystanders or paramedics), as reported in §3.2**,** witness reports were only available in 65/178 (36.5%) of cases. Previous reports have highlighted problems with lack of attempts to secure witness reports in first seizure presentations; for example, in the most recent National Audit of Seizure Management in Hospitals (NASH3), only 70.3% of suspected seizure presentations recorded an attempt to secure a witness report, or else confirmed the event was unwitnessed.[165] This thesis demonstrates that, even when such efforts are made, reliable witness descriptions are difficult to obtain for the majority of first-presentation patients.

Despite being a priority recommendation for research in the 2010 NICE guidance on TLOC,[1] little subsequent work has been done on developing robust systems for securing witness reports. Ongoing work on paramedic responses to suspected seizures has highlighted the informational challenges pre-hospital clinicians face in the assessment of seizures,[166] but subsequent research has focussed on promoting information for admissions avoidance where the diagnosis is already reasonably secure, rather than supporting diagnosis.[167,168] Complementary knowledge exchange between paramedics and clinicians later in the TLOC management pathway could identify opportunities for optimising witness reporting from bystanders who may not be contactable after first responders arrive.

## 1.6.3. Alternative TLOC assessment pathways

Perhaps more important than development and validation of new tools to support the assessment and management of TLOC is implementation research of how care pathways can be improved and standardised across units and countries to ensure optimal access to the best standards of care. A range of different models of TLOC care provision have been developed, though with limited evidence on their effectiveness, relatively few having randomised controlled trial standard evidence of their effectiveness in achieving patient, healthcare utilisation, and economic outcomes.

Current guidelines and recent service evaluations within the UK and across Europe emphasise that there is wide variation in TLOC care and adherence to guidelines. The latest round of the National Audit of Seizure Management in Hospitals (NASH3) found that essential aspects of care were omitted in many patients; only 70% had a documented attempt to obtain a witness report of a first seizure, only 87% an ECG.[165] In the EPIC2 study of patients presenting with seizures, 36.5% received no onward referral, and over half of these had not been seen in the epilepsy clinic.[169] Even broader variation is seen across Europe.[170] Similar variability is also seen in syncope care, and widely different models of syncope assessment are used.[171] Here I review the initial evidence for implementation of some new models of TLOC assessment.

### *1.6.3.1. Blackout triage clinics*

One approach to the challenges of accurate differential diagnosis of TLOC by expert generalists is to improve access to early specialist assessment. Petkar *et al* propose a model of early specialist assessment through a rapid access blackout triage clinics (RABTCs): clinics run by specialist nurses from Cardiology or Neurology backgrounds – with TLOC specialist medical oversight – to which primary and emergency care clinicians could refer for early triage and risk stratification.[172] By requiring that referred patients attend with a witness where possible, performing essential clinical examination and investigation on-site (e.g. ECG, carotid sinus massage where indicated), and using standardised questionnaires for systematic patient assessment and explicit criteria for risk stratification, RABTCs could address some of the most prominent challenges in TLOC assessment.

The RABTC model has not undergone systematic evaluation compared to the standard of care. However, Petkar *et al* did report that in pre- and post-intervention observational cohorts, hospital readmission rates reduced from 46.2 to 6.8%, and 144/327 patients could have a firm diagnosis and treatment plan established within the RABTC. At mean follow-up of 230 ± 153 days, there were no deaths in patients labelled low-risk.

There are significant caveats to this model: Petkar *et al* reported that referrals rapidly outstripped available clinic slots, suggesting that without sufficient capacity RABTCs may not

address existing problems of delays to specialist input. The protocolised assessment and triage used in the RABTC model depends on the development of CDAs such as those explored in this thesis; further research could explore the value added of specialist nurse assessment to the triage process, beyond patient completion of a CDA like that presented in §4.2.

#### *1.6.3.2. Falls and syncope services*

Given the difficulties in certain (especially older) patient populations in differentiating TLOC presentations from those involving falls with preserved consciousness, another model combines TLOC assessment with that for falls from other causes. A Falls and Syncope Service is a specialised team run by geriatricians and primary care physicians with syncope expertise, providing both educational in-reach to ED and general medical settings, as well as urgent outpatient assessments within 1-3 weeks.[173,174] Combining inreach services providing evidence-based algorithms to support expert generalists in management of falls and syncope in older people, with rapid outpatient access to TLOC specialist assessment produced (non-statistically significant) reductions in inpatient admissions with falls or syncope (10.6% v 8.2%), and 30-day readmissions (12% v 0%) in successive audit cycles.[173]

#### *1.6.3.3. Clinical decision aids to support guideline-directed assessment*

In addition to RABTCs, other researchers have explored the potential for online CDAs to support adherence to guidelines for TLOC assessment. Sanders *et al* present an online 'faint algorithm' to support guideline-directed assessment of TLOC, and found that it reduced admission rates from a syncope clinic from 20% to 4%.[175] The tool could be implemented in a clinic run by a nurse practitioner, with remote medical oversight.[176]

#### *1.6.3.4. Syncope units*

For those with a provisional diagnosis of syncope as cause of their TLOC, various American and European Cardiology societies recommend that the standard of care for ongoing assessment involves referral to a syncope unit.[3,177] Syncope units are facilities with dedicated staff (who can be emergency clinicians, general medics, or cardiologists) and access to appropriate diagnostics and therapies, that are able to offer standardised and systematic approaches to diagnosis and management of TLOC.[3]

Different syncope unit models exist. In the USA, they are typically co-located with, and usually run by, EDs, whereas in Europe they are usually rapid-access outpatient facilities run by Cardiology services.[171] The precise nature of assessment and investigation availability varies, but generally it should include history and physical examination, ECG, lying and standing blood pressure, up to 12h continuous cardiac monitoring, and (if indicated by history, ECG, or cardiac examination), transthoracic echocardiography.[171]

Despite their widespread endorsement, there is limited evidence of their overall benefit in the assessment of TLOC. The only randomised trial evidence for syncope units concerns their utility in the management of intermediate-risk syncope presentations. For this patient group, the single-centre SEEDS study found that syncope unit assessment improved rates of achieving a positive diagnosis at time of hospital discharge (67% v 10%) while reducing inpatient admission rates (43% v 98%).[178] A subsequent multi-centre study involving only patients 50 years and older with intermediate-risk syncope reduced admission rates by 77% and mean hospital stay by 18 hours, with a non-significant reduction in 30-day hospital costs, without any difference in 30-day or 6-month serious clinical events.[179]

There is a need for high-quality evidence assessing the effect on patient outcomes, as well as health economic implications, of more widespread implementation of syncope units.[3] Furthermore, their successful implementation requires the first step of accurate discrimination of syncope from other TLOC presentations; they could also be enhanced by extending their use to ES or FDS, potentially with ready access to EEG, given that the yield of this investigation is higher in the early stages (up to 72h) after a first seizure.[180] This could be made feasible without unduly increasing burden on neurophysiologists' workload with the support of AI-automated analysis of interictal EEG.[181,182]

## 1.7. Conclusion

TLOC remains a difficult presentation to manage well in primary and emergency care settings. Both new AI-supported CDAs, and optimisation of existing care pathways, offer opportunities to provide more timely, accurate, and safe assessment to improve outcomes for patients who experience this common but highly disruptive condition. Future research to improve such outcomes needs to be conducted within the setting to which its results are to be applied to ensure validity of its findings, and involve all clinician and patient stakeholders to ensure that innovations are sustainably adopted and benefits maximised.

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# Section 2 Challenges in the initial assessment of transient loss of consciousness

## 2.0. Section abstract

Transient loss of consciousness (TLOC) is a common presentation, accounting for 1.2-2.2% of all adult Emergency Department (ED) presentations. Many causes are benign, but some have high associated short-term morbidity and mortality. Differential diagnosis can be challenging due to the difficulties of eliciting the patient history. Prompt and accurate diagnosis is valuable not just for optimising medical management, but for minimising the holistic impact on patients' quality of life. This section reviews the challenges of accurate history-taking in TLOC (and other seizure) presentations; the ethics and epistemology of history-taking in seizure presentations; and the holistic life impact of a first presentation of TLOC. Abstracts of included papers are listed here.

### The promises and pitfalls of seizure phenomenology

The typical adult patient presenting with a first seizure has a normal clinical examination, uninformative investigations, and often has no witness to their episode. The assessing clinician, therefore, has one primary source of information to guide their assessment; the patient's experience. However, seizure *phenomenology* – the subjective seizure experience – has received relatively less attention by researchers than objective semiology or investigations.

This essay reviews the clinical importance of seizure phenomenology, and the challenges clinicians face in eliciting accurate and clinically relevant descriptions of ictal experience. I conclude by discussing tools that clinicians may use to support the clinical application of seizure phenomenology, and exploring the subjectivity of epilepsy more broadly.

### Epistemic privilege, phenomenology, and symptomatology in functional/dissociative seizures

Much work on clinical testimony assumes that none can know better than the patient what they experience. We show that in certain contexts this assumption is unwarranted; clinician expertise encompasses disease *phenomenology*, to the extent that the clinician *may know better than the patient what the patient is experiencing or has experienced*. Conversations between clinicians and people with functional/dissociative seizures (FDS) show that initial phenomenological reports of FDS (what we call 'surface' phenomenology) are often inconsistent with more fine-grained descriptions produced after detailed inquiry ('reflective' phenomenology). Assuming the initial reports are made in good faith, this process involves the clinician *showing the patient something about their experience they did not already (explicitly) know*.

Failure to engage in this reflective process can result in misdiagnosis and mistreatment. Thus, uncritical acceptance of patient testimony – an unwarranted credibility *excess* – may be as harmful as its unwarranted dismissal. We conclude that: the epistemically just clinician cannot rely on expertise in *le corps objectif* alone, they must also cultivate an understanding of *le corps propre* for the patients they encounter; and epistemic (in)justice cannot be considered solely

something a clinician does to the patient. Instead, epistemic justice in the clinical encounter is an intrinsically collaborative process.

## *"It is just a big question mark":* A qualitative interview study of patient experiences of the initial assessment of transient loss of consciousness

**Objectives:** Transient loss of consciousness (TLOC) is one of the commonest neurological complaints in the Emergency Department (ED), but little is known about the patient perspective. We aimed to explore patient perceptions of diagnostic assessment for TLOC.
**Setting:** ED, Acute Medical Unit (AMU), and Syncope and Neurology clinics in a single tertiary teaching hospital in the North of England.
**Participants:** 20 adult patients (60% female, age range 17-90y) attending or referred with a first presentation of TLOC.
**Primary and secondary outcome measures:** Exploratory thematic analysis of semi-structured qualitative interviews.
**Results:** We identified three themes within the data: satisfaction with care; unanswered questions; and being left in limbo/No Man's Land. Participants explored these themes through four topics: communication; the role of investigations; the role of authority; and the social context of care.
**Conclusions:** Communication (including differential diagnosis, significance of investigations and further assessments, and interim safety advice) is emphasised in supporting ongoing self-management, even before a definitive diagnosis is made.

# 2.1. The promises and pitfalls of seizure phenomenology

## 2.1.1. Introduction

*Language is demanded by epilepsy, as by poetry, that simply does not exist; and no amount of agility can create it any more than tight-rope walking or dancing can create wings. Language can, however … suggest that greater wordless language within from which mental and spiritual discovery issues. It can suggest truths which are the more certain for being inarticulate.* – Margiad Evans, *A Ray of Darkness* [1(p172)]

The typical adult patient presenting with a "first seizure" has a normal clinical examination, uninformative investigations, and is asymptomatic at time of presentation.[2,3] A witness report may be, but is not invariably, available; and will not reliably identify features of greatest interest.[4] This leaves clinician and patient with one key source of information for understanding the patient's complaint; the patient's own experience.

The subjective seizure experience – the *phenomenology* of seizures – is thus clinically indispensable. It guides the differential diagnosis of paroxysmal events like seizures, even in presentations involving apparent loss of awareness;[5] it aids distinction of focal from generalised seizures,[6] or recognition of a prior history of multiple seizures;[2,7] it can be used to guide behavioural or psychotherapeutic adjunctive management strategies for people with epilepsy.[8,9] However, understanding seizure phenomenology has received relatively less attention from researchers than investigations. Consequently, subjective aspects of seizures are under-described and under-recognised.[10]

This relative neglect compounds the difficulties already inherent in 'taking the history' from people who experience seizures. More focused study of the ways in which phenomenological accounts of seizure experience are constructed reveals some of the challenges and pitfalls inherent in this act. People who experience seizures often find it difficult to describe their seizure experiences[11,12] due to problems of articulation[13] or recall,[14] or stigma and embarrassment surrounding certain types of experience.[6,15,16] More fundamentally, work in both the philosophy of medicine and neuroscience of perception and memory challenges the idea that there is a single valid description of 'what it is like' for that person to have a seizure.[16–19]

This paper reviews the clinical significance of, and challenges in describing, seizure phenomenology. It concludes with a discussion of recent efforts to improve elucidation and clinical application of the subjective experience of seizures.

## 2.1.2. The clinical significance of seizure phenomenology

*Listen to the patient. He is telling you the diagnosis.* - attr. William Osler

The proliferation of video recordings of seizures – whether from formal video-EEG, or increasingly from home or smart phone recordings – has produced a wealth of valuable research on semiology – the external, observable appearances, or 'signs' – in the assessment of seizure disorders. What these videos – and thus research based on them – fails to capture, however, is the inside, first-personal experience of the seizure – its phenomenology, or *symptoms*.[20]

The under-recognition of seizure phenomenology has implications for assessment, diagnosis, and management of seizure disorders. Time to diagnosis from first seizure in those with 'non-

motor' seizures (i.e. with predominantly subjective manifestations) is over 20 months, 10 times longer than in people with (visible) motor seizures. The fact that 'non-motor seizures' are essentially characterised by episodic subjective symptoms does not mean that they are clinically irrelevant; 82.6% of motor vehicle accidents in those with undiagnosed epilepsy occur in those who experience nonmotor seizures.[7] The failure to identify subtle subjective symptoms (such as those caused by focal epileptic discharges prior to a generalised seizure) can also affect treatment; epilepsy is likely to be misclassified as generalised when initial ictal 'aura' symptoms have been missed.[6] Consequently they may receive antiseizure medicines with suboptimal effectiveness for their particular epilepsy syndrome or they may not be considered for treatments such as epilepsy surgery. Even if considered, we lack adequate research on how seizure symptoms might support localisation. Despite the value of certain seizure symptoms for localisation being established at least as far back as Hughlings Jackson's writings on the "dreamy state", amongst studies of localisation value of seizure signs or symptoms, only 25% of the most-commonly studied seizure manifestations were subjective.[21]

Recent attempts to redress this imbalance show the potential for clinical application of seizure phenomenology. Systematic inquiry regarding seizure symptoms can improve differential diagnosis of epileptic seizures from functional/dissociative seizures and syncope.[5,22] Detailed phenomenological interviewing shows potential of identifying prodromal symptoms that patients find difficult to articulate, but once identified could be used as target for seizure self-control. Identifying such symptoms now forms part of behavioural interventions in epilepsy.[8,23]

Such results have prompted a renewed interest in characterising seizure phenomenology in greater detail.[9,10,20] Describing the experiences of seizures, however, is not a straightforward task.

## 2.1.3. Challenges in eliciting the seizure history

### *2.1.3.1. Describing the indescribable*

> *[I]t's a feeling that I don't know and cannot associate with something. It's as if you had to describe the colour blue but you don't know what blue looks like*. – Anon. 48-year old male with right temporal lobe epilepsy[9]

In order to make clinical use of seizure phenomenology, the person with seizures has to be able to share that experience with others – most notably, their clinician. We are accustomed to thinking of the sharing of symptoms in clinical encounters as a straightforward issue – the patient comes in with a 'presenting complaint', which the clinician then interprets with reference to other data regarding their history, examination, and investigations. However, in arriving at this 'presenting complaint' the initial experience has already undergone several stages of interpretation –the patient's becoming consciously aware of an anomalous experience,[24] the initial parsing of that experience with reference to our prior expectations,[18,19] and the personal and social negotiations that transform an anomalous experience into one that is a candidate for explanation in pathological terms – a potential 'symptom'.[25,26] Cultural, social and economic context affects 'candidacy' for such explanations,[27] and patients undertake specific conversational manoeuvres in the consultation to represent these experiences as 'doctorable'.[28]

Studies in the phenomenology of illness highlight that, even once in the clinic room, aspects of illness experience can complicate its sharing between patient and clinician. Philosophers of medicine Havi Carel and Ian James Kidd argue that illness experience is often *inarticulable* –

patients may lack the words or concepts to translate those experiences into terms another can understand. Beyond that, it may be *ineffable* – that is, of a kind that can be understood only by going through the experience personally.[17,29]

There is strong reason to believe that people with seizures often find their experiences inarticulable, and some propose that they are ineffable. Attempts to elicit seizure phenomenology in the clinic recurrently demonstrate the difficulties people with epilepsy have in articulation. They will say 'this is hard to describe', or 'I don't know how to say this';[11] linguistic studies have demonstrated that their attempts to relate these experiences are marked by a very high degree of 'formulation effort' – hesitations, false starts, rephrasings and recapitulations, as they struggle to put into words what it is like for them to have a seizure.[11,13,30] They often resort to metaphor as a means of articulating experience for which – as the opening quotation suggests – "language does not exist."[9,31] People with epilepsy – and with other seizure disorders like functional/dissociative seizures (FDS) – are more likely than healthy controls to struggle particularly with identifying and describing emotional experiences; rates of alexithymia in people with epilepsy range from 25.9-76.2%, and 30-90.5% in people with FDS.[32]

Moreover, some such experiences are held not just to be inarticulable, but ineffable. This is particularly the case with 'ecstatic' seizures – focal aware seizures, usually (but not invariably) localising to the temporal lobes; those who experience them may fail to describe them ("*these sensations are outside the spectrum of whatever I have experienced"*); or describe them in nonsensical terms ("*an oscillating erotic sensation, like twinkling polar light*"; "*I can sense the colours red and orange without seeing them*").[33,34] They may draw from spiritual, religious, or erotic metaphor to give some indication of the nature of these experiences,[35] but ultimately find them so far outside the normal realms of intersubjectively understood human experience that they cannot be shared in words.

To Kidd and Carel's list, we can add the difficulties some people with seizures face in finding their experiences *unspeakable* – that is, unable to be shared due to concerns regarding the social or psychological consequences of admitting to them. Some people with seizures report difficulty or unwillingness to describe their experiences due to fears of being labelled mad or otherwise stigmatised; they are surprised and relieved to find, on direct questioning, that their symptoms represent recognised ictal phenomena.[6]

For people with FDS, meanwhile, the unspeakable nature of their symptoms may even play an aetiological role. The role of shame, stigma, and trauma in the precipitation and perpetuation of FDS is nuanced and still controversial, but all three are related both to each other and FDS in ways that may render seizure experiences unspeakable. FDS is a stigmatised condition;[36] such stigma is experienced by people with stigmatised conditions as "shame anxiety", or the chronic anticipation of shame.[37] Shame – a self-conscious emotion of being inadequate, immoral, or otherwise negatively-evaluated in the eyes of (real or imagined) others – provokes responses of withdrawal or attempts to conceal;[38] mechanisms of shame regulation such as self-directed aggression or social withdrawal share semiological characteristics with FDS.[39] Prior traumatic experiences, while not necessary for developing FDS, are seen more frequently in people with FDS than controls (OR 3.1 [1.7-5.6]), and emotional neglect may be still more common.[40] Such experiences both increase general shame-proneness, and can be a source of shame;[39] most strikingly the case in FDS associated with 'unspeakable dilemmas', where people with FDS experience seizure in the context of apparently irremediable social conflicts.[15] This combination renders the experience of FDS particularly vulnerable to being held unspeakable. If the seizure

is understood as a dissociative release from intolerable experiences;[41] the reason for their being intolerable is intrinsically linked to events the person finds shameful;[39,40] and the disclosure of seizure experience might result in a diagnosis that is stigmatised, and thus a source of further shame;[36] then it is not hard to understand how it may be particularly difficult for the person with FDS to share their experiences. Consequently, in initial clinical encounters they expend little effort in, and volunteer little information about, the subjective experience of their seizures – emphasising instead the subjectively-barren 'gap' in their experience.[11]

#### *2.1.3.2. Recall, responsiveness, and awareness*

> *[R]etained awareness usually includes the presumption that the person having the seizure later can recall and validate having retained awareness.* – the Operational Classification of seizure types by the International League Against Epilepsy[42]

If the above problems highlight the difficulties in converting a first-person seizure experience into an interpersonally-shared seizure history, the challenges for seizure phenomenology go still further – the person who experiences seizures may have different recollections of that experience, depending on when and how they are asked to describe the experience. A person's subjective seizure experience, described at one time, may fundamentally differ from that described at another.

This is most strikingly illustrated in the difference between seizure descriptions captured intra-ictally, and from recall afterwards. The difference between seizure experiences narrated intra- and post-ictally is so marked that, as quoted above, the ILAE deemed it necessary to clarify the time point at which 'awareness' is assessed for the definition of focal aware seizures.[42] Intra- and post-ictal accounts differ systematically. Even for some of the most basic ictal features, such as whether or not a person is able to respond to others, post-ictal subjective reporting shows poor concordance (Cohen's $\kappa = 0.434 \pm 0.006$) with ictal assessment.[43]

When looking at more fine-grained description of subjective seizure experience, the differences are still more striking. In one study, only 45.6% of seizure symptoms described by participants intra-ictally were recalled post-ictally.[44] For most symptoms, reporting was greater intra- than post-ictally; given seizure activity often disrupts mesial temporal networks essential for memory encoding and consolidation (and seizure recall correlates with EEG activity in these regions),[45,46] this is perhaps unsurprising. However, disparities between intra- and post-ictal accounts of seizure phenomenology are not simply a function of memory impairment; visual phenomena were found to be more likely to be reported post- than intra-ictally (reported intra-ictally in 4 seizures vs. 8 seizures post-ictally).[44] Seizures with non-dominant parieto-occipital foci have also been reported to produce transient neglect or anosognosia,[47] or transient Anton's syndrome;[48] ictal disruption of attention networks may transiently and selectively impair awareness of or engagement with certain sensory experiences, or produce disconnection syndromes, just as these networks are more persistently impaired with structural lesions affecting those networks.[49]

#### *2.1.3.3. Whose story?*

> *The whole of medical discourse on epilepsy is underpinned by the belief that seizures are sudden, that they cannot be anticipated by the patient. We have observed that this belief considerably hampered the awareness and description by the patient of the early symptoms that could enable him to anticipate and manage his seizures.* – Claire Petitmengin[50]

If these phenomena prove troubling for the clinician attempting to construct a clear account of a person's seizure experience, they at least allow for a single such account in principle to exist – they simply highlight that the patient may find themselves unwilling or unable to share that account, or ictal network disruption may impede its reporting or recollection. Beyond this, however, the clinician must acknowledge that our phenomenal experiences – and their subsequent reports – do not allow for a single, privileged version; they are shaped by our prior expectations, conceptual resources, and intended purposes.

The general phenomenon of top-down influences on perceptual processing has been a subject of neuroscientific research for some decades. Well-established results demonstrate that cognitive manipulations can influence subjective experiences as diverse as sight,[51] sound,[52] pain,[53] and body ownership.[54] More recently, the predictive processing paradigm has explained this by modelling perception as a constructive and active process; internal representations of experience – shaped by past experience, socially-shared conceptual resources, and contextual factors – are contrasted with sensory input, discrepancies ('prediction error') between these modifying subsequent experiential representation.[18,19,55]

Such expectational influences not only moderate our perceptions, but also our memories of them. Prior expectations shape new episodic memories, and bias our recollection of characteristics according to our categorisation of experiences.[56] Translated into clinical terms, this could imply that symptom experiences may be biased toward those expected by prior descriptions of symptom experience – people will remember their illness experiences more, and more in line with, their expectations of how the illness 'should' feel. Experimental evidence of this demonstrates recalled symptom reporting differing systematically from contemporaneous reporting, influenced by psychological conditions (such as negative affect) at the time of reporting, as well as features such as time from the initial experience.[57]

Well before the development of such neuroscientific models, philosophers of perception drew attention to the ways in which our prior concepts shape our experience of the world. As Heidegger puts it: "We never really first perceive a throng of sensations, e.g. tones and noises … rather we hear the storm whistling in the chimney, we hear the three motored plane … we hear the door shut in the house".[58(pp126-127)] However, our world of storms, planes, and doors leaves us open to surprise – sometimes a loud bang will provoke only the response, 'what was that?' Moreover, our response to that question will depend on the reasons for which we wish to answer it; depending on our perspective, 'rapid combustion-induced gas expansion', 'a mistimed ignition spark', and 'a car backfiring' might all be appropriate responses.[16] Each of these descriptions may be adequate for its purposes, while still not capturing all of what is held within the others. The philosopher Paul Ricoeur describes this as the "surplus of meaning"[59] inherent in any description of a phenomenon; the tension between a given interpretation of a phenomenon and this surplus of meaning leaves our description of sensory experience always iterative and ongoing. Hans-Georg Gadamer calls this the "hermeneutical circle", through which our interpretations are shaped by expectation, those expectations then revised in light of new information.[60]

The weight of prior expectations on shaping experience – or experiential recollection – may thus render certain forms of seizure experience more accessible, while concealing others. Experts in the assessment of seizure disorders typically structure seizure experience in specific ways: irrespective of the precise content of seizure accounts, they expect the symptoms to be: sudden and unprovoked, thus unpredictable; short-lasting (excepting status epilepticus);

strange or unfamiliar; stereotyped; and followed by fatigue.[61] Clinicians will look for experiences articulated in such terms in their efforts to understand their patients' seizure phenomenology. It is not just clinicians, however, that may adopt these categorisations. People with seizures – who may be most closely challenged by clinicians to describe their experience, and then learn from the clinician's recapitulating of that experience, may come to adopt this framework too.

In a series of studies using an interview method designed to enhance focus on specific experience without conceptualising or categorising, Claire Petitmengin and colleagues demonstrated that many people – given the right environment – come to identify certain features of their seizure experience that do not readily fall within that description. These patients described a more vague, less abrupt, and more prolonged prodrome – such as fatigue, or being 'ill-at-ease' – for up to 24h prior to the onset of clinical or electrographic seizures.[23,50,62] People with both focal and generalised epilepsy may report such prodromes;[63,64] however, reporting is highly variable dependent on the mode of interrogation, with highly heterogeneous rates of prodrome reporting (7-87% of people with epilepsy) between studies asking about these in different fashions.[65] However, without direct prompting or specific interrogation, such reports are rarely volunteered spontaneously. Petitmengin and colleagues directly relate this to the clinical conceptualisation of seizures – as the quotation at the start of this section describes, they found that the clinician's picture – of the seizure as an unpredictable and paroxysmal event – impeded the patient's ability to articulate the prodrome.

Allowing for these phenomena, we see that no one seizure description will capture all that can meaningfully be said of the phenomenal experience of that seizure; indeed, the phenomenology itself will depend upon current and previous descriptions. Adding this to the difficulties with ictal recall and responsiveness, and the challenges in describing alien experiences, demonstrates just how challenging eliciting seizure phenomenology in the clinical setting may be. In the next section we survey some present and future directions by which clinicians and patients may navigate a course through these challenges.

## 2.1.4. New directions in the subjectivity of epilepsy

*When I was young, I saw this phenomenon for the first time in a 13-year-old boy (…). I heard the child tell that the condition had begun in his leg, and then had gone up straight to his neck, going through the thigh, groin, ribs, and neck up to the head; as soon as his head was reached, he lost consciousness of himself. When questioned by the physicians about the nature of what he felt moving up to his head, the child was unable to answer. Another young man, who was intelligent enough, capable of feeling what was happening to him and more able to explain it to others, answered that a sort of cold breeze* [*αὔρα,* 'aura'] *was rising in him.* – Galen, *Galeni Opera Omnia*, quoted in[66]

To say that experiential accounts of seizures are incomplete, variable, or contradictory, is only to recognise that – like any tool in epileptology – they have their limitations that the clinician must navigate. Compare the situation with observable semiology: lay-witness reports of seizure semiology are notoriously unreliable,[4] but the descriptions obtained from such reports can nonetheless reliably support differential diagnosis.[20,67] Moreover, supporting non-experts with targeted education can improve identification of relevant features and subsequent clinical assessment.[68] Likewise, few would underestimate the value of EEG in the management of epilepsy, even if it is "one of the most abused investigations in clinical medicine […] unquestionably responsible for great human suffering."[69] We close by exploring some

approaches available to help clinicians and researchers navigating the challenges in exploring seizure subjectivity.

One suite of tools can be found in the clinical applications of the field of research that takes as its starting point the detailed analysis and description of subjective human experience – both normal and anomalous. Phenomenological research in psychology and neuroscience takes the subjective experience as its starting point – the foundation of all attempts at inquiry. It aims to explore such experience by: setting aside preconceived notions about the content of experience, aiming to focus on our experiences prior to conceptualisation; looking within this content to identify certain core features; and contrasting between subjects to identify areas of consonance and dissonance in different individuals' subjective experiences.[58] Recognising that subjective experiences represented the primary *explananda* of the field, psychiatry has been the area of medicine that has the most-developed phenomenological research programme,[70] helping to delineate models of mania and delusions able to support new lines of mechanistic inquiry.[71]

Phenomenological research in practice involves in-depth qualitative interviewing that invites subjects to return to the experience in question, using cues that encourage focus on the precise nature of the experience and avoiding prior conceptualisations.[50,72] The rich first-personal accounts thus generated are then suitable for within- and cross-subject analyses to identify persistent and intersubjectively shared features, that can then be used to support others in articulating their experiences,[73] or combined with investigation results to look for anatomical or physiological correlates of certain experiences.[23] As described above, Claire Petitmengin and colleagues have previously used this technique to characterise previously-neglected seizure prodromes, and identify correlative EEG changes;[23] more recently, a similar technique has been used to identify patients' self-understanding of seizure experiences in order to support tailoring of adjunctive psychotherapeutic interventions.[9]

This latter project invites the clinician to integrate the patient's subjective seizure experiences with its broader effects on their life and worldview. This is taken further by narrative medicine projects that seek to enrich clinical and research practice by engaging with the stories patients tell about their lives with and through illness, and encourage clinician competence in the interpreting of these stories.[74] The proliferation of autopathographical accounts of living with seizures (to the point of hypergraphia being suggested – in the Geschwind syndrome – as a core component of the personality profile of some people with temporal lobe epilepsy[75]), combined with the clear social and psychological ramifications of seizure disorders, have made them a particular focus of interest for studies in narrative medicine.[74,76–78] While clinical application beyond the context of medical education has been limited, a recent Italian pilot project demonstrated that, with the support of digital tools to aid communication, patients responded positively to attempts to articulate their illness narrative with clinicians, and clinicians reported the approach enabled clinical application of information that otherwise would not have become apparent in the course of their clinical encounters.[79]

If such phenomenological methods help patients to articulate seizure experiences in their own words, other approaches may provide patients with the words to describe the indescribable. Symptom inventories have been used in phenomenological psychiatry to support patients in articulating anomalous experiences by drawing on the conceptual resources afforded by the descriptions of those who have had similar experiences.[73] The use of such inventories – with lists of potential seizure experiences that patients can either endorse as forming part of their

seizures, or reject as being unfamiliar to them – provides more detailed descriptions of seizures than can be obtained through open questioning alone.[80] Patients report experiences on direct questioning that they might otherwise be afraid to share.[6] Automated classification of ictal descriptions obtained through such systematic enquiry improves differential diagnosis of seizure disorders over the present standard of care;[5,22] similar techniques could also be used to support seizure localisation.[21]

## 2.1.5. Conclusion

*My epilepsy started with the smell of jasmine, and that smell moved into my mouth. And when I opened my mouth after that, all my words seemed colored, and I don't know where this is my mother or where this is my illness, or whether, like her, I am just confusing fact with fiction, and there is no epilepsy, just a clenched metaphor, a way of telling you what I have to tell you: my tale.* – Lauren Slater, *Lying: A Metaphorical Memoir*[81]

What Margiad Evans called 'the patient's half' of understanding seizures – their experience of the events – are often the most important information available in the clinic for the diagnosis, assessment, and management of seizure disorders. But understanding the patient's half is no easy task – for clinician, or indeed for the patient herself. Whether through the limitations of language, the barriers of stigmatisation, the inconsistencies of memory or the feedback effects of our conceptual resources on shaping self-understanding, the process by which seizure experience is converted from subjective phenomenon to an interpersonally-shared list of symptoms is subject to many pitfalls. However, a range of interrogative tools are available for the motivated clinician or researcher to work with their patients in addressing this lack – placing seizure phenomenology alongside semiology and pathophysiology in understanding and treating seizure disorders.

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# 2.2. Epistemic privilege, phenomenology, and symptomatology in functional/dissociative seizures

## 2.2.1. Introduction

There is a commonplace narrative about knowledge exchange in the clinical encounter that goes something like this: a person (the 'patient') experiences a sensation or constellation of such sensations. They consider these sensations to be potentially suggestive of illness, by whatever means such judgments are made.[1,2] They therefore seek medical attention through an encounter with a health professional (the 'clinician'). In this encounter, the patient reports their experience; the clinician pieces together these reports, combined with other bits of information gleaned from targeted questioning, potentially complemented by examination or investigations, to interpret patient reports in terms of a disease process.[3]

This story presents a fairly neat division of epistemic labour in the clinical encounter: the patient is taken to have the phenomenal knowledge of their illness experience while the clinician is taken to have the technical, medical expertise to interpret that illness experience in pathological terms. It is the patient's role to state what is happening and the clinician's role to explain why and discuss how it could be changed. Lauren Freeman describes this distinction in terms of the patient's epistemic *privilege*, arguing that patients "have a unique epistemic route to facts about their bodies", compared with the clinician's epistemic *authority,* whereby the clinician "has expert knowledge to interpret, explain, and if necessary, diagnose, and treat what a [patient] is feeling."[4(p48)] According to this view of epistemic privilege, the phenomenology of illness is readily accessible to the patient – they know what they are experiencing and feeling, although they may struggle to articulate or communicate it to others.[5,6]

This standard account of the epistemic division of labour between patients and clinicians forms the backdrop for many alleged cases of *epistemic injustice* in medicine: a failure to acknowledge patient epistemic privilege in illness experience leads to its description being unjustly disbelieved or dismissed, assigned unduly low credence[7,8] or deemed irrelevant.[9] It may mean that knowledge claims derived from such privilege are barred from shaping the hermeneutical resources supporting clinicians' interpretations.[10–12] It might devalue the patient's interpretations of the significance of illness experience or deny them a role in informed self-management.[13] Conversely, mistaken belief attributions nonetheless grounded in a clinician's appropriate epistemic authority may not be considered epistemic injustices.[14]

According to this story, a clinician may claim legitimate epistemic authority in the interpretation of illness experience – in the form of 'symptoms,' the "scraps of pages" from which a pathological "plot" is formed[3(pp12-13)] – but defining the symptoms themselves falls within the scope of the patient's epistemic privilege. It is often presumed that none can know better than the patient what the patient is experiencing – "we … take each person to be the ultimate authority on his or her own sensations, feelings, and experiences." [5(p46)] It is this common presumption that we want to call into question. As such, we will argue that, in certain contexts, clinician expertise encompasses expertise in disease *phenomenology*, to the extent that, in some cases, the clinician *may know better than the patient what that patient is experiencing or has experienced*. Evidence for this argument can be found in one of the author's (Alistair Wardrope's) field of clinical practice, specifically by drawing on patients' reports of experiencing functional/dissociative seizures (FDS). This condition – involving paroxysmal episodes of altered bodily awareness and control, sometimes mistaken for epileptic seizures – is valuable for

analysing in this context given the extensive body of research devoted to understanding how patients with FDS talk about their experiences and how clinicians interpret it. This research demonstrates that initial phenomenological reports of FDS (what we are calling 'surface' phenomenology) are often inconsistent with the more fine-grained descriptions that can be produced with more detailed interrogation, guided by an expert clinician (what we are calling 'reflective' phenomenology). Assuming the patient's initial phenomenological reports are made in good faith, this process of interrogation involves the clinician *helping the patient come to see and understand aspects of their experience they otherwise would not (explicitly) see*.

If this is correct, then with some illness experiences (such as those which accompany FDS) patients' epistemic privilege must be qualified by clinicians' expertise in disease phenomenology. This makes adjudicating claims of epistemic injustice in the clinical encounter more complicated.[a] The clinician who disbelieves a patient's testimony regarding the phenomenology of illness may not always be dismissing their epistemic privilege in a way that is unjust but rather from their expertise identifying that the patient may need additional support in exploring, understanding and articulating their own experiences in more robust and reflective ways. Epistemic justice and injustice become not simply functions of the clinician's attitude toward the patient as a more or less credible informant but rather reflect dialogical features of the clinical interaction.

### 2.2.2. Epistemic injustice, epistemic privilege, and the distinction between surface and reflective phenomenology

Discussion of epistemic injustice has exploded in the past decade and a half following the publication of Miranda Fricker's influential book, *Epistemic Injustice: Power and the Ethics of Knowing*.[15] For the sake of brevity, we will not provide extensive exegesis of the many concepts and applications of this rich literature.[b] Instead, we will focus primarily on the concepts of *testimonial injustice*[18] and *hermeneutical injustice,*[19] which Fricker describes as different forms that epistemic injustice can take. For our purposes, and in brief, testimonial injustice (TI) concerns how we respond to the testimonial reports of others, in ways that are shaped and influenced by background social facts and features of the testifier's identity. TI is perpetrated when, through prejudicial dismissal of another's ability to reliably provide knowledge, we do not let their testimony sufficiently influence our own beliefs in a way that systematically disadvantages that person.[15(p27)] This could be through affording insufficient credibility to a speaker's testimony, attributing an insufficient degree of relevance to a speaker's testimony,[20] acting toward a speaker in ways that compromise their ability to provide reliable testimony (e.g. manipulation or coercion)[21] or testify at all (e.g., testimonial smothering).[22] Hermeneutical injustice (HI) concerns instead the ways in which the conceptual resources that allow us to understand and share our experiences are constructed. Processes of oppression and marginalisation exclude some groups from equal participation in the construction of these shared conceptual resources, with the result that aspects of their experience are obscured from collective understanding in a harmful fashion. This may take the form of an absence of

[a] In this paper we do not explore in depth the rare, but nonetheless important, situations in which the patient consciously feigns symptoms such as in factitious disorder (i.e., 'Munchausen's syndrome'). However, clearly the possibility of such conscious deception on the part of the patient (however rare such cases may be) further complicates the epistemic position of the clinician and highlights the shortcomings of a position of automatic and unqualified acceptance of patient testimony.

[b] The underpinning concepts are explored extensively elsewhere.[16] Ian James Kidd maintains a bibliography of work on epistemic injustice in health and illness.[17]

resources necessary to articulate some phenomenon (e.g. lacking the concept of 'postnatal depression' to interpret low mood, anhedonia and emotional distance after birth) or the presence of resources that harmfully distort the phenomenon in question (e.g. a concept of homosexuality that treats it as a mental illness).

Much of the literature on epistemic injustice in healthcare focuses on a specific form of devaluing, namely, dismissal of the essentially first-personal experience of illness. This is often parsed in terms of the phenomenological distinctions between the objective (*Körper, corps objectif)* and lived (*Leib, corps propre*) bodies,[4,5,10] with medicine prioritising the material body as object of scientific investigation over the embodied subject experiencing illness. Anita Ho describes an "inter-method hierarchy" that assigns lexical priority to information interpretable in terms of physiological or clinical descriptions of phenomena over other forms of understanding illness.[23(p115),24(p33)] Even prominent clinical researchers have described low status assigned to patient experiences as a key bias of evidence-based medicine.[13(p4)] [c]

Lauren Freeman claims that this prioritisation reflects a systematic devaluing of patient expertise,[d] namely, the expertise that comes from the *epistemic privilege* of the patient:

> [Patients] *have* epistemic privilege *over their bodies insofar as only they have first-personal, immediate access to their bodily sensations, and on the basis of this access, only they can refer to their sensations and give testimony as evidence in support of claims about their bodily states.*[4(p47)]

Freeman's proposal echoes Havi Carel's assertion that "we … take each person to be the ultimate authority on his or her own sensations, feelings, and experiences."[5(p46)] The hypothesis of epistemic privilege – implicitly or explicitly – is invoked in many of the published accounts of TI in healthcare. These arguments all identify situations in which patient testimony is apparently disbelieved or dismissed in ways that prove apparently detrimental to the patient. Epistemic privilege is then invoked to claim that this dismissal is necessarily unwarranted, since claims of epistemic privilege entail that patients have unique access to the knowledge of concern; as such, the clinician has no warranted grounds on which to dismiss it.[e]

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[c] The conventional 'hierarchy of evidence' in evidence-based medicine positions the 'case report' (summary of an individual patient experience) at the lowest rung in the hierarchy and cautions against clinical application of 'anecdotal' evidence. In the context for which this hierarchy was initially developed – assessing the likely efficacy and effectiveness of a given treatment on an otherwise-unspecified patient with a given condition – this status is epistemically warranted. It is difficult to know how one person will respond to a given treatment purely on the basis of what happened to another entirely different person after they were given that treatment. Moreover the case report is subject to many biases that are typically mitigated by forms of evidence higher in the hierarchy, such as randomised controlled trials. However, 'evidence-based medicine' as a social movement can misapply this hierarchy to questions where it is less well suited (e.g. how living with a particular condition in a particular social context affects an individual patient). This expropriation of critical appraisal heuristics can assign inappropriately low status to patient testimony.

[d] We use the term "expertise" here to denote the intimate experiential knowledge and understanding that patients have of experiencing or living with a particular condition. "Expertise" is increasingly the preferred term in clinical and biomedical research contexts, where there is an increasing recognition and promotion of the role of patient "experts by experience". However, we acknowledge that this sense of "expertise" differs in important ways from that in which it connotes a system of qualification or accreditation and is associated with certain social licences – a sense which more accurately reflects the position of clinicians and health professionals.

[e] Our discussion here assumes that "patients," as a broad group, can be the subject of epistemic injustice. Carel and Kidd have argued that, given their positions of lesser power vis-à-vis their clinicians and their state of heightened vulnerability, patients count as marginalized in the context of medicine and

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There is, however, a subtle distinction between Freeman's and Carel's conceptualisations that will become important here. Freeman's epistemic privilege focuses on "first personal, *immediate* access to … bodily sensations", while Carel assigns the patient the "*ultimate* authority on his or her own sensations" (our emphases). Freeman's claim that patients have 'immediate' access to bodily sensations implies that the experience of illness is readily accessible to the patient and *only* the patient. Carel's 'ultimate' authority thesis, on the other hand, holds that the patient gets the final say on whether a given description of illness experience accurately captures their own understanding and experience of it but allows that it might be the case that significant exploration and epistemic work (potentially involving another party) may need to be done in order to arrive at that description.

This difference becomes practically relevant when we consider that the immediately-accessible experience of illness – what we are calling 'surface' phenomenology – may not always be the most complete or accurate description of what a patient is experiencing. Perceptual awareness is not always dichotomous but can permit of gradations, such that there is a fuzziness regarding what we do or do not consciously experience.[26] Determining the content of that experience is not trivial, distorted as it may be by direction of attention, emotional appraisals or prior expectations.[27–29] Beyond this, experience is often not solely individual; it is shared with others, or else constructively and iteratively interpreted through dialogue with others.[1] The upshot is that we do not always have clear, immediate and perfect access to or ability to understand and articulate our experiences. Our impressions and recollections of our experiences can be influenced by a great many things.

Allowing for this, the general argument for TI in healthcare contexts becomes more complex. Epistemic privilege alone does not grant that disbelief in patients' experiential testimony is always unwarranted, since they may be reporting partial or incomplete surface phenomenology only. The next section presents a case of this in practice.

## 2.2.3. The phenomenology of functional/dissociative seizures

Functional/dissociative seizures (FDS) are episodes of altered subjective experience, involuntary movements and reduced self-control, modelled as arising from (possibly heterogeneous) neuropsychological network dysfunction.[30] They often superficially resemble – and are frequently misdiagnosed as – epileptic seizures. Neurologists – who manage both FDS and epilepsy – thus frequently face the problem of deciding whether a person's experience is more likely explained by one or the other condition. However, both these disorders are paroxysmal; it is rarely the case that the clinician can witness the patient having a seizure or that the patient can describe them while the episode is ongoing. Outside the seizures themselves, examination and investigation findings often have little to add in telling the difference between these conditions.

The patient's seizure experience (and their testimonial reporting about it) therefore becomes of paramount importance in differentiating between these two diagnoses. There is a wealth of data reporting not just *what* people with epilepsy and FDS say about their seizures but *how* they say it.[31–36] From this research – and associated work on seizure neurophenomenology[37] – it is

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can thereby be on the receiving end of epistemic injustice in that context.[6] Freeman and Stewart[25] have argued that to properly understand experiences of epistemic injustice, we must consider the intersectional identities of patients and how various aspects of patient identity – race, gender, sexual orientation, etc. – will influence the likelihood that patients will be dis/believed, which are over and above the general vulnerabilities and power differentials inherent in clinician-patient interactions. We flag this to acknowledge that dismissals of patient testimony can be influenced by many things, e.g. racial and gendered stereotypes, which can exacerbate the injustice and the related harm.

evident that *the experience of seizures is not always easily accessible to the person who experiences them*. We highlight two key features of FDS phenomenology here and sketch how expertise in FDS may be employed clinically in responding to patient testimony in each case.

#### *2.2.3.1. Ictal consciousness in FDS*[f]

One of the hallmarks of FDS – and many forms of epileptic seizure – is a phase of reduced self-control, awareness and responsiveness, or what is called a 'gap'.[31(pp63-65)] Most commonly, this takes the form of a 'blackout' – a period of complete absence of conscious awareness. Typically, patients with FDS will describe this gap as complete, encompassing the whole seizure, and struggle to embed it within their peri-ictal experience; by contrast, those with epilepsy will more frequently be able to identify the extent to which they have preserved awareness of different ictal experiences, delineate the 'boundary' of the unaware period and try to interpolate, e.g. from witness reports, what happens during the 'gap' itself.[31] The surface phenomenology of FDS is thus barren – to the patient, it seems that there is not "something it is like" to be in the seizure.

These reports, however, conflict with phenomenological accounts produced by other means. When provided with forced-choice questions regarding the level (self-perception of degree of ictal awareness and responsiveness) and content (specific phenomenal characteristics) of ictal consciousness, patients with FDS actually report *greater* ictal consciousness than those with epilepsy.[38,39] Focussed attention on ictal experience surfaces aspects of ictal phenomenology in FDS that are not immediately apparent to the patient; they are able to recall, to some extent, 'what it is like' to be within an episode previously described only as a 'gap'. This is puzzling, of course, given the previous inability to recall or describe the experience, given the lack of conscious experience while the episode is ongoing.

#### *2.2.3.2. Volition and agency*

FDS are perceived as unwilled events; characteristically the patient will describe attacks as happening without their doing anything to bring them on and with no sense of agency over their occurring.[31] In contrast, those with epilepsy will often attempt to identify things they can do that may alter seizure progression or experience.[32] However, this perceived absolute passivity is in tension with other aspects of seizure experience reports. Patients with FDS tend to describe their seizures in more active terms (as e.g. a space or place they go into) than those with epilepsy (who more commonly describe the seizure as an external agent coming over them).[31,40] Witnesses to FDS often identify a degree of purposeful interaction with others while someone is experiencing FDS.[41]

This tension becomes more apparent with sustained clinician support in exploring the phenomenology of agency in FDS. With careful, fine-grained discussion, patients with FDS often report that they *are* able to identify some features of the attack over which they feel a degree of agency – whether in identifying things that might abort or delay the attack or conversely bring it on (often with a view to 'getting it over with').[42] Identifying these features – and relating them to underlying neuropsychological networks (e.g. autonomic arousal – 'fight/flight/freeze' responses) can help patients to better understand the disorder and can guide therapeutic intervention.[43] Again, these cases demonstrate a dissonance between the surface

[f] 'Ictal' is the adjectival form of the term 'ictus', meaning a sudden attack (from the Latin term for blow, stroke or seizure). It is used medically to describe any paroxysmal event – most commonly in the context of seizures, but also e.g. syncope (fainting) or strokes. 'Peri-ictal' refers to the period around the event.

phenomenology of FDS that patients initially report versus that disclosed in detailed, supportive exploration of its experience.

### 2.2.4. Clinical description of FDS (hetero)phenomenology

How do considerations such as these influence testimonial exchange in the clinical encounter between clinician and patient with FDS? A naïve reading of epistemic privilege would hold that the clinician ought to uncritically accept the testimony (or lack thereof) of the patient with FDS regarding its surface phenomenology. This would leave the clinician accepting that a patient experiences their seizures as a subjectively-barren 'gap' over which they have no agency. To accept this, however, would in fact be to assign an unwarranted *excess* of credibility to the patient's initial testimony in a way that could directly harm the patient – by failure to arrive at the correct diagnosis or identify components of the seizure experience that might be a target for therapeutic intervention.[g]

The epistemically just clinician, therefore, does not simply accept the patient's testimony at face value in such cases. She accepts initial testimony as a starting point for reconstructing seizure phenomenology. She will then interrogate this in greater detail alongside the patient. This could involve asking for clarification on what precisely the patient means when they use certain terms to describe their experience. They might 'open up' different phenomenal possibilities (e.g. of having some kind of phenomenal experience during a 'blackout') or challenge the patient's initial description (e.g. reviewing the possibility of intentional influence on the course of the seizure).[44] The clinician's efforts here will be guided by their initial interpretations of the patient's presentation. This will be shaped by the surface phenomenology but also a range of other considerations (from their medical background to the way they discuss their experiences). The patient can use the clinician's prompts to reflect on their experience, deriving a more nuanced, reflective account of their seizure phenomenology. This is a very different understanding of the epistemic division of labour in the clinical encounter from the standard narrative sketched in the introduction – in this case, the clinician's expertise is used to elucidate not just *why* the patient is ill but also something important about the content of the illness experience itself.[h] Rather than epistemically virtuous practice being simply a matter of responsiveness on the part of the clinician to the testimony of the patient, it is revealed as an interactive and iterative process through which patient and clinician together can create a

[g] Though most of the epistemic injustice literature has focused on unfair credibility deflations and deficits, Jennifer Lackey[21] has compellingly argued that, in some contexts, affording too much credibility to a speaker can also be harmful and damaging (e.g., Lackey focuses on the credibility excesses that occur in cases of soliciting false confessions in the criminal justice context). Similarly here, to afford an FDS patient too much credibility would be a way of undermining their full epistemic agency.

[h] Note: something similar might happen in cases of sexual assault victims/survivors or those with PTSD, who report having "blacked out" for some or all of the traumatic event or who otherwise experience disorientation in the aftermath of trauma.[45] In such cases, as with the case of FDS, to guide a patient in uncovering and making sense of the content of their experiences (e.g. what happened and how it felt), can be essential for healing and can be a way to support and enhance one's epistemic agency in the aftermath of trauma. This is another avenue for exploration and another instance that supports our main thesis: at times, testimonial reports will need to be explored and guided with a caring expert professional in order to allow the patient to make the most possible sense of their experiences, where some of the content of that experience might not be immediately accessible to them. Taking on this collaborative epistemic work ultimately enhances the patient or client's epistemic agency as opposed to undermining it.

shared space of knowledge. Moreover, through this process the epistemic agency of the patient is respected and ultimately enhanced.

This form of clinical exchange shows the importance of the distinction drawn between Freeman's epistemic privilege thesis and Carel's ultimate authority thesis. The FDS patient is not epistemically privileged in the sense of having immediate access to the phenomenology of FDS. Indeed, initially the clinician in some respects knows more about the phenomenology than the patient. The patient does, however, get the last word on what they did or did not experience. The clinician can create the space for the patient to acknowledge or express certain experiences that may not have been readily apparent at first. They cannot, however, adjudicate in the end as to whether those experiences do in fact apply to the patient.

## 2.2.5. Alternative explanations of the distinction between surface and reflective phenomenology of FDS

We demonstrate above that patients with FDS initially report surface seizure phenomenology that is later contradicted by accounts resulting from more detailed inquiry. We take this as evidence that seizure phenomenology is not always immediately accessible and may require additional reflective interrogation and consideration. This process may require clinician expertise to support. There are, however, alternative explanations for these differences between surface and reflective phenomenological reports. We consider three of these here and their implications for questions of TI in clinical encounters.

### *2.2.5.1. Stigma, the unspeakable, and conscious deception*

The first and simplest explanation for the apparent tension between the patient's initial surface phenomenological reports and their later refined phenomenological reports is that the patient's awareness of seizure phenomenology has not actually changed at all; rather, what has changed is their willingness to more accurately report it. There are several potential reasons a patient with FDS may not wish to disclose, or even consider, all aspects of their seizure experience.

Firstly, if somewhat paradoxically, these initial reports might comprise part of their work to be seen as *more* credible. Patients with FDS frequently report that their experiences are dismissed as being 'made up' or 'put on'.[46] Communication strategies that emphasise lack of consciousness or volition may be also be seen as intentional deception to ensure that their true complaints are taken more seriously. This would be in keeping with the strategies adopted by some patients with functional disorders, who describe the work they put in to make their external presentation map to their internal experience.[47]

Secondly, FDS remains a *stigmatised* condition,[48] and there are strong phenomenological and aetiological associations between the experience of FDS and feelings of shame.[49] The experience of shame is one of being exposed to the judgment of another. When shame is experienced, avoidance or withdrawal – rather than subjecting oneself to further judgment – is the habitual affective and behavioural response.[50] This presents a strong motivation to avoid open disclosure of illness phenomenology where stigma and shame are likely to be evoked.

Lastly, it is hypothesised that an important mechanism underlying the altered behaviour and sense of control in FDS is *dissociation*, or disruption in integration and continuity of perceptual, emotional, interoceptive and other processes of bodily awareness and control.[51] Part of the challenge for the patient with FDS in relating seizure phenomenology may then be to create an

integrated whole out of dissociated parts, and the same neuropsychological mechanisms opposing this in FDS would oppose its phenomenological recreation.

There are several reasons to prefer the previously given explanation to these ones. Our proposed explanation does not imply the patient's conscious deception, an implication which can reinforce negative stereotypes about and perceptions of patients as (intentionally or unintentionally) dishonest or deceptive. Moreover, it is known that patients with related disorders (such as epilepsy) also struggle to clearly and effectively describe their illness experiences.[31,37,52] This gives reason to believe that a distinction between surface and reflective phenomenology is at play more generally.

It is worth noting, however, that when it comes to questions of TI in the clinical encounter, the clinician's scepticism about patients' automatic epistemic privilege is still warranted in this situation. While they may not know *more* than the patient about the patient's seizure phenomenology, nonetheless their expertise in seizure phenomenology entitles them to question the patient's initial assertion of e.g. complete lack of conscious awareness, and then by exploring this further to reconstruct a more detailed phenomenological account. It is precisely because of the clinician's technical, medical expertise that they know there could be more to uncover about the patient's illness experience and seizure phenomenology than they initially reported or were even in a position to report. The clinician can then use this initial scepticism about the surface phenomenology to help the patient engage in reflective phenomenology, thereby working together to move the epistemic exploration into more productive terrain.

Furthermore, this alternative explanation would also support our contention that epistemic justice is an interactive and collaborative process. The clinician needs to cultivate an environment in which the patient feels comfortable openly sharing their experience and does not feel the need to engage in conscious deception. The patient needs to trust the clinician in sharing more accurate testimony. We discuss the role of trust in our conception of EI in the clinical encounter in more detail later.

#### *2.2.5.2. Extracted testimony and agential testimonial injustice*

A second possibility is that the modified testimony of the patient with FDS does not provide a 'reflective' phenomenological account at all but an *extracted* one. That is, the later accounts of FDS phenomenology represent manipulated testimony that circumvents the patient's epistemic agency. The inconsistencies between initial and subsequent phenomenological accounts can be accounted for by the clinician's altering the decision space within which the patient chooses how to describe their experience – for example, by artificially restricting the range of possible experiences that could be narrated or by making pragmatic considerations other than accurate articulation of experience, which can come to dominate what the speaker "chooses" to report.[21,i]

Jennifer Lackey describes how such processes can take place in the extraction of eyewitness testimony in criminal contexts.[21] Eyewitnesses' accounts can be *manipulated* (e.g. by selecting people in a line-up such that only one plausibly fits with their previous descriptions) or *coerced*

[i] This is in some ways similar to how Kristie Dotson[22] describes the phenomenon of "testimonial smothering" as a form of coerced self-silencing. Here too, the worry is that while the testimony or the silence appears "chosen" by the speaker, they are not chosen freely or without undue influence imposed by relevant features of the background environment.

(e.g. threatening legal action against the witness, such that considerations of self-preservation dominate over truth-telling). These sorts of manipulation and coercion present an epistemic injustice because they invite people to act ostensibly as epistemic agents, but they are not being treated as informants at all. Instead, the testimony sought from them is predetermined – the manipulator is not interested in what knowledge they may putatively share, as they already know what claim they want it to support. They therefore deliberately manipulate the conditions of knowledge exchange to amplify epistemic weaknesses (in the case of manipulation) or to make non-epistemic ends more salient (in the case of coercion). In each instance, the speaker's epistemic agency is undermined.

It is at least plausible that the clinician's influence could exert a similar effect on the patient. Indeed, there is some suggestion from qualitative accounts of patients with other functional disorders that they modify their self-expression in order not to jeopardise a relationship with the clinician.[47] It is thus at least possible that the patient amends their account of seizure experience to what they think the clinician 'wants to hear'. If this does indeed occur, it would represent a case of what Jennifer Lackey calls 'agential' testimonial injustice;[21(p704ff)] the patient's epistemic agency is undermined by compromising their ability to give testimony, not through disbelief, but rather influencing their epistemic agency such that accurate testimony is either no longer possible or is no longer a rational choice for the patient.

Though it might initially seem plausible that something similar is happening in clinical discussions with FDS patients, the disanalogy with the kinds of criminal justice cases that Lackey describes is that in the context or providing care to FDS patients, there is less of an obvious incentive for the clinician to manipulate the patient's testimony than for, say, the police officer or lawyer to influence the testimony of the eyewitness. It is not immediately clear how such extracted testimony would serve any useful clinical role or work in the interest of the clinician. Therefore, while we acknowledge this possibility, we do not take it to be the most plausible explanation of what is happening here. A more plausible explanation is the one we propose: the FDS patient really is experiencing an inability to immediately and accurately characterize some aspect of the illness experience and seizure phenomenology and the clinician helps guide and aid the essential exploration that helps the patient become better equipped to do so.

#### *2.2.5.3. The third order of the body*

A last possible explanation – one which we think should be taken more seriously – also involves the clinician shaping the patient's testimony through the clinical encounter but in a less deliberately manipulative fashion than the extractive scenario described above. When the patient relays to the clinician their account of their illness experience, the clinician interprets that experience in terms they can render intelligible; not only does this produce a particular transformation of the experiential account (from 'sensation' to 'symptom') – the fact of having their experience interpreted in those terms may have a feedback effect, shaping the patient's own interpretation of their experience through the lens of those terms and concepts.[29(pp406-408)]

Havi Carel describes this process in terms of Sartre's 'three orders of the body': the patient has their initial illness experience – of the 'body-for-me', the clinician interprets this experience in pathophysiological terms, the 'body-for-the-Other', but this alters the patient's relationship to their own body and experience – the clinician's lens shapes the patient's own, producing the 'body-as-seen-by-the-Other'[5(pp52-53),53(p357)]. This is not malicious or intentionally manipulative or coercive. Rather, this is the result of both parties trying to interpret the experience in the ways

they know how or in the ways they have been trained to. When exposed to these framings, they can influence how the patient comes to understand and relate to their bodies and experiences, as language and concepts influence how we see and understand ourselves and our experiences.

This kind of process poses a slightly different explanation for our conflicting accounts of FDS phenomenology than those encountered above. In this case, the patient's initial (surface) account is not mistaken, nor does it reflect any conscious deception; the second account is not a warped, extracted testimony. Rather the first and second accounts provide different interpretations drawn from and shaped by different perspectives – the latter one in which the patient's interpretation of their own experience is in part seen and interpreted through the eyes of the clinician.[j]

How, then, are we to adjudicate the epistemically responsible position for the clinician to take on the patient's testimony in this situation? Though we cannot provide a perfectly complete answer here, we want to argue that one plausible possibility might come from acknowledgement that the process of interpretation – of experience, as any other information – is always *perspectival*, presupposing certain interests, assumptions and objectives. If the account of FDS phenomenology produced by refraction through the clinician's lens is better equipped to serve the ends of the clinical encounter – accurate diagnosis, prognosis and management, let us say – then to that extent the clinician's initial credence or judgement of relevance in the initial surface phenomenological report is warranted. The role such (re)interpretation plays in accurate diagnosis (and the greater diagnostic accuracy of expert clinicians who engage in such processes than generalists who may not) suggests this may be the case. In this case, then, creating the space for patients to engage in practices of reflective phenomenology, guided by expert clinicians and their perspectives on the disease phenomenology, can be a matter of increasing health and epistemic justice alike. It is therefore the appropriate thing to do, epistemically and medically speaking.

### 2.2.6. Towards epistemic peerhood in the phenomenology of illness

If the above is correct, then patients do not always and necessarily have immediate or complete privileged access to their own illness experiences.[k] In their encounter with the patient, a

[j] It is worth noting that this (re)interpretation of one's self-understanding through the lens of dominant medical paradigms and clinical frames can, in some cases, be harmful. For example, dominant medical understandings of sex and gender often presuppose or take for granted the sex binary, which can limit conceptual understandings of trans and non-binary patients experiences. Often, such patients have the dominant understanding imposed on them even when it does not map onto their lived experiences of gender. A clear example of this is the reliance on the "wrong body" narrative of trans experience, which fits for some but not all trans and non-binary people's subjective experience. When this narrative is imposed, the result can be that it encourages people to see and understand themselves through that frame of understanding, which can in very important ways alter their self-understanding (in ways that are inauthentic, and at times, harmful). Moreover, the dominance of these interpretative frames often compel people to conform their reports to fit the dominant narrative, e.g. to access medical resources (e.g. gender affirming care), which might only become accessible if one is able to speak to their experiences in a way that the clinician is likely to understand and accept, e.g. in a way that is in line with their interpretative resources.

[k] Note the qualifications here: we hope to show that this kind of case illustrates that patients do not always and necessarily have immediate and infallible epistemic privilege because there are some cases, such as FDS, where that privilege is mediated or limited by features of the illness experience (e.g. loss of conscious awareness). This is not to rule out that patients in other contexts very well could (and likely do) have this kind of epistemic privilege. Part of the work of epistemic justice in healthcare will be to figure

clinician seeks to assemble from all the information at their disposal – the patient's given story, but also the ways in which they tell it, details of their background, their physical presentation – an interpretation of their experience that can most effectively serve the ends of the clinical encounter. Sometimes there may be dissonance within that assembled interpretation – one reason for which may be that the patient's initial phenomenological account differs from that which can be obtained with targeted, reflective exploration. Part of the clinician's expertise comes from their experience of hearing 'what it is like' to have certain illnesses and to use this 'heterophenomenological' expertise to help patients elucidate and articulate the phenomenology of their own condition.

This has implications for the important project of understanding, illuminating and addressing epistemic injustice in healthcare. It is not always sufficient just to say that clinician expertise lies with the *corps objectif,* the patient's lies with the *corps propre*; sometimes the patient's subjective account is the most important evidence a clinician has to guide their diagnosis. Furthermore, cases like FDS show that clinicians have to be interested in phenomenology proper; it is precisely through identifying the intersubjectively shared aspects of experience across certain conditions that the clinician can work from the surface phenomenological account to the reflective one. Lastly, the necessity for that kind of facilitated guiding in certain occasions shows that recognition of the patient's epistemic privilege cannot be operationalised simply by accepting their testimony regarding their illness experience full stop; sometimes that testimony does need to be probed or challenged in order to better serve the goals of the clinical encounter and to best support the patient's full epistemic agency.

Understanding the conditions that support such practice requires a more nuanced understanding of the epistemic positions of patient and clinician in the clinical encounter and the contributions of both (alongside structuring factors) to the dynamics of clinical communication and knowledge exchange. In her work on the phenomenology of pregnancy and clinical experiences of pregnant people, Lauren Freeman proposes that confronting epistemic injustice in the clinic requires establishing what she calls *epistemic peerhood* between clinician and patient. She writes,

> *One cannot become epistemic peers with an object (*Körper*). One can, however, become epistemic peers with a* living *body, a person who exists in the world, whose claims to knowledge are deemed credible, taken seriously, and engaged with in a supportive, open, dialogic, and comfortable environment.*[4(p61)]

While her argument focuses on the tendency to privilege the reports of investigative technologies over first-person accounts, her descriptions of the dynamics of clinical interactions are perhaps more revealing as to the barriers to achieving this state:

> *patients in clinical encounters often feel intimidated, rushed, and uncomfortable to engage in dialogue and to voice their questions and concerns. Due to the asymmetry of power, patients tend to feel vulnerable and afraid that if they do voice their concerns, they will be dismissed.*[4(p61)]

If the epistemic and broader clinical conditions do not exist such that the patient feels supported and empowered to openly and honestly share their experiences, the clinician and

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out when this is (and isn't) likely to be the case and to support patients by guiding their inquiry and reflection when necessary. Moreover, such cases as FDS highlight that a simple, binary and oppositional account of 'privilege' is unlikely to be flexible enough to allow for the nuances of differing epistemic positions needing acknowledgement to construct an epistemically just clinical encounter.

patient alike are prevented from establishing the kind of dialogue that would permit clinically relevant interrogation of the patient's experience. How, then, might these epistemic and clinical conditions be improved, such that patients are more likely to feel comfortable sharing their experiences and trusting that they will be taken seriously when they do so?

A fuller answer to this question lies beyond the scope of this paper; here we offer only some starting places and suggested directions for future work. This work could look at the individual, interpersonal and structural features that inhibit robust epistemic peerhood in the clinical encounter.

One example of a possible individual-level change follows from recognition that clinicians need to be aware of the limitations of their own perspectives even as they interrogate those of their patients. The virtue of epistemic humility – a "willingness to recognise the limits of one's knowledge and appreciate others' intellectual strengths"[54(p140)] – is often suggested as remedy here.[9,23,24,29] Empowering clinicians to acknowledge the limitations of their own perspectives – whether that be the fallibility of third-personal investigative methods (e.g. discussing how medical investigations only give a partial and fallible picture of a person's condition) or the endemic uncertainty in medical decision-making – may allow them to begin cultivating this virtue. When patients perceive this epistemic humility in their clinicians, they might be more comfortable speaking up and also acknowledging their own limitations, confusions and concerns.[l]

On the interpersonal level, we need to better understand and enact the conversational norms that allow for more effective construction of a shared understanding of illness. Doing so requires acknowledging that the interpretation of human experience for the purposes of the clinical encounter is something clinicians and patients do together – *a joint act*.[57] The clinical interpretation of patient experience requires not just identification of the appropriate attitudes of each party to the epistemic capacities of the other but also coordination of their objectives in that interpretation – in other words, what are we trying to understand this *for*? When shared goals can be identified and mutually endorsed, clinicians and patients are in a better position to work cooperatively toward those goals.

Once the goals are in place and mutually endorsed, it is also important that barriers to trust and cooperation are minimized. Without trust in patients, clinicians will dismiss their testimony. Without trust in clinicians, patients will be unwilling or unable to share their experiences or concerns.[23,24] To build trust, we have to understand what barriers exist to the perception of trustworthiness, to help clinicians and patients alike align trust with trustworthiness.[58] This will require taking stock of the kinds of historical and ongoing injustices that can lead patients to distrust healthcare institutions and practitioners (e.g. historical exploitation and ongoing instances of bias, stereotyping and microaggressions[25]). When we know what kinds of interpersonal problems are likely to produce or exacerbate distrust, we know what kinds of barriers stand in the way of effective communication and cooperation. These, then, must be minimized (or more ideally, eliminated).

Finally, structurally speaking, we must attend to the social and institutional forces that may constrain both clinician and patient from successfully engaging in these processes. If there is an

[l] While some authors are sceptical of the possibility of individual virtues like epistemic humility to address epistemic injustice,[55] there is evidence that (an operationalised definition of) epistemic humility is associated with precisely the ameliorative interactional features required here, such as a reduced myside bias and increased tendency to expose oneself to opposing perspectives.[56]

"inter-method hierarchy"[23] between first- and third-personal sources of clinical information or descriptions of illness experience, then we should ask whether that is a function of what clinicians do or how clinical knowledge is expropriated for non-medical purposes.[12,59] Or if, as a result of top-down time and resource pressures imposed on clinicians, patients feel too rushed to meaningfully engage in dialogue, we need to attend to the structural changes that can ensure that clinicians have the appropriate time and resources to enact more productive dialogues during the clinical encounter, allowing patients to have the adequate time and attention required for their needs to be heard, understood and met. Addressing the structural factors that impose limitations on clinical dialogue will be crucial for fostering effective relationships of epistemic peerhood between clinicians and patients. More conceptually, healthcare interactions are structured by certain conceptions of health, disease and illness, that may represent "overworked tools"[59] that do not necessarily address the most important problems people are confronting. Resisting the biomedical scientism that insists medical descriptions of illness contain all that is relevant to understand illness might help to promote the epistemic peerhood of patients and others who can contribute different and more robust understandings of illness phenomena.[60,61]

## 2.2.7. Conclusion

A naïve view of the relative epistemic positions of patients and clinicians in the clinical encounter assumes that the patient (alone) provides the first-personal illness experience and the clinician (alone) provides the third-personal expertise to interpret the patient's account. The case study of testimonial exchange in FDS, however, demonstrates that the clinician may also need to bring skills in elucidating the phenomenology of illness itself to support subsequent clinical discovery and understanding and that epistemically virtuous practice requires active collaboration between patient and clinician. While the patient has the ultimate authority regarding what they have or have not experienced, the clinician should not always accept initial reports of surface phenomenology unquestioningly.

This makes clearer the demands of testimonial justice in the clinical encounter – in particular, the hard, collaborative work required to achieve it. Uncritical acceptance of patient testimony regarding surface phenomenology – an unwarranted credibility *excess* – may in some cases, such as FDS, end up being as harmful as its unwarranted dismissal. Epistemically just clinical practice cannot be reached by quick fixes. If this case study does demonstrate anything regarding what such practice might look like, it is that the clinician cannot rely on expertise in *le corps objectif* alone; they must cultivate an understanding also of *le corps propre* for the patients they encounter – perhaps, even, more of an understanding than the patients themselves first have. And they have no means of achieving this other than by listening to their patients – with humility, though never uncritically. Instead, clinicians and patients must work together to arrive, collaboratively, at the best phenomenological and clinical understanding, that is, they must become epistemic peers. To understand better how to enable clinicians and patients to achieve robust epistemic peerhood will require interrogating the individual, interpersonal and structural features of epistemically just clinical knowledge exchange.

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# 2.3. *“It is just a big question mark”:* A qualitative interview study of patient experiences of the initial assessment of transient loss of consciousness

## 2.3.1. Introduction

Transient loss of consciousness (TLOC) is a common Emergency Department (ED) and Acute Medical Unit (AMU) presentation.[1] Over 90% is due to syncope, epilepsy or functional/dissociative seizures (FDS, also known as ‘psychogenic nonepileptic seizures’ (PNES) or ‘non-epileptic attack disorder’ (NEAD)).[2] Accurate differentiation can be challenging; at present 20-30% are initially misdiagnosed, while others receive no working diagnosis at first presentation.[3,4] This has implications for health and everyday life: patients who could be reassured that they have experienced uncomplicated syncope are told they cannot work or drive pending expert assessment; patients who should be investigated by cardiologists are referred to neurologists and vice versa; investigations for potentially life-threatening pathologies are delayed. Patients are left in positions of uncertainty.[1,3,5–7]

Professional guidance thus emphasises early specialist involvement; for example, the UK’s National Institute for Health and Care Excellence (NICE) recommends that all patients with a suspected seizure are reviewed within two weeks by a clinician with a special interest in epilepsy for diagnosis, and that all except uncomplicated syncope presentations are assessed by a syncope specialist.[8] The European Society for Cardiology (ESC) guidelines provide reference for clinicians on assessment of syncope risk and information prior to specialist assessment.[9] However, this guidance does not address patient experience of TLOC assessment, nor implications for patients of the interval between initial presentation (usually to expert generalists in primary or emergency care) and TLOC specialist (typically Cardiology or Neurology) assessment.

There is a lack of research aiming to understand patients’ experiences of first TLOC assessment. Previous explorations of patient experiences of seizure care pathways in primary and emergency care more generally have emphasised the importance of service responsiveness, efficiency, and continuity, while information and support and consistent communication emerged as particular patient priorities.[10] People with syncope have been found to prioritise clarity surrounding their diagnosis, report insufficient communication, but prominently report needing to be seen, heard, and cared about by their assessing team.[11]

However, the emphasis on specialist diagnoses may have had the unintended consequence of causing generalist clinicians to become deskilled or to lack confidence in assessing such presentations.[12–14] In one study of patients referred to a tertiary TLOC unit, 51% had no provisional diagnosis at time of referral; of those with a provisional diagnosis, 80% nonetheless considered their episodes ‘unexplained’.[15]

#### *2.3.1.1. Research question*

To improve clinical care pathways, it is important to understand patient experiences and needs of the assessment process.[16] Given the lack of previous research on this topic, we therefore conducted an explorative study of salient issues within the initial assessment for a patients with a first presentation of TLOC. We sought to explore:

- Overall impressions of initial assessment

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- Primary patient needs from the initial assessment
- Holistic life impact of a first presentation of TLOC and its assessment.

## 2.3.2. Methods

### *2.3.2.1. Methodology and design*

This study comprises a concurrent nested qualitative study within a quantitative project calibrating and validating a differential diagnostic tool for transient loss of consciousness.[17] We recruited interview participants from the larger pool of participants recruited to the quantitative study.

### *2.3.2.2. Setting and participants*

#### Setting

We conducted this study within a single large teaching hospital Trust in the United Kingdom, with an adult major trauma centre ED, and tertiary Neurology and Cardiology services, recruiting from 10th February 2022 to 9th January 2023.

#### Participants

One team member (DH) screened all patients presenting to the ED or AMU with TLOC, and all new referrals to first seizure and syncope clinics, within the window of 10th February 2022 to 9th January 2023. Eligibility for the quantitative study (which involved completion of an online questionnaire by the patient and, if available, a witness) was assessed according to the following criteria:

Inclusion criteria:

- Patients first presenting with TLOC, with no previous specialist assessment of TLOC
- Referred to secondary care for diagnostic evaluation; OR given firm diagnosis of syncope in accordance with European Society of Cardiology guidelines for syncope presentations not requiring further investigation[9]
- Adult over the age of 16 years
- Able to complete English-language questionnaire (used in quantitative study) independently
- Able to give informed consent to research participation

Exclusion criteria

- Previous specialist (neurological or cardiological) assessment of TLOC
- Secondary cause of TLOC identified

DH approached eligible patients either in-person (if still in hospital or at clinic) or via retrospective letter, providing them with information on the study and inviting them to participate. Participants could give initial consent at invitation, with consent confirmed prior to completion of the quantitative questionnaire.

When seeking consent for participation in the quantitative study, we separately sought consent for contact to be approached for qualitative interviews. From those who gave consent to contact, one team member (DH) recruited a convenience sample of participants, aiming for a diverse mix of age and genders, approaching them by telephone.

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On the basis of empirical studies showing that 24 participants reliably achieve saturation, the narrow specification of subject matter, and the study team’s expertise in the subject matter, we expected to reach data saturation within a provisional target of 30 participants.[18]

We determined final diagnoses by two-expert review of all clinical data at the end of follow-up, at least six months after initial presentation. As we sought to perform interviews early to capture initial experiences most effectively, diagnoses had not been confirmed at the time of approach and so we could not aim for representativeness across diagnoses.

#### *2.3.2.3. Interviews*

Two researchers, AW (a specialty registrar [resident] in Neurology, with extensive prior clinical experience working as a core trainee [junior resident] in ED and Cardiology) and DH (a non-medical healthcare researcher with a background in qualitative and quantitative health research) conducted semi-structured interviews following a pre-defined interview schedule (Appendix 1, §2.3.8). We conducted all interviews remotely, either via video call (Microsoft Teams) or telephone call, due to the Covid-19 pandemic. We recorded interviews (either via recording mic, or with Teams inbuilt recording) with explicit patient consent for recording and transcription. Recordings were transcribed by a professional, academic non-clinical transcription service. Interviewers noted initial reflections in contemporaneous logs, to support reflexive engagement with later analysis.

#### *2.3.2.4. Analysis*

We used all interview transcripts as data for thematic analysis[19] following a reflexive approach,[20] which we adopted in light of our exploratory aims and experiential focus. In this approach, we did not use a pre-specified codebook; one researcher (LB; an experienced healthcare qualitative researcher with no clinical background and no prior personal or professional TLOC experience) imported transcribed interviews into NVivo, coded transcripts, and developed initial themes. Two researchers (LB and AW) used these initial themes, alongside prior beliefs and knowledge, in iterative data coding for refinement of the themes. We identified recurrent foci of discussion within and across themes as topics. We then discussed themes within the wider research group prior to final development.

We conducted interim analyses to assess for saturation at various recruitment points, and ceased qualitative recruitment when saturation was deemed to have been achieved.

#### *2.3.2.5. Ethics, review, and pre-registration*

We pre-registered the study protocol on clinicaltrials.gov (ID: NCT05367999). Ethical approval came from NHS Health Research Authority Edgbaston Research Ethics Committee (IRAS: 304114).

#### *2.3.2.6. Reporting*

We structure reporting according to the Standards for Reporting Qualitative Research (SRQR); we include SRQR checklist in an appendix (§2.3.9).[21]

#### *2.3.2.7. Patient and public involvement (PPI)*

We involved patients at all points. We sought feedback on the study protocol from patient organisation partners (Epilepsy Action, FND Hope, Syncope Trust and Reflex Anoxic Seizures [STARS]), revising it in light of input. We maintained PPI oversight through recruitment of a Research User Group (RUG), who: reviewed study resources; responded to study progress; reviewed results; and supported dissemination.

## 2.3.3. Results

### *2.3.3.1. Participants and demographics*

Of 2,811 potential participants screened for recruitment, 1,181 were eligible. Of these, 186 responded to the invitation to participate, and 133 also consented to approach for interview.

We approached 40 participants for interview. After 20 interviews, we achieved data saturation. Figure 2.3.1 gives participant flow through the study.

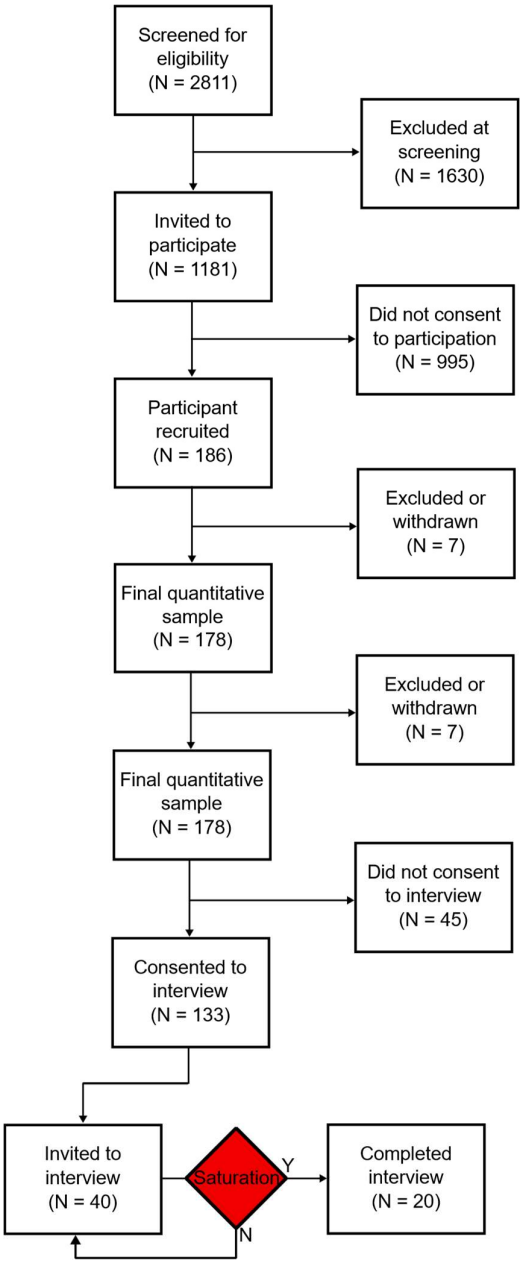


*Figure 2.3.1. Participant flow diagram.*

Of interview participants, 14 (70%) received final diagnoses of syncope, and 6 (30%) epilepsy. 12 participants (60%) were female. Median age was 69 years (interquartile range [IQR] 39-

74.25y, range 17-90y). Interviews were held a median of 69 days (IQR 39-117, range 35-283) from initial presentation. 19 patients (95%) presented via the ED, the remainder via Same Day Emergency Care (SDEC; ambulatory general medical assessment unit[22]). 5 patients (25%) were discharged after initial assessment, 7 (35%) referred for outpatient specialist assessment (6 Neurology, 1 Cardiology), the remainder (40%) were admitted or attended SDEC.

#### *2.3.3.2. Themes*

We developed three core themes (patterns of shared meaning, united by a central concept or idea). Across these themes, we identified four cross-cutting topics (foci of discussion),[20] providing 12 sub-themes altogether. Table 2.3.1 summarises themes and topics.

| Table 2.3.1: Summary of themes and topics | | **THEMES** | | |
|---|---|---|---|---|
| | | **Satisfaction with care** | **Unanswered questions** | **Limbo / No Man’s Land** |
| **TOPICS** | **Communication** | Perception of attention | (Dis)empowering explanations | Communicating plans |
| | **Investigation** | Perception of activity | Need for investigation | Awaiting tests |
| | **Authority** | Joined up care | Accepting uncertainty | Awaiting experts |
| | **Social** | Systemic pressures | Alternate sources | Social implications |

*Table 2.3.1. Summary of themes and topics.*

#### Theme 1: Satisfaction with care

The majority of respondents were satisfied with the care they received. Where shortcomings were identified, these were attributed to systemic pressures within the National Health Service (NHS). (Dis)satisfaction with care was driven by: a need for communication (topic 1); desire for investigation (topic 2); appeals to different authorities (topic 3); and the social context (topic 4) of care; illustrative quotations are given in Table 2.3.2.

| **SUB-THEME** | **ILLUSTRATIVE QUOTATIONS** |
|---|---|
| 1.1. Perceptions of attention | • *I thought when I went to A & E that it would be kind of just, just seen as that. I did, I think, get an ECG scan. I did feel listened, listened to and like notes and that were, were taken.* [TL169]<br>• [The GP] *basically wanted to talk about […] sleep apnoea and they just kind of took me away and asked a few questions […] they set up like a double appointment and then I was literally in there thirty seconds*. [TL176] |

| | |
|---|---|
| 1.2. Perceptions of activity | • *During [my time in the ED] there was, there were tests and things going on all the time, you know, I wasn't just hanging around, it was […] really impressive.* [TL099] |
| 1.3. Joined-up care | • *I'm quite close to my GP cos he's been my GP since I was a child, so I keep him updated on anything […]. So he's trying to push me to get into the major head trauma department, [and] neurology assessment as a step forward.* [TL174]<br>• *[A] month later [I] ended up at the point we could have been at […] if the two teams had […] agreed that that was a sensible course of action … it was just frustrating that we felt we needed an MRI, […] the medical team felt there needed to be an MRI and the shoulder team said "Absolutely no way is this happening."* [TL184] |
| 1.4. Systemic pressures | • *That initial going to A & E, that was difficult […] I'm obviously aware why the wait times […] are so long at the moment, but […] it was tough having to stay in there so long when I […] had no idea really what was going on. [TL176]*<br>• *I've got sort of private medical insurance through work […] and […] I'm starting to wonder if I should explore that and just see if there's any value in following that up […]it would be nice to […], if I'm having tests, have them sooner rather than later.* [TL188] |

*Table 2.3.2. Illustrative quotations of sub-themes for Theme 1.*

*Perceptions of attention*

Respondents felt satisfied with care when attended to by staff. The act of note-taking in response to a patient's story showed concerns were being heard (TL169). Conversely, dissatisfaction arose when respondents did not feel their concerns were being addressed adequately. Multiple respondents reported this occurring when clinician and patient priorities diverged (TL095; TL176).

*Perceptions of activity*

Alongside attention, clinical activity - in particular, performing investigations - was considered a metric of good care. Multiple respondents couched their satisfaction in terms of clinicians having "checked everything possible" (TL178). Conversely, some respondents (TL174; TL184) expressed dissatisfaction as a result of investigations they felt were indicated (in both cases advanced imaging) not being performed.

*Joined-up care*

Such clinical activity needed to be coordinated between services with different perceived levels of expertise. Primary care played diverging roles: for one respondent (TL174), their general practitioner (GP) served as champion, securing them access to specialist care; for others the GP was distant (TL176), or even implicated in the cause of their TLOC through lack of coordinated care (TL101). One respondent felt a disagreement between two inpatient care teams delayed their ongoing management (TL184).

*NHS pressures*

Overwhelmingly respondents attributed shortcomings in their care to systemic pressures rather than individual clinical failings. Long waiting times in the ED, for specialist clinic appointments, and for outpatient investigations were attributed to staff and resource shortages. Two respondents (TL184, TL188) supplemented their NHS care with private provision.

### Theme 2: Unanswered questions

Respondents mostly felt that they did not have a clear understanding of what had happened, and did not receive adequate information regarding the cause of their TLOC. Communicating intelligible explanations (topic 1) that supported self-management could address this, as could authoritative reassurance (topic 3); in the absence of this, there was an expectation that investigations (topic 2) could provide the sought-for answers. Without these, some turned to alternative sources of information in their broader information environment (topic 4), but expressed ambivalence about what could be found there. Illustrative quotations are given in Table 2.3.3.

| SUB-THEME | ILLUSTRATIVE QUOTATIONS |
|---|---|
| 2.1. (Dis)empowering explanations | • *[It] almost clouds the issue that [...] my blood pressure dropped [...] whether that was as a result of the pain and that was my body's way of, of managing it, I don't know, but in my mind it's, it's the pain that's caused the blackouts."* [TL184]<br>• *I think they were just basically assessing for concussion but they didn't really like explain anything about why I might have fainted or like follow-up or anything like that [...] I don't know what caused it [...] I've tried all sorts to stop it from happening but nothing stops it.* [TL095]<br>• *I just wonder if I can do anything else to avoid the situation cos I don't want to end up in A&E again.* [TL180] |
| 2.2. Need for investigations | • *But I've had lots of scans and things and tests and you name it and I've no idea what's going off; I wish I do.* [TL146]<br>• *[A]t the [district general hospital], he, he just said that "Oh well" he said "we can't find anything so" he, he said, you know "that's it." I was sort of; what do you call it? Dismissed or..."* [TL109] |
| 2.3. Accepting uncertainty | • *[N]o-one seems to know why [...] it happened. But I guess if, if they come to the conclusion there's not a problem then it, it was purely an isolated occasion and hopefully it won't happen again.* [TL150]<br>• *I think that they provided me with enough clarity on what they thought had happened. I mean they couldn't obviously pinpoint what had happened, but they just put it down to an unfortunate incident [...] I thought OK, yeah, these things can happen, they do happen and I'm just gonna move on, I'm not gonna dwell on it and, yeah, just carry on as I am.* [TL152] |
| 2.4. Alternate sources | • *Q: And when they let you out of hospital did they tell you what they thought had caused your blackout?*<br>*A: Not really, they [...] used some words I didn't quite understand and I can't quite remember, but [...] personally I put a lot of it down to the fact that it was the week where we had all the very hot weather and I've never been sort of good with hot weather, and I think it was an accumulation of that.* [TL106]<br>• *I've [...] done quite a lot of Googling, but, [...] not come up with anything [...] not anymore explanations or how I can avoid it"* [TL180] |

*Table 2.3.3. Illustrative quotations of sub-themes for Theme 2.*

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*(Dis)empowering explanations*

Respondents who felt that their condition had been explained to them in ways they could assimilate into their illness understanding were empowered to self-manage their condition and return to their lives. Those who lacked such explanation felt it more difficult to manage the distress of the original incident (TL109), or mitigate against future occurrences (TL180).

One respondent (TL181) presented an initial explanation of their symptoms (as being a transient ischaemic attack [TIA]) dissonant to the assessing clinician’s (who felt she had experienced a syncopal episode). In contrast to those who felt dissatisfied due to a lack of investigation (1.2), the effort taken by her clinicians to explain how her symptoms did not fit those of a TIA, but could be fully explained by syncope, helped her acceptance of this diagnosis and resolution of the tension.

*Need for investigations*

The emphasis on medical investigations as providing an observer-independent - and thus definitive - explanation recurred. Many felt they would not have required answers until they either underwent further investigations, or received results of those already performed.

Many felt clinicians - particularly generalists - placed a lot of weight on investigation results. Awaiting investigation was frequently cited as a reason for diagnostic delay (see 3.2 below). Within this investigative paradigm, negative tests could become a barrier to legitimate diagnosis, with patients being “dismissed” (TL109) when investigations failed to yield a positive diagnosis.

*Accepting uncertainty*

While most participants had unanswered questions regarding their TLOC, some felt able to move beyond it even in the face of uncertainty. Key to accepting this uncertainty was reassurance from someone they deemed sufficiently authoritative that sinister causes had been excluded and they could be “*reassured […] that it was just a one-off incident*” (TL152). Sufficient exploration of other causes, integration of negative or reassuring test results into the narrative, and concordance with the respondent’s own recovery and lack of ongoing symptoms, were cited factors in accepting such reassurances.

*Alternate sources*

Facing unanswered questions, several turned to other sources of information. Some felt they had sufficient understanding that they could explain their TLOC without the clinician’s endorsement, particularly given they “*didn’t understand*” and “*can’t quite remember*” the clinician’s account (TL106). Otherwise, the most commonly cited alternative was information gained through internet search engines (TL169, TL180, TL188). Generally participants expressed ambivalence about information thus obtained, being concerned about its reliability and potential adverse effects (TL169), or finding that it failed to enhance understanding (TL180). Those who were able to accept uncertainty regarding their TLOC felt less need to pursue alternative information sources (TL188).

### Theme 3: Limbo/No Man’s Land

To many respondents, the experience of TLOC was of an abrupt change in their experience of and relation to the world; in one respondent’s words, “*twelve hours before I’d been absolutely fine and now everything had changed overnight*.” (TL176). Assessments often failed to achieve resolution, leaving respondents in an interstitium variously described as “*limbo*” (TL146) or “*no man’s land*” (TL157). This stasis was exacerbated in cases where respondents had no clear

understanding of what they were being referred for (topic 1). This waiting phase was attributed to the need both for investigations (topic 2), and for specialist input (topic 3); some described multiple primary care contacts, the upshot of which would be simply being told to “*just wait for Neurology”* (TL122); this waiting time could be prolonged (a median wait of 48 days in the UK and Ireland[23]).

In this condition, respondents struggled to negotiate social implications (topic 4). Some reported possible diagnoses that restricted their activities (notably driving), without the social licence granted by a definite diagnosis. Those equipped with empowering explanations (2.1) or the ability to accept and manage uncertainties (2.3) experienced less disruption. Illustrative quotations are given in Table 2.3.4.

| SUB-THEME | ILLUSTRATIVE QUOTATIONS |
|---|---|
| 3.1. Communicating plans | • *[T]hey gave me [...] a leaflet about seizures and said [...] it’s a working diagnosis, it’s [...] not confirmed yet... ...so that’s kinda where I’m at, I’m a bit in no-man’s land at the moment, I’m not entirely sure what’s going on.* [TL157]<br>• *[T]his kinda period of, of not knowing what it, what it is and not knowing when you’re kind of gonna be seen it [...] makes it a little [...] bit difficult cos obviously I don’t want to have to keep going to my GP or the A&E [...] every time I experience these episodes.* [TL169] |
| 3.2. Awaiting investigations | • *I had to ring my GP to find out is there a plan [...] and they were like “Well we don’t know at the moment; they’re doing their investigations”* [TL157] |
| 3.3. Awaiting experts | • *I went to the GP, I think it was earlier this year, around April/May time, and they recommended that if I had another kind of episode to, to go to A & E. I think I went to A & E a few months back and I think they did an ECG and I was just advised to go home and wait for an appointment with the neurologist.* [TL169]<br>• *They just kept an eye on me again and did some blood tests and everything come back fine. So they said “Just wait for neurology, try and get a quicker appointment.”* [TL122] |
| 3.4. Social implications | • *[I]t’s difficult to [...] speak about it with friends because it [...] is just a big question mark. But it is really starting to [...] affect my life.* [TL169]<br>• *[M]y experience with the seizure nurse, I feel like that has definitely exceeded my expectations. [...] she was really knowledgeable, she really, you know, explained everything [...] she expanded on a lot of the things I could [...] and couldn’t do and [...] I had to be careful with. [...] I do feel like if I’ve got any questions that she’s [...] my first point of call to go to.* [TL176]<br>• *[I]t’s been quite [...] life changing [...] I’m gonna have to go part-time at work [...] I think a follow-up a week later, even just a phone call, would have been really helpful.* [TL157] |

*Table 2.3.4. Illustrative quotations of sub-themes for Theme 3.*

*Communicating plans*

Several respondents felt clinical activity was happening around them, but without involving them, leaving them feeling unable to proceed despite believing the clinical teams may be closer to a diagnosis or management plan. Many reported being informed of the need for follow-up, but fewer were clear why they were being referred (TL188). Interim communication of information (working diagnoses, information leaflets) went some way to address this, but incompletely (TL157). Respondents were unsure how to self-manage in the interim without further information being shared (TL169).

*Awaiting investigations*

Some respondents reported difficulties in making progress while awaiting outstanding investigations. Results of the investigations were a barrier to progress both for patients (TL099) and clinicians (TL157).

*Awaiting experts*

Respondents felt stuck waiting for specialists. The outcome of initial assessments was often not a provisional explanation or interim management plan but a recommendation to await specialist assessment. Some felt passed between primary and emergency care (TL169), while long secondary care waits left them with no clear end in sight (TL122; theme 1.4). Patients were unwilling to re-present in the interim as they expected they would just be advised to await a specialist again (TL169, TL173).

Some respondents had already undergone specialist assessment by time of interview; while contact with these services helped to resolve the feeling of stasis for some (e.g. TL176), others reported remaining in a similar situation (TL146), even with a provisional diagnosis.

*Social implications*

The social implications of TLOC were particularly difficult to manage in this limbo period. For some, these related to specific practical limitations, e.g. driving restrictions (TL176) or work modifications (TL157); for others, ongoing symptoms affected their career path (TL174).

Others encountered the social implications of lacking a diagnosis, their TLOC being a “big question mark” (TL169). Clear diagnoses would allow people to determine what may or may not need to change in their lives, whereas being in limbo imposed restrictions without associated social licence for deviation from their previous role (TL146).

For respondents who had undergone specialist assessment, available services proved valuable in negotiating these social challenges; one respondent (TL176) singled out the role of the epilepsy specialist nurse in navigating the psychosocial as well as biomedical ramifications of their condition.

## 2.3.4. Discussion

This study explores patient experiences of the initial assessment of TLOC - of the care delivered, and its impacts on their subsequent life. For many, this was significant; “*twelve hours before I’d been absolutely fine and now everything had changed overnight*” (TL176). We interpret this as TLOC presenting a “biographical disruption”[24] that demanded major re-evaluation of personal narratives and social circumstances. This disruption could be ameliorated if respondents were reassured - by appropriate clinical authorities, and ideally with evidential support from investigations - that the event was an “unfortunate one-off incident” (TL152; 2.3). Prolonged delays to specialist assessment drew out this disruption, and its psychosocial consequences.

#### *2.3.4.1. Satisfaction with care*

Respondents were largely satisfied with the care they received at their initial TLOC assessment. Drivers of (dis)satisfaction included: feeling paid attention to and feeling heard; having investigations performed; being kept informed; and (lack of) prolonged waits. After initial assessment - but before specialist review - informational needs drove satisfaction, with a lack leaving respondents with unanswered questions (theme 2) or feeling left in limbo (theme 3).

Respondents used the extent of investigation as a barometer of good care (1.2); many of their unanswered questions related to investigation results (2.2); and clinicians and respondents alike found it difficult to proceed until investigation results returned (3.2). This is despite evidence that, in the assessment of TLOC, investigations are of limited utility - typically normal or misleading.[25,26] Patient and witness histories of the TLOC remain the cornerstone of diagnosis,[27] but respondents felt less comfortable with a focus on such accounts over test results (e.g. considering the history *“my interpretation”,* whereas investigations are *“an objective method, […] of seeing what I, how I am”* (TL099)). Two respondents were specifically dissatisfied due to not receiving what they perceived to be necessary investigations - in both cases advanced imaging. However, such imaging is rarely of much benefit in supporting the differential diagnosis of TLOC; in one study of older adults presenting with transient loss of consciousness, CT or MRI was performed in 63% of presentations, but only in 2% of those was any abnormality found (overwhelmingly when such abnormalities were expected based on other symptoms or examination findings).[28]

However, the authority of investigations was not absolute; one respondent (TL181), who initially felt she needed investigation for a TIA, was instead reassured by her assessing clinician’s explanation of how her presentation fit far better with syncope. Effective communication with empowering explanations of the cause of TLOC that supported self-management (2.1), especially when delivered by individuals perceived as having relevant authority (2.3, 3.4) could support patients in navigating the biographical disruption.

Our findings are consonant with Clouser *et al*’s research into the experiences of patients with syncope (the majority of whom had chronic/recurrent presentations). Their respondents also reported that clinicians demonstrated their care and attention both by clear communication and aggressive investigation, and that they sought clear explanations.[11] Similarly, people with suspected seizures describe largely consonant needs, emphasising the value of time being available for care and the issues of waiting, the need for care continuity, and the cross-cutting importance of communication.[10] Our findings enhance their conclusions, by demonstrating that similar concerns are relevant across TLOC causing presentations (rather than just syncope or seizures), at first presentation (rather than in chronic/recurrent populations), and that the topics of communication and testing recur across broader themes including the holistic, social impact of TLOC on patients’ lives.

#### *2.3.4.2. Impact of TLOC on patients’ lives*

Our respondents demonstrate the holistic impact of TLOC, beyond the paroxysmal event itself. By the time of interview, most were asymptomatic (some experienced symptoms related to comorbidities, or from complications of their TLOC e.g. injuries sustained in collapse). Nonetheless, TLOC provides a striking discontinuity in many respondents’ narratives, an abrupt disruption that, unlike most chronic illnesses, does not ‘creep up’ on the patient but throws them into a ‘critical situation’.[24] Even respondents who felt less disabled by their TLOC refracted their future plans through the lens of biological considerations appropriate to the explanations

afforded for their TLOC (2.1). This transformation undermined confidence in their independence, leaving them feeling adrift with significant social implications (Theme 3). These findings are consonant with the quantitative evidence that people with syncope – even when not recurring – score lower on quantitative measures of health-related quality of life than reference populations, and show a high degree of disability (with a mean functional impairment in 33% of listed activities).[29] Furthermore, this impact – while ameliorated – persists at 1 year from initial presentation.[30]

We also found that people who experience TLOC need tools to navigate this disruption. National guidance mandates that people who experience TLOC merit referral for specialist assessment, but does little to address their interim needs - e.g. explanations to support empowered self-management (2.1) or help in navigating the social implications of possible diagnoses (3.4). Diagnoses like epilepsy have a range of associated psychological and social implications (e.g. employment and driving).[5,31] Our respondents frequently described situations where they were informed they might have epilepsy - and thus faced the associated psychosocial implications - but had no firm diagnosis that would allow them to access the available resources to help them navigate these life changes. In some cases, normal investigations blocked the process of the patient’s experience becoming a medical concern (with associated social value), leaving the patient “*dismissed*” (TL109; 2.2).

#### *2.3.4.3. Implications for practice*

Our study provides novel insights into the care needs of this high-incidence patient group. Our data are largely consonant with Graham et al’s typology of ED patient needs, emphasising their communication needs (both in feeling heard, and being given information); their emotional needs (tools for managing uncertainty and empowering self-management); competent care needs; and waiting needs (which our respondents were very careful to attribute to systemic and political problems, rather than individual staff shortcomings).[16] The social and psychological implications of the biographical disruption created by the TLOC event extends beyond the individual occurrence, however, and our respondents demonstrated how empowering explanations (2.1) and tools to manage uncertainty (2.3) provided at initial assessment could be valuable in meeting their needs in the immediate aftermath. Provision of information resources to allow exploration of their understanding of TLOC, its causes, and the assessment process, may help meet these needs in the interstitium between initial presentation and specialist assessment. Reducing barriers to specialist assessment, by improving timely access to appropriate specialist services, is clearly also required; our respondents showed the significant benefit of talking with professionals with relevant expertise (e.g. seizure nurses).

#### *2.3.4.4. Limitations and reflexivity*

It is important to note some limitations to our study. Most prominently, as an exploratory study the themes developed and topics identified are relatively high-level. We found themes saturated at 20 participants, but a richer interview protocol interrogating each of our themes in further detail could enhance our findings. This would particularly be complemented by quantitative measures of some of our respondents’ main concerns, such as holistic impact (e.g. through measuring health-related quality of life [HRQoL]), or level of functional impairment (e.g. by using the ICF-2001 framework[32]). Previous quantitative research has demonstrated the impact of syncope on HRQoL,[29,30] but mixed-methods exploration could enhance this approach and ours.

While we aimed for a diverse mix of gender, age, and diagnosis in our sample, the nature of the study and the interviews meant that our interview sample is not representative of the entire

population experiencing TLOC. Most notably, given that we aimed to conduct interviews sufficiently soon that participants were still able to recollect their initial presentation, we did not have final diagnoses available when recruiting participants for interview. As such, we did not recruit any patients with a final diagnosis of FDS to interview. This was the least frequent diagnosis in our study, and the relative proportions of syncope and epilepsy patients in the interview sample reflect their frequencies in the wider study population. From other qualitative studies, we know that people with FDS report similar experiences – notably that of being left in limbo – to those reported here.[33] Additionally, those with clinically certain uncomplicated syncopal presentations were under-represented in our sample, which may have made themes of uncertainty and delay more prominent.

Beyond this, we were limited to people with sufficient English language comprehension to participate in the quantitative study; this not only means that some communities’ voices are not captured in this study, but also that certain patient groups in whom TLOC is particularly prevalent (e.g. those with cognitive impairment or intellectual disability) are not captured here. Further work should seek to amplify these voices.

The quantitative study (of which the sample for this study is a subgroup) also had a low overall recruitment rate, with just 15.7% of those deemed eligible at screening consenting to participate. If there were systematic differences in recruitment by diagnosis (or e.g. patient demographics), this would bias the external validity of our results.

We acknowledge that the prior expectations and background of the research team will have shaped the interpretation of our results; we view this as inevitable, but take measures to allow our results to temper these biases. The semi-structured nature of the interviews allowed participants to direct dialogue down paths not proposed by the interviewer. One interviewer (DH), and the team member who performed initial development of themes (LB) were not clinicians or people who would otherwise work with people experiencing TLOC, thus were less subject to clinical biases; this was balanced with interview and analytic input from AW, and subsequent revision from the rest of the study team, who brought specific Neurology, Cardiology, and ED expertise to refine analysis in view of grounding knowledge. The iterative process of working back and forth between themes and data allows for the ‘surplus of meaning’[34] within the data when constrained to any particular coding to reshape interpretation; the themes described above represent an equilibrium reached through this hermeneutical circle.[35]

## 2.3.5. Conclusion

Communication (including differential diagnosis, significance of investigations and further assessments, and interim safety advice) is key to supporting ongoing self-management for people who experience TLOC, even before a definitive diagnosis is made. Much recent research - including the quantitative arm of this present study - has been focused on developing tools to maximise information available to the clinician in the differential diagnosis of TLOC; future work should explore whether such tools could also be used to support patients in understanding their presentation, assessment, and interim self-management while awaiting a definitive diagnosis and management plan.

Beyond this, even after extensive investigation and specialist review, TLOC remains a challenging presentation and many patients will not receive a clear diagnosis or definitive management plan. Such uncertainty is pervasive throughout clinical practice, and our

respondents highlight how important it is for patients that clinicians acknowledge and manage that uncertainty.[36] Our data shows how the promise of further tests or assessments can be used as a delaying strategy, avoiding the need for clinicians to acknowledge the limitations of medical technology and expertise to parse human experience. This process often left people in ‘limbo’, unequipped to manage the uncertainty with which they were left. From even the first point of contact with health services, clinicians working with people experiencing TLOC need to provide them with the resources to understand and manage this uncertainty.

## 2.3.6. Acknowledgements

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## 2.3.8. Appendix 1: Interview schedule

**Clinical decision aid for transient loss of consciousness – interview schedule**

Introduce myself and explain that the purpose of the interview is primarily to talk about their views about their presentation, their clinical trajectory, and experience of using the iPEP. I will also ask about any additional questions or modifications they would think suitable.

Complete consent form, answer any questions and remind interviewee they may terminate the interview at any stage, or choose not to answer a question if they prefer.

**Interviewee data:**
Firstly I would like to ask a few questions about you and your condition:

1. Check demographic information
2. Brief background about their current condition

    Prompts: How long ago / when did your blackouts start? What happens / what are they like / how often do they happen?

**Perspectives about initial TLOC assessment**

1. How did you first present with your blackouts? (GP, Emergency Department, other)
2. Have you received a diagnosis for the cause of your blackouts, or do you have further assessment/follow-up arranged?
3. Do you feel your assessment thus far has been adequate?
4. Do you feel you have unanswered questions about your blackouts?
5. Do you feel confused about what the next steps are in managing your blackouts?

    Prompts: What services, where accessed, how long, how often

**Perspectives on using the iPEP**

1. General opening – how did you find using the iPEP?
2. Do you think the questions were appropriate?
3. Do you think the questions captured the most important aspects of your experiences of your blackouts?
4. Did you struggle to understand any of the questions?
5. Did you struggle to answer any of the questions?
6. How did you complete the iPEP? Did you find it easy to complete?

**Perspectives on improving the iPEP**

1. Do you think using a tool like the iPEP would have improved your experience of your initial assessment with the GP/in ED?
2. Do you think your experience of the iPEP could be improved? How?
3. Would you change the questions of the iPEP?
4. Would you change the interface?

    Prompts: Barriers to use; barriers to understanding; overlooked aspects; understanding intended use of iPEP

Thank you for your time today, is there anything else you think might be helpful for me to know / is there anything you want to ask? Thank you…

## 2.3.9. Appendix 2: SRQR checklist

| No. Topic | Item | Page |
|---|---|---|
| **Title and abstract** | | |
| S1 Title | Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended | 84 |
| S2 Abstract | Summary of key elements of the study using the abstract format of the intended publication; typically includes objective, methods, results, and conclusions | 52 |
| **Introduction** | | |
| S3 Problem formulation | Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement | 84 |
| S4 Purpose or research question | Purpose of the study and specific objectives or questions | 84-5 |
| **Methods** | | |
| S5 Qualitative approach and research paradigm | Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., positivist, constructivist/interpretivist) is also recommended | 85-6 |
| S6 Researcher characteristics and reflexivity | Researchers’ characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, or presuppositions; potential or actual interaction between researchers’ characteristics and the research questions, approach, methods, results, or transferability | 86; 95-6 |
| S7 Context | Setting/site and salient contextual factors; rationale[a] | 85 |
| S8 Sampling strategy | How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[a] | 85 |
| S9 Ethical issues pertaining to human subjects | Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues | 86 |
| S10 Data collection methods | Types of data collected; details of data collection procedures including (as appropriate) start and stop | 86 |

| | | |
|---|---|---|
| | dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[a] | |
| S11 Data collection instruments and technologies | Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study | Appendix 1 |
| S12 Units of study | Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results) | 87-8 |
| S13 Data processing | Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts | 86 |
| S14 Data analysis | Process by which inferences, themes, etc., were identified and developed, including researchers involved in data analysis; usually references a specific paradigm or approach; rationale[a] | 86 |
| S15 Techniques to enhance trustworthiness | Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[a] | 86, 95-6 |
| **Results/Findings** | | |
| S16 Synthesis and interpretation | Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory | 87-95 |
| S17 Links to empirical data | Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings | 87-95 |
| **Discussion** | | |
| S18 Integration with prior work, implications, transferability, and contribution(s) to the field | Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field | 93-6 |
| S19 Limitations | Trustworthiness and limitations of findings | 95-6 |
| **Other** | | |
| S20 Conflicts of interest | Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed | Title page |
| S21 Funding | Sources of funding and other support; role of funders in data collection, interpretation, and reporting | 97 |

# Section 3 The external validity of research on diagnostic features in transient loss of consciousness

## 3.0. Section abstract

The external validity of research is the extent to which the context in which research is performed is representative of the setting to which its results will be applied. For diagnostic accuracy studies, it is essential that estimates of diagnostic accuracy are valid in the settings within which diagnosis occurs. Forms of bias compromising external validity include spectrum bias (the variation in diagnostic test performance across patient subgroups) and ecological validity (the extent to which the study setting and environment translates to the real world, or whether the artificial setting affects the subject of inquiry).

This section provides an attempt to overcome the barriers to ecological validity of semiological diagnostic features for seizure disorders derived from artificial inpatient settings, with a video diagnostic accuracy study of seizure semiology performed in a residential epilepsy monitoring unit setting. It also provides empirical demonstration of the external validity (or otherwise) of existing literature on features to support the differential diagnosis of functional/dissociative seizures, with external validation of diagnostic features to support FDS diagnosis in the first-presentation setting. Abstracts of included papers are listed here.

### Peri-ictal responsiveness to the social environment is greater in psychogenic nonepileptic than epileptic seizures.

(Note for readers: At the time of publication of this manuscript, the ILAE-recommended terminology for FDS was psychogenic nonepileptic seizures [PNES]; hence this manuscript employs that term. It can be considered in this context as interchangeable with FDS).

**OBJECTIVE:** To look for evidence of peri-ictal social interaction in psychogenic non-epileptic seizures (PNES) and epileptic seizures exploring the notion of PNES as form of nonverbal communication.
**METHODS:** Video recordings of typical seizures experienced by patients with epilepsy and PNES were obtained in a naturalistic social setting (residential epilepsy monitoring unit). Video analysis by three non-expert clinicians identified 18 predefined semiological and interactional features indicative of apparent impairment of consciousness or of peri-ictal responsiveness to the social environment with assessment of inter-rater reliability using Fleiss' κ. Features were compared between epileptic seizures and PNES.
**RESULTS:** 189 seizures from 50 participants (24 epilepsy, 18 PNES, 8 combined) were analysed. At least fair (κ>0.20) inter-rater agreement was achieved for 14 features. The PNES and epileptic seizures compared were of similar severity in terms of ictal impairment of consciousness (κ=0.34; OR = 1.11 [0.62-1.96]) or responsiveness (κ=0.52; OR = 1.01 [0.55-1.86]). PNES were more likely to: be preceded by attempts to alert others (κ=0.52; odds ratio (OR) = 12.4 [95%CI 3.2-47.7, $p$<0.001]); show intensity affected by the presence of others (κ=0.44; OR = 199.4 [12.0-3309.9, $p$<0.001]); and display post-ictal behaviour affected by the presence of others (κ=0.35; OR = 91.1 [17.2-482.1, $p$<0.001]).
**SIGNIFICANCE:** Non-expert raters can, with fair to moderate reliability, rate features characterising ictal impairment of consciousness and responsivity in video recordings of

seizures. PNES are associated with greater peri-ictal responsiveness to the social environment than epileptic seizures. These findings are consistent with a potential communicative function of PNES and could be of differential diagnostic significance.

## Diagnostic features of functional/ dissociative seizures in the first presentation of transient loss of consciousness

**Objectives:** Previous studies have identified features in patient's history and seizure descriptions supporting a clinical diagnosis of functional / dissociative seizures (FDS). However, most studies involved patients with chronic seizure disorders. This study explores the value of reported features for a clinical diagnosis of FDS in an adult population with a first presentation of transient loss of consciousness (TLOC).
**Methods:** We prospectively recruited patients newly presenting with TLOC to an Emergency Department (ED), Acute Medical Unit (AMU; admitting ward for general medical patients), first seizure or syncope clinic. We invited participants to complete an online questionnaire, either at home or at time of initial assessment. Two expert raters determined cause of participants' TLOC after 6-month follow-up. We also reviewed clinical records at this timepoint to extract relevant information for assessment of putative diagnostic features (13 categorical variables and 6 interval or continuous variables), and validation of two previously-developed diagnostic classifiers.
**Results:** We included 178 patients in final analysis (134 syncope, 32 epilepsy, 12 FDS). 3 categorical variables were significantly more common in FDS: fluctuating course or waxing/waning movements ($p$ = 0.0037), asynchronous limb movements ($p$ = 0.0024), and preserved ictal awareness or responsiveness ($p$ = 0.0013). Three interval/continuous variables supported diagnosis of FDS: younger age at onset (area under receiver-operating characteristic curve [AUC] = 0.865 (0.771-0.960)); total non-ictal symptoms reported on structured review of systems (AUC = 0.834 (0.730-0.928)); and total peri-ictal symptoms self-reported on structured questionnaire (AUC = 0.864 (0.781-0.948)).
**Conclusions:** Our study does not find support for some clinical features previously reported as diagnostic of FDS in adult patients with a first presentation of TLOC. Features suggestive of preserved ictal responsiveness (reported by witnesses) and awareness (in the form of total number of self-reported peri-ictal symptoms) support FDS diagnoses.

# 3.1. Peri-ictal responsiveness to the social environment is greater in psychogenic nonepileptic than epileptic seizures

## 3.1.1. Introduction

Psychogenic nonepileptic seizures are defined by their superficially similar phenomenology to epileptic seizures although these two seizure types have markedly different aetiologies. Whereas the manifestations of epileptic seizures are caused by epileptic activity in the brain, most psychogenic nonepileptic seizures (PNES) are interpreted as an automatic experiential and behavioural response to internal or external stimuli interpreted as aversive.[1]

The ICD-11 classifies most PNES as a form of dissociative disorder, while in the DSM-5[2] most presentations would fit the diagnostic criteria of functional neurological symptom (conversion) disorder.[3] These putative mechanisms suggest an important role for social interaction in the aetiology of PNES: The dissociative interpretation highlights that PNES are often a consequence of traumas or dilemmas, many of which are of an interpersonal nature,[4] while the conversion hypothesis suggests that PNES can be understood in part as a nonverbal means of communication. Research exploring the aetiology of PNES, however, has largely focussed on subjective or objective characteristics observable in patients themselves. Only a small number of observations suggest important contributions of the social environment to the occurrence of PNES. For instance, it has been reported that certain environments may make PNES more likely: PNES appear to occur more commonly than epileptic seizures during clinic attendances[5] (and show greater response to suggestion when patients have experienced seizures in clinical settings[6]). PNES are also more likely than epileptic seizures to happen in interpersonally challenging situations such as during psychotherapy sessions.[7] One previous study examined the influence of social environment on ictal phenomena, finding that the intensification or alleviation of seizures by the presence of others is a specific marker of PNES.[8] A case report suggests that prolonged PNES can be stopped by talking to patients.[9]

In addition, a small number of studies have compared families of patients with epilepsy and PNES, but these studies have not specifically examined the role or effects of the seizures themselves in patients' social environment.[10–13] At least a subgroup of patients with PNES is characterised by insecure attachment and particular anxieties about interpersonal relationships.[14,15] There is also evidence that carers differ in affective expression and that they experience their relationships with patients with seizures disorders differently, depending on whether the seizures are epileptic or nonepileptic.[16,17]

This exploratory study looks for evidence that – unlike epileptic seizures – PNES may arise as a consequence of objectively identifiable interpersonal constellations or whether the interactional consequences of PNES support the notion of PNES as a nonverbal form of communication.

To this end independent raters examined video recordings of peri-ictal behaviour from a residential video-EEG (vEEG) monitoring unit, in which people who experience seizures may move freely around a shared monitored living environment (including living room, kitchen and garden). This environment permits more natural social interactions than the traditional ward-based epilepsy monitoring unit (EMU), as residents, visitors, and staff can engage in typical daily and leisure activities while still undergoing vEEG monitoring. We hypothesise that people experiencing PNES will display greater responsiveness to those around them ictally and peri-ictally.

## 3.1.2. Methods

### *3.1.2.1. Participants and setting*

We invited a consecutive sample of adult patients referred to the Scottish Epilepsy Centre (Glasgow, United Kingdom), a residential EMU specialising in the evaluation and medical treatment of seizure disorders, to participate in this study. This unit differs from conventional EMUs in that, instead of patients being confined to their bed or bedroom during the monitoring period, time-locked video-EEG recording takes place in a much more home-like environment, in which patients inhabit a communal living space. Video recording is available throughout the building and permits continuous monitoring of seizure activity in a less artificial setting and enable recording of seizures in a wider variety of different social situations. The 12-bed unit features a network of cameras that continuously record patients and any of these cameras can also be linked to ambulatory EEG for patients on telemetry. Such flexibility does not compromise patient safety compared to national standards in video telemetry units, and most seizures are attended by a member of staff in less than one minute.[18]

All participants were given information about intended teaching and research uses of seizures recorded while resident in the EMU and gave written consent for the use of their videos for these purposes.

All diagnoses of individual seizures and patients' seizure disorders were made by an experienced epileptologist on the basis of all available clinical information including vEEG capture of episodes typical of the patient's reported episodes. The epileptologist classified all individual seizures as epileptic, non-epileptic, or (for patients with comorbid epilepsy and PNES) mixed or indeterminate based on semiology and vEEG (if occurring while on EEG monitoring). Seizures were also diagnosed and included in this analysis if they were captured only on video but if semiologically similar seizures had previously or subsequently been recorded during vEEG monitoring allowing the epileptologist to make a definite diagnosis. No "indeterminate" seizures or seizures thought to contain mixed elements of epileptic and nonepileptic seizures were included in our comparisons of characteristic associations of these two seizure types.

### *3.1.2.2. Sample*

An epileptologist identified the first five recorded seizures for all participants (or all recorded seizures for those with fewer than five recorded events) and manually selected the cut-off points for start and end of recording, allowing the viewer to see the full event, as well as proceedings immediately pre- and post-ictally. Given the exploratory nature of this study and the lack of previous work permitting us to estimate a clinically-important difference we did not undertake a formal sample size calculation. Instead, we specified *a priori* a target of at least 100 epileptic seizures, with a matching number of PNES to capture the variety of semiologies of both seizure disorders and a range of different social settings.

### *3.1.2.3. Video analysis*

From anecdotal reports and review of previous literature we identified 18 peri-ictal semiological and interactional features of interest potentially indicative of conscious impairment or of peri-ictal responsiveness to the patient's social environment (see Table 2 below). Three non-expert clinicians (two Core Psychiatric Trainees [postgraduate year three]; one Foundation Year 2 doctor [postgraduate year two]) reviewed each seizure recording and classified each feature of interest as present or absent. The raters were blinded to all clinical information regarding the participants including diagnosis and EEG findings; they were also blinded to the scores

assigned by the other raters. Presence or absence of each feature in each seizure was determined by majority rating.

#### *3.1.2.4. Statistical analysis*

We evaluated the inter-rater reliability of the determination of presence/absence of features of interest by Fleiss' κ. Using conventional thresholds,[19] we performed further analysis on only those features displaying at least fair (κ>0.20) inter-rater agreement. We compared differences in each feature between epileptic seizures and PNES (two-tailed Fisher's exact test). We defined statistical significance using the Bonferroni correction for multiple comparisons with family-wise error rate α = 0.05. We estimated odds ratios (ORs) for PNES and 95% confidence intervals (CIs) using Gart's logit interval.[20,21] As patients with PNES and intellectual disabilities (ID) are sometimes thought to represent an aetiologically distinct group, with greater emphasis on environmental or social interaction in both explanation and treatment,[22,23] we tested whether between-group differences persisted after controlling for intellectual disability by conducting hierarchical logistic regression, and compared differences in interactional features in PNES in participants with and without ID (two-tailed Fisher's exact test). We performed statistical analysis using MATLAB R2017b (The Mathworks Inc, Natick MA), except for logistic regression, which was performed using SPSS v26.0 (IBM Corp., Armonk NY).

## 3.1.3. Results

#### *3.1.3.1. Descriptive analysis*

50 patients consented to participation, with ages ranging from 16-79 years. 24 had diagnoses of epilepsy, 12 PNES, and 14 comorbid epilepsy and PNES (see Table 3.1.1 for demographic details). Age did not differ significantly between groups (one-way ANOVA, $p = 0.365$). Sex distribution differed significantly between groups, with more women in the PNES and combined groups than in the epilepsy group ($\chi^2(2) = 6.124$, $p = 0.047$). Significantly more participants in the epilepsy group had some degree of intellectual disability ($\chi^2(2) = 10.506$, $p = 0.033$).

| | ***N* (% female)** | **Mean age (SD)** | **Intellectual disability (*N*, %)** |
|---|---|---|---|
| **Epilepsy** | 24 (37.5) | 33.9 (13.4) | 13 (54.2) |
| **PNES** | 12 (58.3) | 41 (16.9) | 2 (16.7) |
| **Epilepsy+PNES** | 14 (78.6) | 39 (11.1) | 2 (14.3) |

*Table 3.1.1. Participant demographics.*

Participants with epileptic seizures had diagnoses of idiopathic generalised (6 participants), or focal epilepsy (22 participants: 16 with purely focal aware or impaired awareness seizures, 6 with focal to generalised seizures). The epilepsy type could not be clearly specified in 10 participants.

We reviewed a total of 193 seizures (100 epilepsy, 89 PNES, 4 combined or indeterminate). Those that could not be clearly diagnosed as either epileptic seizures or PNES were excluded from further analysis. We did not have ratings from all raters for two episodes; these were also excluded from analysis.

3.1. Peri-ictal responsiveness to the social environment is greater in psychogenic nonepileptic than epileptic seizures

### *3.1.3.2. Comparison of seizure characteristics*

At least fair interrater agreement was achieved for 14 of the 18 features examined: substantial agreement was seen in two ($0.60<\kappa\leq0.80$), moderate in seven ($0.40<\kappa\leq0.60$) and fair in five ($0.20<\kappa\leq0.40$). The raters did not reliably agree on the presence of four features (pre-ictal behaviour change, post-ictal agitation or behavioural difficulty, autonomic features, and evident injury). The PNES and epileptic seizures compared were of similar severity in terms of ratings of apparent ictal impairment of consciousness ($\kappa=0.34$; odds ratio [OR] = 1.11 [95% CI 0.62-1.96]) and responsiveness ($\kappa=0.52$; OR = 1.01 [0.55-1.86]).

Several features indicating peri-ictal responsiveness to social cues were more prominent in PNES than in epilepsy. PNES were more likely to: be preceded by attempts to alert others ($\kappa=0.52$; OR = 12.4 [95%CI 3.2-47.7, $p<0.001$]); show intensity affected by the presence of others ($\kappa=0.44$; OR = 199.4 [12.0-3309.9, $p<0.001$]); and display post-ictal behaviour affected by the presence of others ($\kappa=0.35$; OR = 91.1 [17.2-482.1, $p<0.001$]). The intensity of 51% of PNES (but none of the epileptic seizures) were judged to be influenced by the presence of others; post-ictally only 1% of epileptic seizures were thought to show behaviour influenced by others compared to 58% of PNES. Differences in peri-ictal responsiveness remained statistically significant after controlling for ID. There were no significant differences in peri-ictal responsiveness in PNES in participants with and without ID.

Inter-rater reliability for all variables studied is displayed in Table 3.1.2. For those variables with at least fair inter-rater agreement, the table also displays corrected ORs with 95% CIs and proportion of patients with epilepsy and PNES displaying each feature. ORs with 95% CIs are displayed graphically in Figure 3.1.1.

| Feature | Inter-rater agreement (Fleiss' κ) | Proportion patients displaying feature (%) | | OR for PNES (95% CI) |
|---|---|---|---|---|
| | | Epilepsy | PNES | |
| **Fall to ground/sideways** | 0.74 | 21.2 | 23.3 | 1.13 (0.57-2.23) |
| **Interacting with others at onset** | 0.68 | 33.0 | 45.6 | 1.69 (0.94-3.03) |
| **Cluster of seizures** | 0.57 | 1.0 | 8.9 | 6.83 (1.18-39.7) |
| **Ictal emotional outburst (crying, laughter)** | 0.53 | 19.2 | 14.4 | 0.72 (0.34-1.54) |
| **Apparent impaired responsiveness** | 0.52 | 68.4 | 68.5 | 1.01 (0.55-1.86) |
| **Apparent attempts to alert others at onset** | 0.52 | 2.0 | 23.9 | **12.4 (3.23-47.7)** |
| **Apparent pre-ictal warning/aura** | 0.52 | 2.0 | 21.3 | **10.9 (2.82-42.1)** |
| **Post-ictal confusion** | 0.45 | 30.3 | 12.6 | 0.343 (0.161-0.727) |

3.1. Peri-ictal responsiveness to the social environment is greater in psychogenic nonepileptic than epileptic seizures

| | | | | |
|---|---|---|---|---|
| **Seizure intensity affected by presence of others** | 0.44 | 0.0 | 50.6 | **199 (12.0-3309)** |
| **Fluctuating intensity of signs** | 0.39 | 2.0 | 50.1 | **39.5 (10.5-148.3)** |
| **Post-ictal behaviour affected by presence of others** | 0.35 | 1.0 | 58.0 | **91.1 (17.2-482.1)** |
| **Apparent impairment of consciousness** | 0.34 | 42.9 | 45.5 | 1.11 (0.624-1.98) |
| **Sudden onset** | 0.33 | 86.0 | 65.5 | **0.295 (0.146-0.599)** |
| **Apparent attempt to take safety precautions** | 0.30 | 5.0 | 13.5 | 2.80 (0.983-7.98) |
| **Apparent pre-ictal behaviour change** | 0.17 | 11.7 | 30.3 | **3.19 (1.49-6.85)** |
| **Evident injury** | 0.16 | 1.0 | 0.0 | 0.366 (0.015-9.11) |
| **Evident post-ictal agitation** | 0.08 | 3.0 | 1.1 | 0.478 (0.069-3.30) |
| **Autonomic features (flushing, pallor, sweating)** | -0.02 | 1.1 | 2.3 | 1.82 (0.235-14.1) |

*Table 3.1.2. Inter-rater agreement and ORs for PNES of seizure variables. Statistically significant results are highlighted in **bold** (FWER=0.05, Bonferroni correction)*

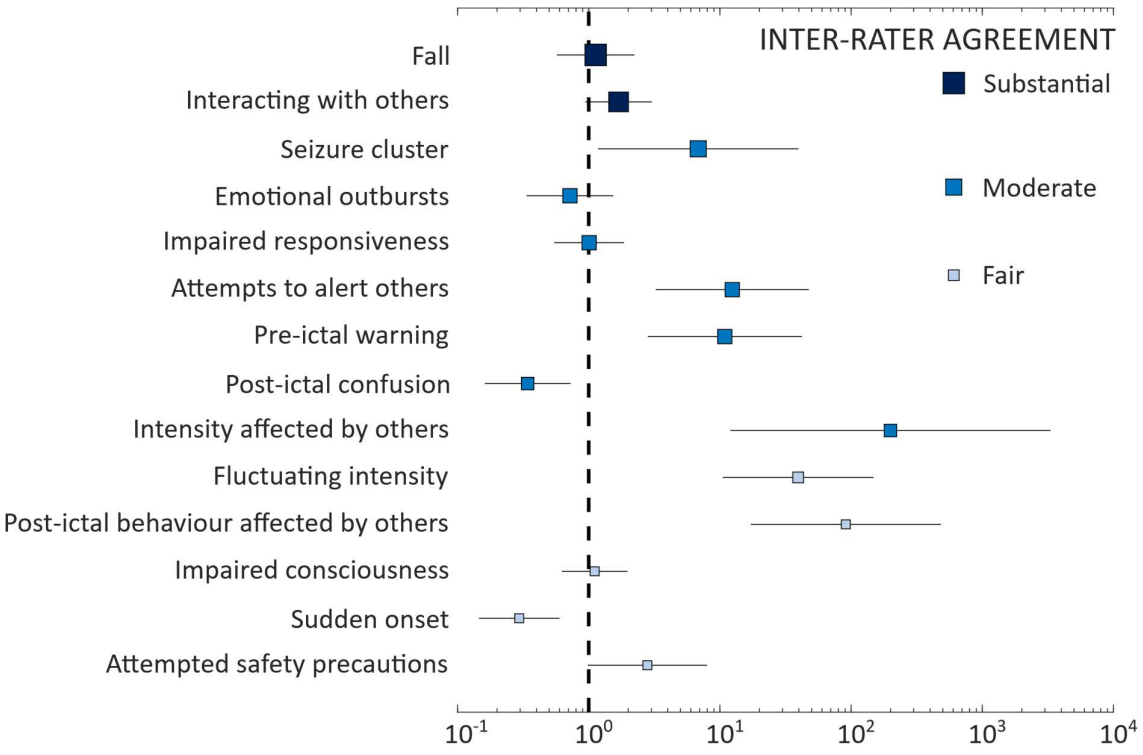


*Figure 3.1.1. ORs for PNES of selected variables. Bars represent 95% CIs. Marker size is proportional to inter-rater agreement (Fleiss' kappa).*

## 3.1.4. Discussion

### *3.1.4.1. Ictal consciousness and social responsiveness*

Our results demonstrate that, when in an environment permitting normal social interactions, PNES differ systematically from epileptic seizures in the degree of peri-ictal responsiveness to the social environment they are associated with. The presence of others affected people before, during, and after PNES significantly more than in epileptic seizures; in no epileptic seizure did the presence of others affect ictal intensity, compared with over half of PNES.

One previous study also identified the ability of others to alleviate or intensify PNES but not epileptic seizures; however, in that study all video recordings were from seizures recorded in traditional EMUs, and thus represent a more artificial setting less representative of people's usual social environments. Furthermore, raters in that study were all expert epileptologists, who may have been more likely to identify the underlying diagnosis correctly and thus be biased in their identification of particular features. Indeed, only 18% of lay eyewitnesses agreed with epileptologists' assessment of this form of ictal social responsiveness.[8] By contrast, we show that in a more naturalistic social environment the influence of others on ictal intensity clearly distinguishes PNES from ES, and can be identified by non-expert clinicians. This finding has potential diagnostic and therapeutic implications, as well as providing evidence for the communicative function of PNES discussed in the introduction.

Diagnostically, we demonstrate that video-documented peri-ictal social responsiveness can be identified with fair to moderate reliability by non-expert observers and that this is a highly specific sign for PNES compared with epilepsy (with just 1% of epileptic seizures demonstrating post-ictal responsiveness to others, and none showing ictal responsiveness). Thus ictal social responsiveness could be considered as a candidate criterion for diagnostic tools to assist in the differential diagnosis of seizures[24–29], although it is important to stress that our study evaluated social responsiveness objectively, by video analysis, rather than relying on carer- or family-reported responsiveness. There is some evidence from a previous study that attending to the communicative dimensions of ictal phenomena may aid diagnosis, with psychiatrists identifying socially-responsive ictal features such as 'putting oneself at the centre of attention' or 'mirror movements imitating the examiner' in video recordings of seizures as suggestive of PNES. However, in contrast to this previous study, the observations described here all achieved at least fair levels of inter-rater reliability.[30] Given the general consensus that no semiological feature is pathognomonic of PNES and that individual features are of limited diagnostic value,[8,29,31–33] it is particularly striking to observe that a noticeable increase in seizure intensity in response to the presence of others was observed in over one half of all PNES studied here, whereas this was not identified in a single epileptic seizure. In view of the increasing importance of home video recordings in the diagnostic process, our findings therefore suggest that the observation of ictal social responsiveness may be very helpful in clinical practice.

Therapeutically, our observations have immediate relevance to the information patients and families should be given when the diagnosis of PNES is communicated and advice is provided on the management acute management of PNES by any caregivers. These individuals should be made aware that their interaction with the patient during the PNES can potentially make these seizures worse and that they should carefully monitor the effects of their actions on the patient's seizures.[34] Our observations are also relevant for psychological therapies which are considered the standard of care for further treatment of PNES.[35–38] Typical CBT approaches for PNES utilise a fear-avoidance model. A central feature of this approach is the identification of

stimuli that may provoke an avoidant response, and helping those with PNES to understand the role their attacks can play in such responses.[39] Our study suggests that, in the search for potentially relevant stimuli, particular attention should be paid to potential interpersonal and social triggers. This approach will fit naturally into Psychodynamic Interpersonal Treatment approaches which have also been proposed for PNES.[40]

As discussed above, the putative communicative function of PNES (for instance as an expression of distress or other emotions, in some cases as a nonverbal representation of an unspeakable dilemma or traumatic memory[4]) is a feature of multiple aetiological accounts of the mechanisms underlying PNES. Our findings of social responsiveness intra- and peri-ictally in PNES could be interpreted as behavioural, dissociative, or conversion responses to varying social stimuli. Indeed, it is likely that our PNES participants represented an aetiologically heterogeneous group; the fact that our findings were, nonetheless, robust (and that there were not significant semiological differences between the participants with and without ID) support efforts to develop integrated models of PNES that can incorporate distinct psychological mechanisms into understanding the phenomenon.[1,41]

#### *3.1.4.2. Seizure semiology*

Our results also demonstrate that non-expert raters could identify significant differences in other (not necessarily interaction-associated) features between video recordings of PNES or epileptic seizures and immediately peri-ictal scenarios. We found that a fluctuating intensity of ictal phenomena was highly predictive of PNES (OR 39.5, 95% CI 10.5-148.3, sensitivity 95.7% and specificity 69.1%); these figures are consistent with those found for expert rating of video recordings by Syed et al,[8] and broadly match those reported in other studies evaluating video-EEG recordings,[31] though they are better than those reported by Azar et al., whose findings were based on questionnaire data.[42] We found that sudden seizure onset and post-ictal confusion were more common in epilepsy than PNES (OR 0.925 [0.146-0.599]), associations with conflicting support in the previous literature.[8,31] Our other findings were broadly consistent with older reports, and would also support the conclusion of other authors that non-expert assessors can be supported in identifying semiological features to aid the differential diagnosis of seizures.[43]

Four features showed low inter-rater reliability in identification: pre-ictal behaviour change, post-ictal agitation or behavioural difficulty, autonomic features, and evident injury. The nature of the study (review of video recordings from cameras sometimes at some distance from the patient) may explain the lack of agreement on presence of autonomic features or injury, as both of these would normally be evaluated by closer assessment (e.g. physical examination for features of autonomic arousal or evidence of injury). The other two features, meanwhile, refer to immediate pre- or post-ictal behaviour change; disagreement here may relate to differing assessment of when the ictal period proper starts and finishes (and thus which behaviours are considered seizure phenomena, and which pre- or post-ictal).

#### *3.1.4.3. Limitations*

There are several limitations of note to this study. Most prominently, while the raters were not experts in seizure disorders, they were all qualified medical professionals. The reliability of seizure classification by healthcare professionals varies throughout training,[44] and differs from that of lay witnesses.[45] Thus our results do not necessarily generalise to other groups (especially non-expert carer), and despite their lack of epileptological expertise raters may have been able to identify the underlying diagnosis from the semiology alone. This could have influenced their

determination regarding the presence/absence of features of interest. Furthermore, we found at least some disagreement between raters in their evaluation of all variables of interest, highlighting that simple reports of the presence/absence of particular features in clinic (in the absence of video documentation) do not unambiguously indicate that the feature was actually present in any seizure. None of the features examined showed more than substantial inter-rater agreement, highlighting that even witness reports from healthcare professionals or video interpretations by non-experts cannot serve as completely unambiguous guides to seizure semiology and that diagnoses always need to consider the full semiological, clinical and social context.

Importantly, our findings are based on the interpretation of high quality video recordings of seizures including the scenario before and after the ictal event. This means that the findings cannot be directly generalised to the interpretation of videos only capturing parts of seizures (most commonly the seizure ending) or to situations in which seizures are directly observed but not recorded. Furthermore we acknowledge that the nature of the peri-ictal behaviour of patients may have been influenced by which people were present (rather than only by whether others were present or not). Unfortunately, we did not collect information on the status of third parties visible in the seizure videos (e.g. whether others were visitors, members of staff or other patients. Finally, our comparisons between PNES and epilepsy are based on seizures of similar severity in terms of ictal awareness and responsiveness as rated by our non-expert observers. We acknowledge that, in the absence of patient self-report, this assessment of consciousness has significant limitations: There is evidence from previous studies that subjective and objective measures of ictal consciousness can discriminate between groups of patients with epilepsy and PNES. For instance, in one study patients with PNES displayed a higher level and content of consciousness than those with epilepsy on the Ictal Consciousness Inventory (ICI),[46] and in others patients with epilepsy and PNES were shown to differ in self- and witness-report in response to several questions regarding ictal awareness and responsiveness.[24,25,47] Differences have also been observed in the characterisation of PNES-related impairment of consciousness of patients themselves and eye witnesses.[48] What is more, patients with PNES report that degrees of loss of awareness – the absence of subjective experience – and loss of responsiveness – interaction with the surrounding environment – vary considerably (intra- and intersubjectively) across different seizures, with many describing one phenomenon occurring independently of the other.[47] Overall, our results suggest a relative preservation of some functions of consciousness (responsiveness to social stimuli) in contexts of ostensible loss of awareness within PNES.

### 3.1.5. Conclusions

We demonstrate exploratory evidence that PNES show greater peri-ictal responsiveness to the social environment than epileptic seizures, and that non-expert raters can, with at least fair reliability, identify a range of features suggestive of this, with over half of PNES showing ictal intensity influenced by the presence of others, a phenomenon not seen in epileptic seizures. This provides support and stimulus for further investigation into potential communicative functions of PNES. It shows that the observation of social interaction may serve as a diagnostic criterion in the diagnostic interpretation of ictal video recordings and suggests also has implications for the treatment of PNES. Correlating the subjective experience and objective manifestations of conscious behaviour in epilepsy and PNES with physiological and psychological differences may contribute to understanding better the functions and mechanisms of human consciousness.

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# 3.2. Diagnostic features of functional/dissociative seizures in the first presentation of transient loss of consciousness

## 3.2.1. Introduction

Functional/dissociative seizures (FDS) are paroxysmal episodes of altered subjective experience, behaviour, awareness or responsiveness, and self-control, resulting from neuropsychiatric dysfunction.[1] FDS are included in the list of three common causes of 'transient loss of consciousness' (TLOC or 'blackouts'),[2] despite the disruption of 'consciousness' in FDS often being incomplete, variable and difficult to elicit.[3–6] The most important reason for the inclusion of FDS in this list is that they frequently resemble – and are mistaken for – epileptic seizures, but can also be misdiagnosed as other paroxysmal disorders causing TLOC, such as syncope.[7] Misdiagnoses are particularly common at first presentation.[8] Of the three commonest causes of TLOC, the misdiagnosis of FDS is particularly common, with delays of many years from initial manifestation to diagnosis.[9,10] Diagnostic delay is associated with worse long-term outcomes,[11] increased healthcare demand,[12] and high healthcare costs (estimated at $100 000 lifetime cost per patient in investigations and medications),[13,14] as well as exposing patients to iatrogenic harm through treatment for misdiagnosed conditions.[15,16]

Diagnosis at initial presentation can be challenging because FDS may lack unique distinguishing clinical or semiological features,[17,18] and inter-ictal investigations are frequently non-contributory.[19,20] Collateral histories from witnesses can support diagnosis, but are frequently unavailable, and - even when obtained - may not be reliable.[21] This makes the patient's history the most important resource for supporting earlier recognition and diagnosis of FDS.[18,22]

However, given the lack of single distinguishing items of patient-reported information supporting diagnoses with adequate sensitivity or specificity,[2] previous work has explored how such information about a range of patient reportable features can be combined to maximise diagnostic yield.[23–26] Understandably such research has largely focussed on patients with "gold-standard", video-EEG confirmed, diagnoses of FDS.[23,24,27] The majority of these studies have been performed at epilepsy services, where the most relevant differential diagnosis is one of epileptic seizures. It is important therefore to determine the ecological validity of such findings in the population for whom differential diagnosis is most relevant – those who are first presenting to health care – and in contrast to other conditions in the differential diagnosis of TLOC, most prominently syncope.

In this study we seek to validate potential diagnostic features of FDS in a sample of patients with a first presentation of TLOC. We study both individual features suggested as supporting the diagnosis,[26] and classifier models trained to distinguish FDS from epilepsy and syncope on the basis of symptom profiles or feature combinations.[24,25]

## 3.2.2. Methods

### *3.2.2.1. Setting and participants*

This study is a secondary analysis of a dataset obtained during a project seeking to develop and validate a machine-learning based clinical decision aid for the differential diagnosis of TLOC. Full details of study design, setting, and inclusion criteria are reported elsewhere.[8] We recruited consecutive adult patients with a first presentation of TLOC to the Emergency Department (ED), Acute Medical Unit (AMU), first seizure or syncope clinic, within a single large acute hospital

trust in the United Kingdom, for an 11-month period between 10th February 2022 and 9th January 2023. We asked recruited participants to complete a short online questionnaire regarding their past medical history and peri-ictal symptoms (Paroxysmal Events Symptom Questionnaire [PESQ]), and, if possible, to identify a witness to complete a questionnaire regarding peri-ictal semiology (Paroxysmal Events Witness Questionnaire [PEWQ]). The questionnaires are included in a supplementary appendix (§4.2.7).

We determined best possible reference standard diagnoses for all participants by an independent review of all clinical data performed by two expert epileptologists (MR and SJH) at least six months after enrolment.

#### *3.2.2.2. Study instruments*

##### PESQ and PEWQ

To extract participant symptoms and witness semiology reports, we used two brief questionnaires derived from our previous development work (one for patients themselves, one for witnesses if available),[18] with additional features identified in reviews published subsequent to the initial development work.[13,26] A 52-item patient questionnaire (the PESQ) comprises 3 brief demographic questions (age, gender, years of formal education), 14 questions regarding previously-experienced (non-ictal) somatic symptoms, and 35 regarding peri-ictal symptoms. An 18-item witness questionnaire (the PEWQ) comprises 18 questions regarding witnessed ictal semiology. Participants and witnesses could complete the PESQ and PEWQ either online via a dedicated online user interface, hosted on a secure university server; or on paper.

##### Individual diagnostic features

Two recent reviews describe a range of individual clinical criteria that could be used to support the diagnosis of FDS.[2,26] While many candidate criteria have been suggested, not many of these have been replicated in further studies. We therefore sought to validate only those criteria that had been found to have discriminating value for the diagnosis of FDS in more than one study.[26]

Additionally, there is qualitative and quantitative evidence supporting the idea that people with FDS have a subjectively-richer experience than those with other forms of TLOC,[3,28] and as such may be able to say more about 'what it is like' to experience their form of TLOC. We therefore also report whether – irrespective of content – the total number of peri-ictal symptoms (as captured in total reported symptoms in the PESQ) could predict a diagnosis of FDS in our dataset.

##### Diagnostic classifiers

In addition to individual clinical features, a range of scores, scales, or classifiers have been suggested to be able to predict a diagnosis of FDS.[26] However, many of these are impractical or impossible to translate to the first presentation context, for example because they require knowing the results of specialist investigations e.g. EEG,[23] or assume that the person has already undergone assessment and treatment for a seizure disorder.[29] We therefore evaluate two diagnostic classifiers for FDS that are applicable to the first-presentation population.

The Dissociative Seizures Likelihood Score (DSLS) is a classification model trained and prospectively validated on a population of patients admitted for video-EEG evaluation for differential diagnosis of seizure disorders at a single centre in the USA. It determines a probability of FDS or epileptic seizures on the basis of 19 features drawn from a patient's history, subjective seizure experience, and witness-reported semiology.[24] In prospective validation in a cohort of patients with chronic seizure disorders with frequent-enough seizures

for video-EEG confirmed diagnosis, the DSLS classified 77% (95% confidence interval [CI] 74-80%) of patients accurately as either having FDS or epilepsy.

The initial Paroxysmal Event Profile (iPEP) classifier is a classification model trained and validated on a population of patients with video-EEG confirmed diagnoses of FDS or epilepsy, or tilt table or cardiac monitoring-confirmed diagnoses of syncope.[25] It uses patient responses to a questionnaire (with witness responses if available) regarding peri-ictal symptoms and semiology as inputs to a random forest to classify patients into likely diagnoses of FDS, epilepsy, or syncope. In a separate validation sample, a classifier based on 36 witness and patient symptom reports classified 86% (95% CI 76.9-96.2%) of patients correctly.

#### *3.2.2.3. Data extraction*

Where possible, we used answers from self-report questionnaires to obtain relevant data. We supplemented questionnaire responses with data extracted from patients' clinical records for the duration of the study (minimum 6 months). A single member of the study team (AW) reviewed all clinical records for relevant patient, witness, or clinician reports, coding for presence/absence of binary variables as documented in the clinical record, and extracting from the record values for interval/continuous variables. Where multiple values were given at different points in the record for numerical variables, the median response was used. A single positive occurrence was taken as indicating presence of binary variables.

We coded a witness report as being available when either a witness completed the study questionnaire, or the clinical record contained a detailed witness account. Sometimes a full witness report was not available, but limited witness details could be inferred (e.g. from bystander accounts to paramedics). For these cases we marked a witness report as not being available, but noted presence/absence of features specifically referenced in the limited accounts.

#### *3.2.2.4. Statistical analysis*

For individual categorical variables, we determined whether FDS differed significantly from other diagnoses using Fisher's exact test, with Holm-Bonferonni correction for multiple comparisons. We summarise diagnostic performance using diagnostic statistics sensitivity, specificity, and positive and negative prediction values (PPV and NPV), with 95% binomial confidence intervals (CIs). For interval and continuous variables, we first determined whether there was a significant difference across diagnoses (Kruskal-Wallis test with df = 2); if the null hypothesis was rejected here, we performed pairwise post-hoc comparisons of FDS against the other diagnoses (Mann-Whitney U test), again using the Holm-Bonferroni correction. For those variables that both differed significantly between groups, and for which FDS differed from both epilepsy and syncope, we plotted receiver-operating characteristic (ROC) curves and evaluate performance using area under the ROC curve (AUC) with 95% CIs.

To validate the DSLS, we excluded patients with syncope from analysis (as the publicly-available DSLS discriminates between FDS and epilepsy only). We calculated DSLS probability of FDS for each patient, and classified those with >50% probability of FDS diagnosis as predicted FDS. We compared the performance of the DSLS to our reference-standard diagnoses to determine classifier accuracy, sensitivity, specificity, PPV, and NPV.

To validate the iPEP, we used the training sample (*N*=100) from the primary study to calibrate the classifer, then evaluated classification performance of the calibrated classifier on the validation sample (*N*=78). Again, we compared classifier performance to reference standard diagnosis.

#### *3.2.2.5. Sample size*

This paper presents a secondary analysis of data, and as such we do not provide formal *a priori* power calculations for determination of sample size. However, illustrative calculations demonstrate the utility of our study to identify variables of potential clinical utility. For the categorical variables, given the ratios of participants with each diagnosis, to detect a difference in probabilities of 0.2 between those who do and do not have FDS (assuming one-tailed $\alpha = 0.05$, $\beta = 0.8$) would require 10 participants with FDS and 129 without. Alternatively, assuming a target diagnostic test statistic (e.g. sensitivity, specificity, PPV or NPV) of 0.75, and that we wish to determine at least that the test performs better than chance – i.e. test statistic > 0.5, or 95% confidence interval +- 0.25, produces a sample size requirement of 11.5 participants with FDS.[30]

## 3.2.3. Results

#### *3.2.3.1. Descriptive analysis*

At end of follow-up, data from 179 participants were available for analysis. Expert raters could not agree on final diagnosis for one participant, therefore they were excluded from further analysis. Of the remaining 178, only 12 (6.7%) had a best possible clinical reference standard diagnosis of FDS confirmed by two independent neurologists at the end of the study; the most common diagnosis was syncope (134 participants; 75.3%), followed by epileptic seizure (32 participants; 18.0%). We summarise basic demographics in Table 3.2.1; full recruitment and demographic details are reported elsewhere.[8]

46 participants identified a witness who completed the witness questionnaire. Additional data from witnesses was available from the clinical records of 65 participants.

| Diagnosis | *N* (% total) | Median age (range) | N (%) female |
|---|---|---|---|
| **Syncope** | 134 (75.3) | 64 (17-94) | 75 (56.0) |
| **ES** | 32 (18.0) | 47.5 (16-86) | 14 (43.8) |
| **FDS** | 12 (6.7) | 31 (16-57) | 9 (75.0) |

*Table 3.2.1 . Summary of participant demographics. ES = epileptic seizure. FDS = functional/dissociative seizure.*

#### *3.2.3.2. Individual FDS diagnostic features*

##### Categorical diagnostic features

From the list of categorical diagnostic features obtained from the previous literature, we excluded two from further analysis (presence of trauma and postictal breathing pattern). The reason for these exclusions were that the clinical records only provided any information on a history of prior traumatic experience in five cases and that witnesses and clinical records did not often differentiate between post-ictal stertorous breathing (previously reported as predictive of epilepsy[21,31]) and rapid or shallow breathing (predictive of FDS[32]). We had excluded trauma history from our patient questionnaire on the basis of pilot testing where it was felt to be a less acceptable question for patients in the context of a first TLOC presentation.

Of the remaining categorical variables, only three showed a statistically significant difference between FDS and other diagnoses. All of these were witness-reported semiological features: fluctuating course or waxing/waning movements ($p = 0.0037$), asynchronous limb movements ($p = 0.0024$), and preserved awareness or social responsiveness ($p = 0.0013$). Table 3.2.2 summarises diagnostic test statistics for all categorical variables.

We present raw reporting counts for categorical variables in the Supplementary Worksheet.

3.2. Diagnostic features of functional/dissociative seizures in the first presentation of transient loss of consciousness

| TYPE | VARIABLE | Diagnostic statistics for FDS (95% CI) | | | |
|---|---|---|---|---|---|
| | | SENSITIVITY | SPECIFICITY | PPV | NPV |
| WITNESS REPORT | Eye closure | 0.20 (0.01-0.72) | 0.92 (0.78-0.98) | 0.25 (0.01-0.81) | 0.89 (0.75-0.97) |
| | Side-side head movements | 0.00 (0.00-0.71) | 0.97 (0.87-1.00) | 0.00 (0.00-0.98) | 0.93 (0.80-0.98) |
| | **Fluctuating course** | **1.00 (0.29-1.00)** | **0.88 (0.75-0.96)** | **0.38 (0.09-0.76)** | **1.00 (0.91-1.00)** |
| | **Asynchronous limb movements** | **0.75 (0.19-0.99)** | **0.95 (0.84-0.99)** | **0.60 (0.15-0.95)** | **0.98 (0.87-1.00)** |
| | Incontinence | 0.33 (0.07-0.70) | 0.84 (0.75-0.90) | 0.14 (0.03-0.36) | 0.94 (0.87-0.98) |
| | **Preserved awareness or social responsiveness** | **0.67 (0.22-0.96)** | **0.94 (0.83-0.99)** | **0.57 (0.18-0.90)** | **0.96 (0.86-1.00)** |
| | Opisthotonos | 0.25 (0.01-0.81) | 1.00 (0.92-1.00) | 1.00 (0.03-1.00) | 0.94 (0.83-0.99) |
| PSYCHIATRIC COMORBIDITY | Any mental health problem | 0.33 (0.10-0.65) | 0.78 (0.71-0.84) | 0.10 (0.03-0.23) | 0.94 (0.89-0.97) |
| PRE-ICTAL SYMPTOMS | Palpitations | 0.17 (0.02-0.48) | 0.96 (0.92-0.99) | 0.25 (0.03-0.65) | 0.94 (0.89-0.97) |
| | Diaphoresis | 0.25 (0.05-0.57) | 0.67 (0.60-0.74) | 0.05 (0.01-0.15) | 0.93 (0.86-0.97) |
| | Fear of dying | 0.50 (0.21-0.79) | 0.83 (0.76-0.88) | 0.17 (0.07-0.34) | 0. 96 (0.91-0.98) |
| HISTORICAL VARIABLES | Chronic fatigue | 0.25 (0.05-0.57) | 0.88 (0.82-0.92) | 0.13 (0.03-0.34) | 0.94 (0.89-0.97) |
| | Family history of seizures | 0.42 (0.15-0.72) | 0.91 (0.86-0.95) | 0.25 (0.09-0.49) | 0.96 (0.91-0.98) |

*Table 3.2.2. Summary diagnostic test statistics for categorical variables. Variables highlighted in bold differ significantly at Holm-Bonferroni corrected $p < 0.05$. CI = confidence interval. PPV = positive predictive value. NPV = negative predictive value*

### Interval and continuous diagnostic features

Of non-categorical variables, only age at onset, total historical symptoms reported on review of symptoms (ROS) questionnaire, and total peri-ictal symptoms on questionnaire, differed significantly between diagnoses. These are summarised in Table 3.2.3. Average seizure duration, monthly seizure frequency, and time since onset of first seizure did not differ significantly across post-hoc pairwise comparisons with epilepsy.

| Diagnosis | Median (range) age at onset (y) | Median (IQR) ROS questionnaire items endorsed (*n*) | Median (IQR) peri-ictal symptoms endorsed (*n*) |
|---|---|---|---|
| **FDS** | 22.5 (12-56.5) | 6 (4.5) | 12 (6.75) |
| **Epilepsy** | 41.5 (16-83) | 3 (4) | 6 (4) |
| **Syncope** | 64 (17-94) | 3 (4) | 4 (5.75) |

*Table 3.2.3. Summary of continuous/interval variables that differ significantly between FDS and other diagnoses. FDS = functional/dissociative seizures. IQR = interquartile range.*

Age at onset differed significantly across all diagnoses ($p < 0.001$), and in pairwise comparisons between FDS and syncope ($p < 0.001$), and between FDS and epilepsy ($p = 0.020$). Contrary to previous reports,[33,34] however, patients with FDS were younger at seizure onset than those with syncope or epilepsy. The ROC curve for age at onset as diagnostic of FDS had an AUC of 0.865 (0.771-0.960) (see Figure 3.2.1(a)); an optimal cut-off of age at onset<30y yielded sensitivity for FDS of 0.750 and specificity of 0.846.

Total historical symptom count on the PESQ differed significantly across all diagnoses ($p < 0.001$), and between FDS and epilepsy ($p = 0.001$), and syncope ($p < 0.001$). AUC for total

historical symptom count was 0.834 (0.730-0.928), a cut-off of 6 or more symptoms reported having sensitivity 0.750 and specificity 0.720 for FDS. See Figure 3.2.1(b).

Total number of peri-ictal symptoms endorsed on the PESQ also predicted FDS, differing between groups ($p$<0.001), and between both FDS and epilepsy ($p$<0.001) and syncope ($p$<0.001). AUC for total peri-ictal symptoms reported was 0.864 (0.781-0.948). 9 or more reported symptoms predicted FDS with sensitivity 0.920 and specificity 0.720. See Figure 3.2.1(c).

We present full details of these analyses in the Supplementary Worksheet.

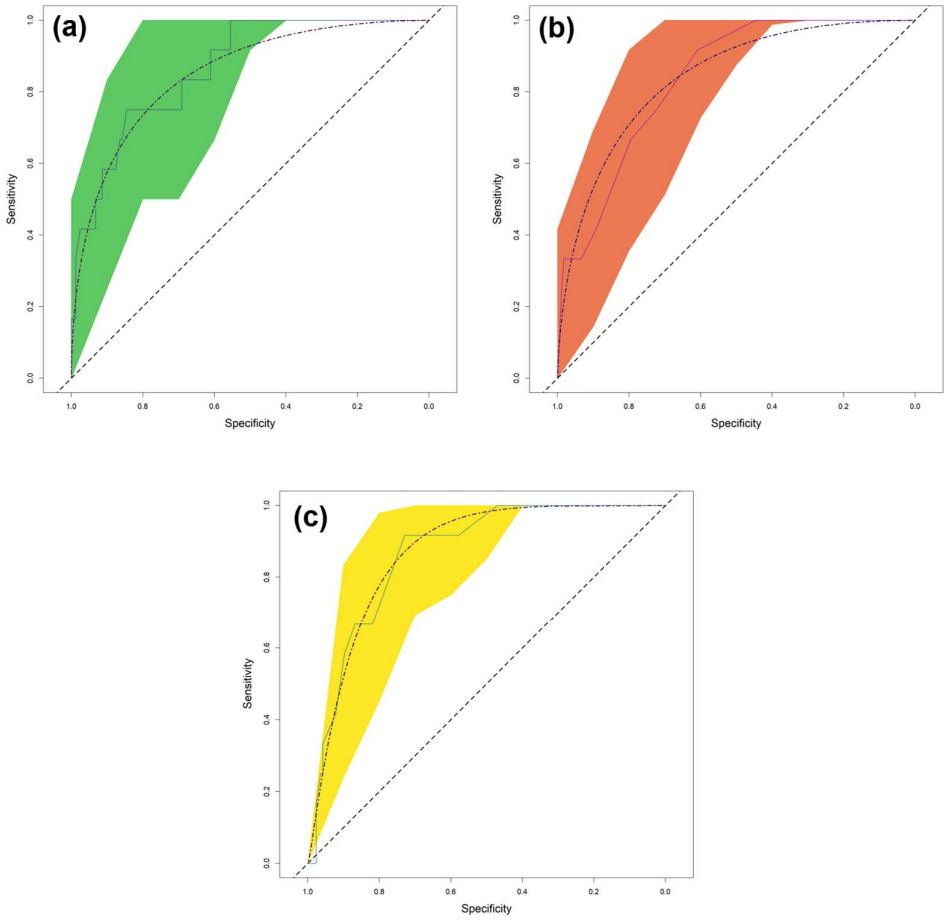


*Figure 3.2.1. Receiver-operating characteristic (ROC) curves for the diagnosis of functional/dissociative seizures (FDS) for: (a) age at seizure onset; (b) number of historical symptoms endorsed on review-of-symptoms questionnaire; and (c) number of peri-ictal symptoms endorsed on seizure experiences questionnaire. The continuous line represents the empirical ROC curve, the dotted line the smoothed curve, and the coloured shape the 95% confidence space for sensitivity.*

## Classifiers

### *Dissociative seizures likelihood score (DSLS)*

The DSLS provides an estimate of the probability of a patient having either epileptic seizures or dissociative seizures.[24] As such, data from only the 44 participants with diagnoses of either epilepsy or dissociative seizures could be used for this validation. Of those 44 participants, only 15 had identified a witness providing definite answers to all semiological questions included in

the DSLS. Therefore we provide two estimates of DSLS performance: an evaluation based only on the 15 participants with full witness reports available ('no witness-excluded'); and, where limited witness information was extracted from the clinical record assuming that if the witness did not positively identify the presence of a semiological feature, then it was absent ('no witness-negative').

In 'no witness-excluded' validation, the DSLS classified 53.3% of participants accurately, with sensitivity and specificity for FDS of 0.750 and 0.455 respectively. In 'no witness-negative' validation, the DSLS classified 65.9% accurately, with sensitivity and specificity 0.833 and 0.594 respectively.

*Initial Paroxysmal Event Profile (iPEP) classifier*

Previous iterations of the iPEP classifier provided diagnostic classifications of likely FDS, epilepsy, or syncope both on the basis of witness and patient questionnaires ('witness-patient') and patient questionnaires alone ('patient-only'). However, as no participant with FDS identified a witness able to complete the full witness questionnaire, we had to limit our validation to the performance of the patient-only questionnaire here. We calibrated the classifier on the first 100 participants, and treated the remaining 78 as the validation sample. In validation, the patient-only iPEP classifier identified diagnoses with overall accuracy of 0.758 (95% CI 0.688 – 0.818). Table 3.2.4 summarises diagnostic test statistics for each diagnosis.

| | Diagnostic test statistics (95% confidence interval) | | | |
|---|---|---|---|---|
| | **Sensitivity** | **Specificity** | **PPV** | **NPV** |
| **Syncope** | 0.858 (0.785-0.910) | 0.568 (0.411-0.713) | 0.858 (0.785-0.910) | 0.568 (0.411-0.713) |
| **Epilepsy** | 0.375 (0.217-0.563) | 0.986 (0.946-0.998) | 0.857 (0.562-0.975) | 0.878 (0.815-0.922) |
| **FDS** | 0.667 (0.354-0.887) | 0.867 (0.804-0.913) | 0.267 (0.130-0.461) | 0.972 (0.928-0.991) |

*Table 3.2.4. Summary of diagnostic test statistics in validation for the iPEP classifier.*

## 3.2.4. Discussion

This is the first study to our knowledge that has attempted to validate variables previously found to support a diagnosis of FDS in the cohort to whom they are most relevant – those with a first presentation of TLOC. In our study, the majority of variables previously cited as diagnostic features of FDS in cohorts of patients with established and video EEG-proven diagnoses were less strongly associated with FDS, or even had an association in the opposite direction. Our study fails to demonstrate the ecological validity of diagnostic studies for FDS conducted only in patients with a long history of seizure disorder or video-EEG proven diagnoses, when generalised to other settings. Since many people with FDS will never have a seizure captured on EEG (only 53% participants had video-EEG confirmed diagnoses in the recent CODES trial,[35] while this number is estimated at just 2% in lower-income countries[36]), this demonstrates a need for more work in the first presentation setting to support earlier, more accurate identification of FDS.

Furthermore, of the categorical variables we tested, the only ones that differed significantly between FDS and the other TLOC presentations were witness-reported semiology. Given the majority of our participants did not identify a witness able to report reliably on seizure semiology, this further underscores the challenge faced, and highlights the need for new techniques or approaches to TLOC differential diagnosis. In particular, improved methods are needed: to capture witness descriptions (e.g. via enhanced point-of-assessment history taking by paramedics or first responders, who may be able to elicit bystander accounts that are no longer reachable after first contact); and to maximise the utility of other information that is available at first assessment (such as subjective experience, medical history, clinical

examination, and first-line primary care investigations). Importantly, these methods should be assessed and validated in first-presentation patient cohorts to ensure their ecological validity at the point of initial diagnosis.

While age at onset did predict FDS diagnosis, this was in the opposite direction from that identified in previous cohorts, where FDS had older age at onset. This demonstrates the importance of validating diagnostic features in the patient cohorts and healthcare settings to which they will be applied. Previous studies have examined patients with established diagnoses, and overwhelmingly in epilepsy centres. Therefore syncope (which is more common in older patients) is underrepresented, and those with childhood-onset epilepsy are highly represented. This latter group are unlikely to present in adulthood with a first episode of TLOC, and as such are less relevant to the initial diagnosis of FDS in adult patients.

Our results also offer support for some hypotheses regarding the pathophysiology of FDS. We found that individuals with FDS had a higher self-reported peri-ictal symptom count (suggesting greater subjective ictal awareness), and were more likely to have witness-reported preserved social responsiveness, than those presenting with other causes of TLOC. This underscores the importance of interrogating the nature of the disturbance of consciousness in TLOC presentations, as 'consciousness' may be less profoundly disrupted in FDS than in patients with epilepsy or syncope.[3,28] Such phenomenological and semiological interrogation of consciousness in FDS complements other research seeking to understand its psychology (e.g. dissociation or emotional dysregulation),[4,5] physiology (e.g. ictal EEG),[37] and neuroanatomy (e.g. through imaging studies).[38,39]

Multiple existing diagnostic scores use symptom endorsement on ROS questionnaires or number of non-seizure comorbidities as diagnostic of FDS.[23,24,40] We also found that those with FDS reported more historical non-ictal symptoms on the PESQ. It has been hypothesised that higher rates of somatisation[41] may lead to increased numbers of self-reported physical comorbidities,[42] and impaired interoceptive awareness[43] may lead to interpretation of emotional responses through their somatic consequences.

#### *3.2.4.1. Limitations*

Our evaluation of the diagnostic value of the variables and models assessed must be read with the caveat that our reference standard diagnosis – two-independent expert-rater review – does not meet the gold standard for any of our differential diagnoses. The diagnoses of FDS were largely only 'probable' or 'clinically established' according to ILAE criteria.[44] However, given this reflects the reality of care for people with seizure disorders around the world,[36,45] our pragmatic reference standard is justified in order to secure a more representative sample than that obtained purely from those with gold-standard diagnoses.

Our sample also contained a low absolute number of participants with FDS, and as such there are wide CIs on the sensitivity estimates for diagnostic features. While the low number of FDS patients may have failed to capture some modes of presentation of a heterogeneous disorder, this is not only a weakness: it also gave us a more representative estimate of the prevalence of FDS in first-presentation TLOC populations. This means that estimates of diagnostic test statistics such as PPV and NPV that depend on prevalence are likely to be more valid if they are based on real-world samples than on artificially balanced patient cohorts reported elsewhere. As demonstrated by our illustrative sample size calculations, we would have expected to capture a statistically significant difference in this study for variables with a large-magnitude

population difference between FDS and other diagnoses; however, this study was not powered sufficiently to detect subtle differences in frequencies of reporting for all variables of interest.

Our data also did not allow for fine-grained distinction regarding the precise characterisation of certain variables (e.g. eye-closure or post-ictal breathing pattern) where the specific nature of the sign or its timing has been suggested to be of diagnostic utility.[31,32,46,47] Capturing these subtler details in first TLOC presentations may require educating primary and emergency care clinicians on history-taking to support accurate diagnosis.

A minority of our participants had good-quality witness reports available, despite clinical follow-up and requests for research participants to identify a witness to complete a specific questionnaire. Our conclusions regarding witness-reported semiology are thus limited by this reduced sample size. It also highlights a significant problem in clinical practice, and a priority for further research – identifying means to support better extraction of witness reports for first TLOC presentations.

We were not able to extract reliable reporting of all potentially-relevant variables from our existing data, either because it was not reliably recorded in clinical documentation, or we had deliberately elected to exclude from our patient questionnaires. Therefore we cannot comment on the value of trauma history or post-ictal breathing pattern to support a diagnosis of FDS in the first presentation.

## 3.2.5. Conclusions

Despite these limitations, our analysis allows us to conclude that there are clinical features which should help clinicians with the differential diagnosis when adults first present with TLOC. However, our study does not find support for the diagnostic value of many features found to be discriminatory in patients with more chronic TLOC disorders. Future studies should seek to combine the features described here with better data from witnesses and other clinical parameters available at the time of first presentation with TLOC to provide clinicians with more reliable clinical decision aids when initial TLOC diagnoses are formulated.

## 3.2.6. Funding

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# Section 4 Development of a clinical decision aid for the differential diagnosis of transient loss of consciousness

## 4.0. Section abstract

This section documents the piloting, development, internal validation, and acceptability assessment for a patient-completed clinical decision aid (CDA) for the differential diagnosis of transient loss of consciousness (TLOC). §4.1 describes the pilot and feasibility study of using patient and witness questionnaire answers combined with machine learning techniques to support differential diagnosis. §4.2 applies this method to a prospectively-recruited cohort of patients with a first presentation of TLOC, describing the development, internal validation, and comparison to the current standard of care of a patient-completed CDA. §4.3 complements this with qualitative assessment of patients' experiences of using the CDA.

### Machine learning as a diagnostic decision aid for patients with transient loss of consciousness

(Note for readers: At the time of publication of this manuscript, the ILAE-recommended terminology for FDS was psychogenic nonepileptic seizures [PNES]; hence this manuscript employs that term. It can be considered in this context as interchangeable with FDS).

**BACKGROUND**: Transient loss of consciousness (TLOC) is a common reason for presentation to primary/emergency care; over 90% are due to epilepsy, syncope, or psychogenic non-epileptic seizures (PNES). Misdiagnoses are common and there are currently no validated decision rules to aid diagnosis and management**.** We seek to explore the utility of machine-learning techniques to develop a short diagnostic instrument by extracting features with optimal discriminatory value from responses to detailed questionnaires about TLOC manifestations and comorbidities (86 questions to patients, 31 to TLOC witnesses).
**METHODS:** Multi-centre retrospective self- and witness-report questionnaire study in secondary care settings. Feature selection by iterative algorithm based on random forest analysis. Data randomly divided in 2:1 ratio into training and validation sets (163:86 for all data; 208:92 for analysis excluding witness reports).
**RESULTS:** 300 patients with proven diagnoses (100 each: epilepsy, syncope and PNES) recruited from epilepsy and syncope services. 249 completed patient and witness questionnaires: 86 epilepsy (64 female), 84 PNES (61 female), 79 syncope (59 female). Responses to 36 questions optimally predicted diagnoses. A classifier trained on these features classified 74/86 (86.0% [95% CI 76.9-92.6%]) of patients correctly in validation (100[86.7-100]% syncope, 85.7[67.3-96.0]% epilepsy, 75.0[56.6-88.5]% PNES). Excluding witness reports, 34 features provided optimal prediction (classifier accuracy of 72/92 (78.3[68.4-86.2]%) in validation,83.8[68.0-93.8]% syncope, 81.5[61.9-93.7]% epilepsy, 67.9[47.7-84.1]% PNES]).
**CONCLUSIONS:** A tool based on patient symptoms/comorbidities and witness reports separates well between syncope and other common causes of TLOC. It can help to differentiate epilepsy and PNES. Validated decision rules may improve diagnostic processes and reduce misdiagnosis rates.

## Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

**OBJECTIVE:** To develop and validate a machine learning classifier based on patient and witness questionnaires to support differential diagnosis of transient loss of consciousness (TLOC) at first presentation.
**METHODS:** We prospectively recruited patients newly presenting with TLOC to an Emergency Department (ED), Acute Medical Unit (AMU), first seizure or syncope clinic. We invited participants to complete an online questionnaire, either at home or at time of initial assessment. Two expert raters determined cause of participants' TLOC after 6-month follow-up. We used independent development and validation samples to train a random forest classifier to predict diagnosis from participants' questionnaire responses, and validate classifier performance. We compared classifier performance against penalised linear regression and referrer diagnosis.
**RESULTS:** We included 178 participants in the final analysis, of whom 46 identified a witness able to complete an additional witness questionnaire. Given low witness recruitment, we developed a classifier based on patient answers only. A classifier trained on 9 items correctly identified 63/78 (80.8%) (95% CI 70.0 - 88.5) of diagnoses, an increase over the accuracy of initially-assessing clinicians who were only able to diagnose 70.5% correctly. Within this, 96% (87.0 – 99.4%) of those expertly-rated as having syncope were correctly classified by the classifier (classifier sensitivity); 40% (20 – 63.6%) of those expertly-rated after follow-up as having either epilepsy or FDS were similarly classified as being non-syncope (classifier specificity).
**CONCLUSION:** A machine learning classifier for differential diagnosis of TLOC has comparable performance in differentiating between three main causes of primary TLOC as the current standard of care, but is insufficiently accurate in its current form to warrant incorporation into routine care. A system including information from witnesses might improve classification performance.

## Acceptability and utility of an online patient-completed clinical decision aid for the differential diagnosis of transient loss of consciousness: a qualitative interview study

**BACKGROUND:** Online patient-completed clinical decision aids (CDAs) have the potential to reduce inefficient resource use and patient risk in acute and emergency settings while minimising additional clinician time burden. However, such interventions must be acceptable for use by their target audience - patients.
**OBJECTIVE:** To assess acceptability and utility to patients of a novel online patient-completed CDA for the differential diagnosis of transient loss of consciousness (TLOC).
**METHODS:** Within a larger validation study of a patient-completed CDA, we conducted nested qualitative semi-structured interviews with a purposive sample of 20 patients who used the CDA in the study, and performed thematic analysis of interview transcripts.
**RESULTS:** We identified 10 themes within the data: 3 addressing the content of the CDA; 3 addressing the online implementation; and 4 addressing usability and acceptability of the CDA. Respondents generally felt an online CDA was easy to complete and acceptable, though felt that increased options to personalise descriptions of their experience would be helpful, and offered guidance on how to make it a more useful resource for patients as well as clinicians. We present good practice points for the design of patient-completed online CDAs on the basis of

our thematic analysis.
**CONCLUSIONS:** Patient-completed CDAs can be accessible and feasible for patients to use in acute and emergency settings. In designing such tools, clinicians should endeavour to maintain their accessibility for all relevant patient groups, and to utilise them to provide direct patient benefit, as well as to support clinical decision-making, e.g. through simultaneous patient-directed outputs.

# 4.1. Machine learning as a diagnostic decision aid for patients with transient loss of consciousness

## 4.1.1. Background

Transient loss of consciousness (TLOC) – impairment of consciousness with real or apparent loss of awareness, amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration, with full spontaneous recovery, not due to head trauma[1,2] – is a common presenting complaint, accounting for 3% of UK Emergency Department (ED) attendances.[3] Estimated lifetime prevalence is 50%.[4] Over 90% are explained by one of three aetiologies: syncope, epilepsy, and psychogenic non-epileptic seizures (PNES). Diagnosis can be difficult as most patients are asymptomatic with no examination abnormalities by the time they are assessed by a clinician.[3,5] Inter-ictal investigations are often uninformative or misleading.[5,6] Individual features in a patient's history or witness descriptions (*e.g.* acquisition of ictal injuries or apparent occurrence from sleep) have been shown to distinguish between syncope and tonic-clonic seizures, but their ability to distinguish between the common diagnoses in unselected patient populations (including those with PNES or other types of epileptic seizures causing impaired consciousness) is unproven.[7,8] Misdiagnoses are common, with estimates ranging from 25-42%. [9–11] Correct diagnoses, especially of PNES, are often delayed by several years.[12] Diagnostic errors put patients at risk of iatrogenic injury and death.[12,13]

Despite low sensitivity or specificity of individual clinical features in the differential diagnosis of TLOC, clusters of such features can discriminate between syncope, epilepsy, and PNES.[8,14–17] The use of such clusters can be operationalised via clinical decision rules (CDRs) that quantify the contribution of different features to a pre-defined clinical threshold and provide criteria for different courses of action. Correctly employed in the appropriate setting, CDRs can improve clinical decision-making.[18] While candidate CDRs for the diagnosis of TLOC have been suggested,[16] none is endorsed in current management guidelines.[4] Guidelines do, however, exist for risk stratification and management of syncope and seizures on first presentation,[2,4] highlighting the importance for clinicians of reaching a working initial diagnosis for appropriate triage and ongoing management. There are a considerable range of candidate clinical features to discriminate between causes, but prospective validation of most is lacking.[19] A CDR appropriate for use in primary care or ED settings would require a modest number of features jointly to discriminate between common diagnoses with a sufficient level of accuracy. We previously demonstrated that comprehensive TLOC symptom or witness observation profiles (captured by the 86-item Paroxysmal Event Profile, PEP, and the 31-item Paroxysmal Event Observer Questionnaire, PEO) could separate with a high level of accuracy between the three commonest causes of TLOC.[14,20]

One challenge in developing a CDR for TLOC is that simple scores assume features combine linearly – that a given clinical feature counts for or against a given diagnosis to the same degree irrespective of the presence/absence of other features. However, clinicians working with patients who experience TLOC will interpret features very differently depending on what others are also present (for example, pre-ictal palpitations when accompanied by pallor and sweating may suggest syncope, but point to PNES when associated with a fear of dying). Such non-linear combinations are hard to incorporate into simple scoring rules but are easily handled by automated classifiers. A range of such tools is available in the machine learning literature, and

previous work demonstrates their applicability to differentiating between causes of TLOC.[15] While the more complex decision rules used by such classifiers require computer-based implementation, in an era of widespread smartphone availability and increasing use of electronic patient records, this should not present a barrier to implementation. Indeed, such computerised tools are widely used for other clinical problems in both primary care (e.g. QRISK[21]) and emergency (e.g. NELA[22] and P-POSSUM[23]) settings.

The purpose of the present study is to identify a manageable set of features suitable for a CDR for patients first presenting with TLOC. and to evaluate the diagnostic performance of a classifier trained on these features. We perform this both for clinical scenarios in which a TLOC observer can provide witness information and for presentations in which TLOC occurred unobserved. The identification of a modest subset of diagnostic features from the extensive PEP and PEO questionnaires would help future development and validation of a CDR for TLOC in primary and emergency care settings.

## 4.1.2. Methods

### *4.1.2.1. Primary research question*

We sought to determine whether a questionnaire based on witness and symptom reports of TLOC could be used to train a diagnostic classifier that could reliably distinguish between epilepsy, syncope, and PNES.

### *4.1.2.2. Patient recruitment*

This study is based on data previously used to explore the discriminatory potential of TLOC symptom and witness observation profiles.[14,20] Patients with diagnoses of epilepsy or documented PNES[24] were identified from the clinical databases of the Department of Clinical Neurophysiology, Royal Hallamshire Hospital in Sheffield, UK, and the National Hospital of Neurology and Neurosurgery in London, UK. Typical episodes involving TLOC had been captured in all participants by video-EEG. Clinical diagnoses were made by a neurologist with a particular interest in seizure disorders and based on video-EEG findings as well as all other available clinical data. Some patients with syncope were identified from the same sources, but most had been diagnosed by the Falls and Syncope Service, Newcastle upon Tyne, UK. All diagnoses were made by experts, supported by pathophysiological evidence (e.g. tilt-table testing results consistent with the diagnosis, or syncopal or presyncopal symptoms co-occurring with explanatory ECG or blood pressure changes). We have given further details on recruitment method and formulation of 'gold standard' diagnoses previously.[14]

From 2004-2009 we approached patients ≥16 years old with TLOC and a confirmed diagnosis of epilepsy, syncope, or PNES by post until we had received 100 completed questionnaires for each group. We asked participants to identify an observer of their events and ask them to complete and return a questionnaire about witness-observable TLOC manifestations.

### *4.1.2.3. Sample size*

Neither our research question nor our proposed method of data analysis (see below) straightforwardly permit sample size calculations. Given the large number of potential predictor variables, we use methods designed for analysis of small-*n* large-*p* datasets (sample size $n$ <<< number of predictor variables $p$) that demonstrate robust performance with smaller sample sizes and more predictors than in our dataset.[25]

#### *4.1.2.4. Questionnaires*

##### Clinical and demographic features

Patients were asked to provide information about basic demographic features (age, sex), family history of blackouts, and 17 selected common cardiovascular or neurological comorbidities.

##### Paroxysmal Event Profile (PEP)

We asked patients to report the presence or absence of peri-episodal symptoms using the PEP, an 86-item questionnaire describing frequency of symptoms on a 5-point Likert scale ('always' to 'never'). Construction, content, and diagnostic contribution of the PEP are described elsewhere.[14]

##### Paroxysmal Event Observer (PEO) questionnaire

We asked witnesses to describe episodes using the PEO questionnaire. The PEO includes questions on duration of witness' acquaintance with the patient and number of witnessed episodes, followed by 31 observable episode manifestations classified on a 5-point ('always' to 'never') Likert scale. Construction, content, and diagnostic contribution of the PEO are described elsewhere.[20]

#### *4.1.2.5. Statistical analysis*

To reflect the likelihood of many patients presenting with TLOC only having experienced one or very few episodes, we recoded Likert-scale frequency responses used in the PEP and PEO into binary 'ever' ('always', 'sometimes', 'frequently', 'rarely') or 'never' ('never') responses. We excluded questionnaire responses for items that would be unintelligible at first seizure presentation (e.g. age at onset, previous hospitalisations due to episodes), and also excluded age as we recruited syncope patients from a healthcare setting primarily attracting older adults.[14] We then randomly assigned respondents to training and validation datasets in a 2:1 ratio.[a]

For variable reduction, we utilised a technique recommended in consensus guidance on CDR construction,[26] ensemble bootstrap-aggregation (using ensembles of classification trees, AKA a 'random forest', RF).[27] We employed an iterative algorithm designed for small-*n* large-*p* genomics datasets based on RFs.[28] Decision trees provide an easily-interpretable supervised learning method for classification problems, but fitting algorithms tend to be unstable in their selection of variables in large-*p* datasets.[28] Constructing ensembles of trees using bootstrap sampling and aggregation improves performance significantly.[27] For feature selection, we trained a RF of 1000 trees (allowing all predictors to be sampled at each node split to improve discrimination between variables)[25] and ranked predictor importance by increase in out-of-bag prediction error with permutation of predictor values. We then trained progressively smaller RFs by removing the least-important 20% of predictors at each step, and calculated the out-of-bag error for each RF. The selected set of variables is that which minimises the out-of-bag error ('0 standard error (s.e.) rule'). We performed this procedure twice: once using history, symptom, and witness report data ("witness-patient", reflecting scenarios in which a TLOC patient presents with an observer of the event); and once using only history and symptoms ("patient-only", to reflect scenarios in which no such observer is available). To evaluate predictive performance of the reduced-dimension model, we used the resulting RFs to classify patients in

[a] Using a sequence $S = \{s_1,...s_N\}$ of $N$ pseudo-random numbers [Mersenne Twister, seed=0] with uniform distribution over the real-number interval [0,1]; $n^{th}$ patient assigned to training group iff $s_n \leq 2/3$, otherwise assigned to validation.

the validation sample into diagnoses of epilepsy, syncope, or PNES, and compared these to reference standard diagnoses.

All analysis was performed using MATLAB R2017b with Statistics and Machine Learning Toolbox (The MathWorks; Natick, MA). All code, including RF classifiers, is available from the authors on request.

#### *4.1.2.6. Standard Protocol Approvals, Registrations, and Patient Consents*

Ethical approval for this study was granted by the Northern and Yorkshire Multi-Centre Research Ethics Committee.

Invitations, information sheets, and questionnaires were sent to potential participants as previously described,[14] with specific information that return of completed questionnaires would be interpreted as consent to participate.

#### *4.1.2.7. Data availability*

All data and statistical analyses are available from the authors on request.

### 4.1.3. Results

#### *4.1.3.1. Descriptive analysis*

300 respondents returned PEP questionnaires (219 female), 100 with each diagnosis. Of these, 249 also returned PEO (witness) questionnaires: 86 (64 female) had diagnoses of epilepsy, 84 PNES (61 female), and 79 syncope (59 female). The demographic characteristics of this subpopulation are similar to those of the whole study sample reported previously.[14,20] Further details of between-group differences on individual PEP and PEO items are described elsewhere.[14,20]

For patient-only analysis the training group comprised 208 participants (73 epilepsy, 72 PNES, 63 syncope), of whom 149 were female, with the remaining participants assigned to validation. For witness/patient, the training group comprised 163 participants (58 epilepsy, 52 PNES, 53 syncope), of whom 114 were female; the validation group comprised the remainder.

Although 96.3% of questionnaire items were answered by respondents, 104/249 (41.8%) of participants had at least one missing value in their responses. RF analysis with surrogate splitting is robust to missing values.[27]

#### *4.1.3.2. Feature selection*

##### Witness/patient

RF-based iterative feature selection identified 36 features that were jointly predictive of diagnosis (Figure 4.1.1). These included: six historical or non-ictal complaints (35.3% of historical features inquired about); 20 peri-ictal symptoms (23.3% of PEP items); and 10 witness-reported signs (29.4% of PEO items). Relative importance of selected predictors is shown in Figure 4.1.3(a).

##### Patient-only

Feature selection identified 34 features (Figure 4.1.2): eight historical (47.1% of history questionnaire features) and 26 peri-ictal symptoms (30.2% PEP items). Relative importance is shown in Figure 4.1.3(b).

## 4.1. Machine learning as a diagnostic decision aid for patients with transient loss of consciousness

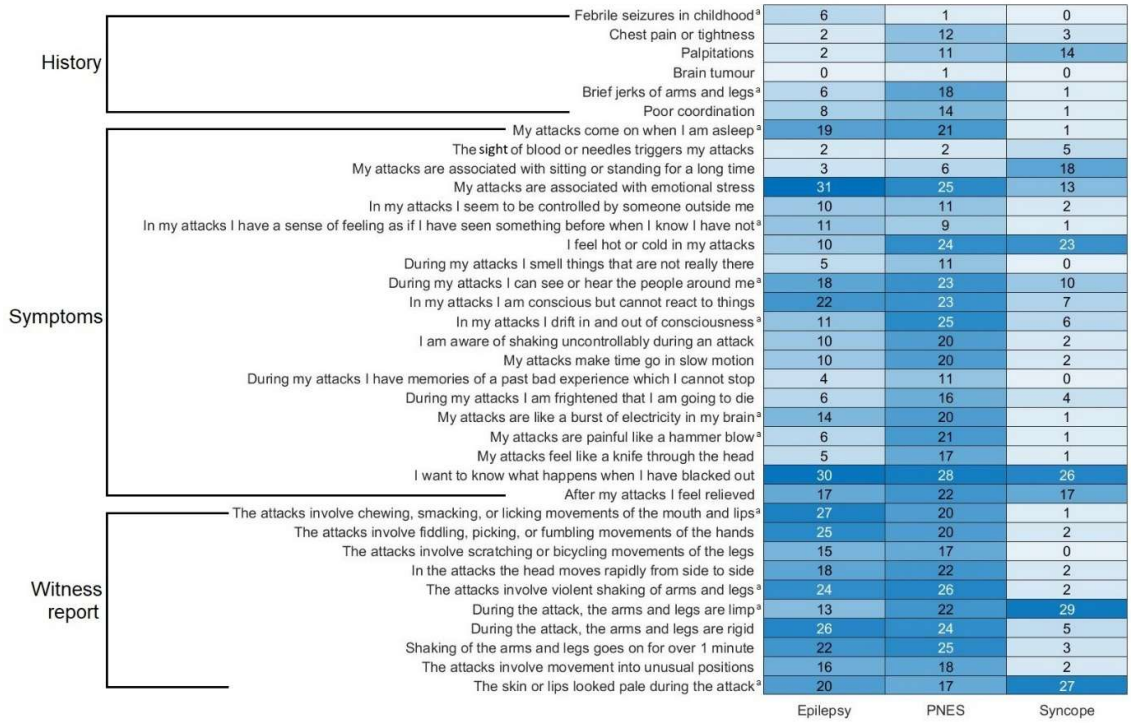


*Figure 4.1.1. Features selected from patient and witness report data (N=249). Counts display percentage of patients reporting each feature by diagnosis. A darker colour indicates higher percentage reporting the feature as present.*

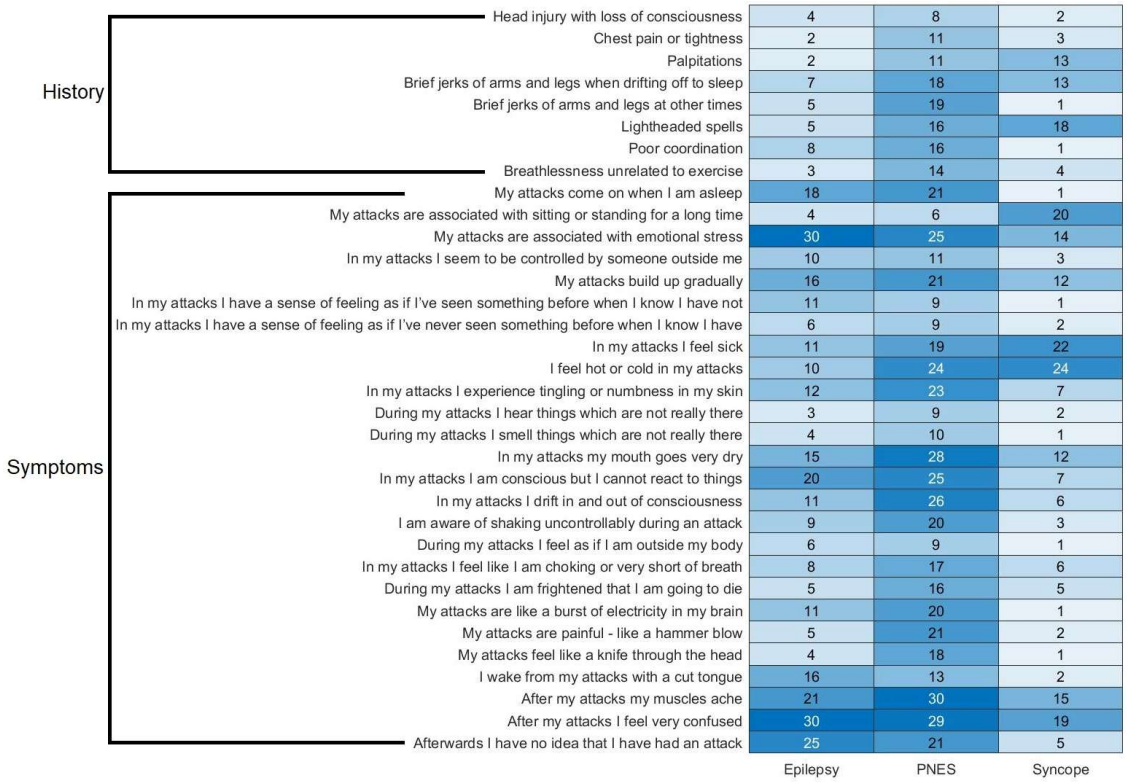


*Figure 4.1.2. Features selected using only patient reports (N=300). Counts display percentage of patients reporting each feature by diagnosis. A darker colour indicates higher percentage reporting the feature as present.*

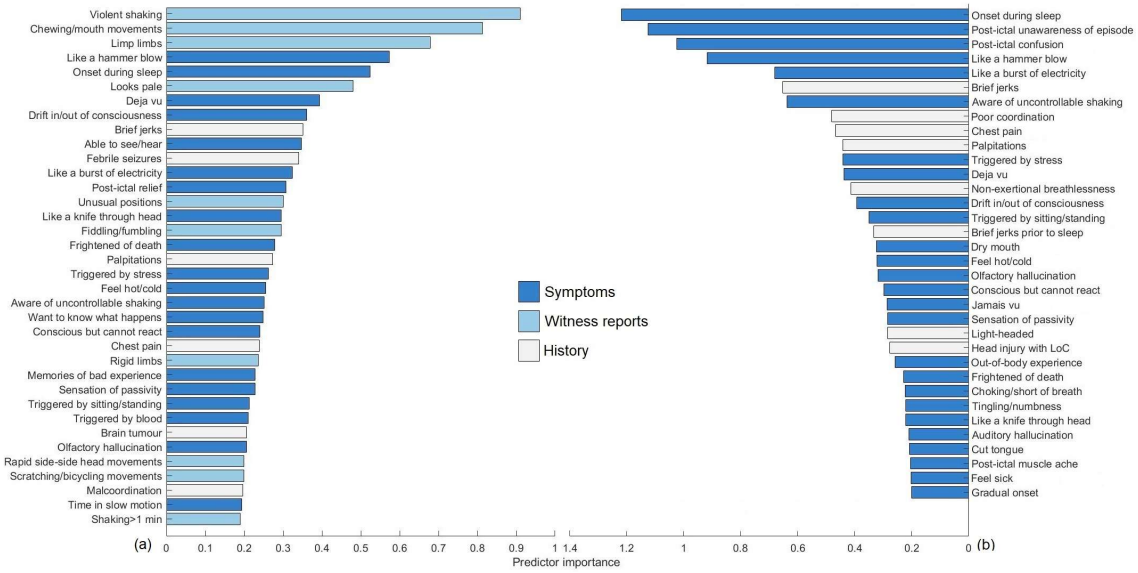


*Figure 4.1.3. Predictor importance (relative change in classification error with predictor permutation) for witness and patient data (a) and patient-only (b).*

### *4.1.3.3. Predictor performance on validation sample*

#### Witness/patient

The 36-feature RF classified 74/86 (86.0%; 95% CI 76.9-92.6%) of patients in the validation sample correctly. 100% of syncope diagnoses were identified correctly, 85.7% epilepsy and 75.0% PNES. Full predictor performance by diagnosis is summarised in Table 4.1.1. Of patients who were incorrectly classified, equal numbers of patients with epilepsy were classified as syncope or PNES, while slightly more patients with PNES were classified as epilepsy than syncope (see Table 4.1.2).

| | | Epilepsy | PNES | Syncope |
|---|---|---|---|---|
| Witness + patient | Sensitivity (%) | 85.7 (67.3-96.0) | 75 (56.6-88.5) | 100 (86.7-100) |
| | Specificity (%) | 91.4 (81.0-97.1) | 96.3 (87.3-100) | 91.7 (81.6-97.2) |
| Patient only | Sensitivity (%) | 81.5 (61.9-93.7) | 67.9 (47.7-84.1) | 83.8 (68.0-93.8) |
| | Specificity (%) | 80.0 (68.2-88.9) | 93.8 (84.8-98.3) | 94.5 (84.9-98.9) |

*Table 4.1.1. Predictor performance of RF models (with 95% CIs) by reference diagnosis for witness-patient (N=86) and patient-only (N=92) classifiers (see text for definition of groups). Terms are defined as follows, where TP = true positives, FP = false positives, TN = true negatives, FN = false negatives: sensitivity = TP/(TP+FN); specificity = TN/(FP+TN).*

| | | | Reference standard diagnosis | | |
|---|---|---|---|---|---|
| | | | Epilepsy | PNES | Syncope |
| RF classifier prediction | Witness +patient | Epilepsy | 24 | 5 | 0 |
| | | PNES | 2 | 24 | 0 |
| | | Syncope | 2 | 3 | 26 |
| | Patient only | Epilepsy | 22 | 8 | 5 |
| | | PNES | 3 | 19 | 1 |
| | | Syncope | 2 | 1 | 31 |

*Table 4.1.2. Validation set misclassifications by diagnosis for witness-patient. Cell counts represent number of patients assigned to each diagnostic group by reference standard diagnosis.*

### Patient-only

The 34-feature RF classified 72/92 (78.3%; 95% CI 68.4-86.2%) of patients in the validation sample correctly (83.8% syncope, 81.5% epilepsy, 67.9% PNES). See Table 4.1.1 for summary of predictor performance by diagnosis. Of patients who were incorrectly classified, both PNES and syncope patients were more commonly classified as epilepsy than the alternative, while one more epilepsy patient was classified as having PNES than syncope (see Table 4.1.2).

#### *4.1.3.4. Comparison of classifiers and sensitivity analysis*

### Comparison to regression-based classification

We compared performance of the witness/patient RF against a multinomial logistic regression model that used the 36 predictors selected in our witness/patient variable reduction procedure. The RF outperformed the regression model (classification accuracy 77.9% v 86.0%; McNemar's test for difference in performance $p = 0.096$). We provide further details in Supplementary Analyses (§4.1.7.1).

### Sensitivity analysis

We report post-hoc sensitivity analyses of the effects of selected witness and patient variables on classifier accuracy in the Supplementary Analyses (§4.1.7.2). Duration of witness acquaintance, number of events witnessed influenced, and time since onset of blackouts did not effect classifier accuracy. We found an association between number of events in the past year and classifier accuracy, which may be a consequence of the over-representation of PNES amongst participants reporting higher frequency of events.

## 4.1.4. Discussion and limitations

Our results demonstrate that, when both patient and witness reports are available, a CDR with a modest number of questions distinguishes very well between syncope and the two types of seizures. Pending validation, such a tool could be usefully employed in the ED or primary care to direct patients to either cardiological or neurological investigation and referral. The CDR also provides some guidance for differentiating epilepsy from PNES. Previous studies suggest that questions about other domains (for instance previous trauma, coping styles, current psychopathology) could improve the discrimination between epilepsy and PNES;[19] however, the inclusion of such questions might reduce patient acceptability of the CDR.[15,29,30]

The reduction in performance seen with patient-only classification emphasises the clinical importance of the collateral history. Included witness report features corresponded to semiological features previously used in the differential diagnosis of TLOC;[31] assessment of these features in witness reports thus remains clinically valuable, despite the fact that when considered individually, untrained observers may not report their presence reliably.[7,32]

### 4.1. Machine learning as a diagnostic decision aid for patients with transient loss of consciousness

Automated classification using RFs successfully reduces number of predictor variables without sacrificing accuracy. Our RF classifier improved upon classification accuracy relative to regression-based methods using all features, even using a separate validation sample to control for overfitting.[20] This may be due to the ability of machine learning methods such as RFs to exploit non-linear interactions between predictors.[15] The importance of non-linear interactions to RF classification can explain some apparently anomalous divergences between features selected by our witness-patient and patient-only classifiers, for example that post-ictal unawareness or confusion are important features in the patient-only classifier but not selected in the witness-patient classifier. This suggests that, when no witness data is available, these features contribute importantly to diagnosis, but in combination with information available from witnesses, other features become relatively more important.

Several previous attempts have been made to derive CDRs for diagnosis of TLOC although, to date these have concentrated on the simpler problem of binary classification, as opposed to our three category approach which provides a finer classification. Direct performance comparison against these previous published offerings is therefore difficult; however, our results are largely consistent while offering notable theoretical and practical advantages. Our 36-feature RF includes all items of the 9-point regression-based CDR presented by Sheldon *et al*.[16] except episodal diaphoresis (the PEP does not include pre-episodal sweating; post-episodal sweating had a negative predictor importance score on our analysis, indicating a negative contribution to correct classification). Sheldon *et al.* claim 94% sensitivity and specificity for the distinction between syncope and epilepsy (86.5% sensitivity and 92.1% specificity in independent prospective validation),[33] but their CDR does not discriminate between epilepsy and PNES, their epilepsy group only included tonic-clonic seizures and diagnoses in their study were not supported by objective findings during typical episodes. These limitations also apply to Hoefnagels *et al.*'s 4-feature regression-based score,[34] which includes age as a predictor (we could not include age in our analysis due to sampling bias, as discussed further below). While our classifier was less successful in distinguishing epilepsy and PNES than syncope from either, results are comparable to those of Syed *et al.* who used a similar variable-reduction followed by machine-learning classification to use 53 questionnaire items to distinguish PNES from epilepsy with a sensitivity of 85-94% and specificity of 83-85%: more sensitive but less specific than ours (though their analysis included no syncope group).[15] Their classifier included more extensive demographic details and a range of psychosocial variables, suggesting the potential for further improvement of performance through consideration of other non-historical variables.

Our feature selection identified important contributions to differential diagnosis from patient symptoms, past medical history, and witness reports. Consistent with previous reports, PNES patients endorsed a higher number of comorbid complaints.[35,36] The classifiers included several features suggesting a greater preservation or fluctuating level of ictal consciousness in PNES patients than those with epilepsy, consistent with previous reports of post-event recall of ictal events and quantitative studies of ictal impairment of consciousness in epilepsy and PNES.[37–39] Both classifiers highlighted the relevance of ictal panic and dissociative symptoms to identifying PNES, an association previously identified.[14,40,41] Reported onset during sleep contributed to diagnosis in the symptoms-only model, being predictive of both epilepsy and PNES. This observation might be considered surprising given differences in sleep patterns between epilepsy and PNES;[42] however, while onset during EEG-confirmed sleep is highly predictive of epilepsy, onset from sleep-like states ('pre-ictal pseudosleep') is common in PNES.[31] Given our

focus on original presentation, distinguishing between such states may be of limited value in this context,[43] though potentially of importance in ongoing management.[42]

We stress the difference between diagnostic triage and risk stratification tools. Our CDR provides the former, and may help to enable non-expert clinicians to consider whether a cardiological or neurological diagnosis is more likely and so direct investigations and referral appropriately. Each of our diagnostic classes are, however, heterogeneous, and clinicians need to consider underlying aetiology and risk stratification within each condition. Existing guidance and candidate CDRs exist to help clinicians once they have established a working TLOC cause;[2,4,44,45] the function of tools such as ours is to aid clinicians in directing patients down the appropriate TLOC pathway.

Several important limitations to this study should be addressed in future work. Most notably, we recruited participants from secondary/tertiary care settings to which patients had been referred for further investigation of TLOC. These patients are likely to differ from those at first presentation of TLOC in numerous respects, including: duration and severity of symptoms, diagnostic difficulty, response to first-line treatment, and knowledge of their own diagnosis. Given the difficulty in establishing gold-standard diagnoses for causes of TLOC, these disparities are inevitable when seeking to obtain a patient sample with objectively confirmed diagnoses. Importantly, certain groups may be under-represented in our sample (e.g. 'low-risk' reflex syncope not requiring secondary care referral, idiopathic generalised epilepsies not requiring vEEG confirmation for clinically-established diagnosis, or patients with very infrequent seizures that would be unlikely to be captured during vEEG assessment). Due to the case identification method, focal-onset seizures and neutrally-mediated syncope are probably over-represented in our sample. This limitation emphasises the need for stringent validation of any such tool within the target clinical setting prior to routine application; furthermore, differences between primary care settings need also be taken into account.[46] Our specific sampling procedure may also have introduced bias: age and population prevalence are both important in determining prior probabilities of different conditions,[15,34] but due to sampling bias in recruitment location for our syncope patients these are not taken into account in our analysis. The sex distribution of our respondents also does not match that seen in the general population for all of the conditions; while it is unclear why our recruitment procedure might have introduced this bias, it may have influenced outcomes.

Another potential source of bias comes from the response rate (28.2%), which is at the lower end of response rates for medical research.[47] This may in part be due to lengthy nature of the questionnaire and the potentially sensitive nature of some of the questions included. The variable reduction performed in this paper would permit further research to utilise a shorter questionnaire, which should improve response rates in future research.[47,48] There is also the potential for recall bias, as participants completed the questionnaire up to 5 years after diagnostic confirmation. However, only 16% of participants stated they had not had a blackout in the last year, suggesting that recall should be adequate in the majority of participants, and in our sensitivity analysis not having experienced any seizures in the past year did not affect classifier performance. In terms of analysis, ideally we would have used separate samples for variable selection, training, and validation; a larger total number of participants would have permitted this.

To demonstrate its theoretical ability to distinguish all classes, the presented RF was trained on equi-sized diagnostic classes and hence aims to minimize overall error rate in this context.

However, in practical primary or emergency care settings the proportion of patients presenting from each class is unlikely to be equal. Additionally, the consequences of patient misclassification are of differential seriousness. Higher patient costs to misclassification of certain classes should also be taken into account in a CDR. To provide the best diagnostic tool for clinical practice, the training of our RF can be tuned to account for both these factors by reweighting/adapting the bootstrap sampling accordingly.

The dependence of our classifier on computer-assisted data processing could introduce applicability challenges. Future research should explore whether predictors identified through computer-based analyses can be used to develop more easily interpretable algorithms suitable for use in the Emergency Department (e.g. simple scores or single classification trees). Alternatively, the increasing availability of portable computer-assisted decision aids (e.g. through smart phone applications) may make machine learning-based classifiers more widely applicable in the primary care setting, and the use of web-based decision aids could allow classifiers to learn and improve over time.

Despite these limitations, our results demonstrate the feasibility of developing a CDR utilising an easily-implemented machine learning algorithm capable of distinguishing accurately between syncope and epilepsy or PNES. Pending validation in target clinical settings, the CDR, administered using an app and using a number of clinical features easily manageable in most primary or emergency care settings, should enable non-expert clinicians to direct patients to the most appropriate cardiological or neurological investigation and management pathways. In addition to speeding up the diagnostic process and reducing the risk of misdiagnosis and inappropriate investigation or referral, the pre-test probability of particular diagnoses provided by such a CDR would enhance clinician interpretation of inter-episodal investigation findings (*e.g.* EEG, neuroimaging, ECG or tilt-table abnormalities).[49]

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## 4.1.6. References

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## 4.1.7. Supplementary analyses

### *4.1.7.1. Comparison of RF classifier to multinomial logistic regression*

For comparison, we derived a multinomial logistic regression model with diagnosis as the dependent variable and the same 36 features selected in our RF variable reduction procedure as explanatory variables (with *K*-nearest neighbours imputation for missing values). The same training data set as for the RF was used for parameter estimation. We then evaluated the predictive performance of this model on the RF validation data set.

The regression model predicted 67/86 (77.9%) of diagnoses correctly, compared with 74/86 (86.0%) correctly classified by the RF ($p$ = 0.0963, McNemar's test). Table 4.1.3 displays the model coefficients with standard errors. Table 4.1.4(a) and (b) shows classification matrices for the RF and regression models respectively, and Table 4.1.5 compares misclassification by the RF against the regression model.

| Variable | $B_{Epilepsy}$ | SE($B_{Epilepsy}$) | $B_{PNES}$ | SE($B_{PNES}$) |
|---|---|---|---|---|
| Intercept | -6.45 | 4.5626 | -4.0019 | 4.4487 |
| Violent shaking | 0.8448 | 5.2932 | -0.0268 | 5.2770 |
| Chewing/mouth movements | 5.6646 | 4.0550 | 4.0541 | 4.0912 |
| Limp limbs | -6.7408 | 4.0119 | -6.5533 | 3.9905 |
| Painful like a hammer blow | 2.7205 | 4.7721 | 4.9788 | 4.5408 |
| Onset during sleep | 7.8146 | 3.4349 | 7.1137 | 3.4138 |
| Looks pale | -4.9309 | 4.2921 | -5.8687 | 4.2943 |
| Déjà vu | 2.9181 | 5.7404 | 0.8144 | 5.6874 |
| Drift in/out of consciousness | 1.8589 | 3.0740 | 2.2568 | 2.9137 |
| Brief jerks | 5.4903 | 5.7330 | 6.0525 | 5.6620 |
| Able to see/hear | 0.2423 | 2.6045 | 0.3919 | 2.5708 |
| Febrile seizures | 3.4462 | 7.1812 | -1.9698 | 7.2783 |
| Like a burst of electricity | -0.5446 | 5.6703 | -0.2595 | 5.6441 |
| Post-ictal relief | 3.0328 | 3.3504 | 3.8606 | 3.3397 |
| Unusual positions | 7.643 | 3.8891 | 7.7988 | 3.7821 |
| Like a knife through head | -1.939 | 5.5195 | -1.1154 | 5.4387 |
| Fiddling/fumbling | -0.2963 | 4.3373 | -0.7123 | 4.3445 |
| Frightened of death | -8.0536 | 4.2060 | -7.3005 | 4.2358 |
| Palpitations | -7.8049 | 3.9913 | -6.9728 | 3.8079 |
| Triggered by stress | 4.668 | 3.8739 | 5.2113 | 3.7779 |
| Feel hot/cold | -2.7679 | 3.8484 | -0.0276 | 3.7365 |
| Aware of uncontrollable shaking | 1.1657 | 4.5324 | 0.0487 | 4.5228 |
| Want to know what happens | 2.1928 | 4.2350 | -0.7131 | 4.1613 |
| Conscious but cannot react | 3.3795 | 3.1273 | 1.5957 | 3.0038 |
| Chest pain | 1.0344 | 6.0808 | 3.6158 | 6.0304 |
| Rigid limbs | 7.7797 | 4.0371 | 9.1151 | 4.0101 |
| Memories of bad experience | 0.4702 | 5.5931 | 1.1412 | 5.5617 |
| Sensation of passivity | 5.6059 | 4.3501 | 5.621 | 4.3263 |
| Triggered by sitting/standing | -12.5156 | 4.3022 | -10.8709 | 4.1160 |
| Triggered by blood | 5.0004 | 5.0800 | 1.6643 | 5.1548 |

| | | | | |
|---|---|---|---|---|
| **Brain tumour** | 10.7517 | 12.9618 | 12.5673 | 12.8911 |
| **Olfactory hallucination** | 2.3941 | 7.6700 | 5.6481 | 7.5934 |
| **Rapid side-side head movements** | 1.8766 | 4.6248 | 1.9854 | 4.5774 |
| **Scratching/bicycling movements** | 2.8356 | 5.6018 | 0.651 | 5.5701 |
| **Malcoordination** | -2.8359 | 4.9373 | -1.4847 | 4.9194 |
| **Time in slow motion** | 3.1623 | 4.3086 | 4.7407 | 4.2089 |
| **Shaking > 1 min** | 2.2210 | 5.2462 | -0.0868 | 5.2150 |

*Table 4.1.3. Regression coefficients and standard errors for multinomial logistic regression model.*

| **(a)** | | **RF predicted diagnosis** | | |
|---|---|---|---|---|
| | | **Epilepsy** | **PNES** | **Syncope** |
| **Gold-standard diagnosis** | **Epilepsy** | 24 | 2 | 2 |
| | **PNES** | 5 | 24 | 3 |
| | **Syncope** | 0 | 0 | 26 |
| **(b)** | | **Regression model predicted diagnosis** | | |
| | | **Epilepsy** | **PNES** | **Syncope** |
| **Gold-standard diagnosis** | **Epilepsy** | 20 | 7 | 1 |
| | **PNES** | 6 | 22 | 4 |
| | **Syncope** | 0 | 1 | 25 |

*Table 4.1.4. Comparison of predicted v gold-standard diagnoses for (a) RF classifer and (b) multinomial logistic regression model.*

| | **RF correct** | **RF incorrect** |
|---|---|---|
| **Regression correct** | 62 | 5 |
| **Regression incorrect** | 12 | 7 |

*Table 4.1.5. Comparison of classification errors by RF and regression models.*

### *4.1.7.2. Effect of witness and patient characteristics on classifier performance*

We performed a series of post-hoc sensitivity analyses to determine any effect on classifier performance of various witness and patient characteristics. All sensitivity analyses used the full dataset to ensure adequate representation of all groups (as none of these characteristics were included in the procedure for separating training and validation samples this should provide unbiased estimation of relative performances, though the absolute classification accuracies are liable to be inflated by testing on a set including the training sample).

#### Number of witnessed events

Witnesses provided information on whether they had seen one, two to five, or more than five of the person's blackouts. 213/249 (85.5%) of witnesses answered. We summarise classifier performance by number of witnessed seizures in Table 4.1.6. Differences were non-significant ($\chi^2(2) = 3.46$, $p = 0.177$).

| | **Number of witnessed events** | | |
|---|---|---|---|
| | **1** | **2 to 5** | **5+** |
| **Correct (N)** | 16 | 45 | 140 |
| **Incorrect (N)** | 1 | 0 | 11 |
| **Accuracy (%)** | 94.1 | 100 | 92.7 |

*Table 4.1.6. Classifier performance by number of witnessed events.*

4.1. Machine learning as a diagnostic decision aid for patients with transient loss of consciousness

### Duration of acquaintance between witness and subject

We asked witnesses to report how long (in years) they had known the subject. 212/249 (85.1%) of witnesses answered. We used binary logistic regression to evaluate whether duration of witness acquaintance predicted classification success. We summarise the regression model in Table 4.1.7. Duration of acquaintance did not significantly predict classification success ($\chi^2(1) = 0.377$, $p = 0.539$, Nagelkerke $R^2 = 0.005$).

| | *B* | $e^B$ (95% CI) | *p* |
|---|---|---|---|
| **Constant** | -2.497 | 0.082 | 0.000 |
| **Duration of acquaintance** | -0.012 | 0.99 (0.95-1.03) | 0.548 |

*Table 4.1.7. Summary of binary logistic regression model for effect of duration of witness-subject acquaintance on classification success.*

### Frequency of events

We asked subjects to report how many events they had experienced in the past year. 247/249 (99.2%) responded. We summarise classifier performance by number of seizures in the past year in Table 4.1.8. Classifier performance varied significantly with number of witnessed seizures per year ($\chi^2(3) = 33.8$, $p < 0.001$), with worse performance in classifying those patients who reported more than 50 spells in the past year. Excluding this group, the difference was no longer significant ($\chi^2(2) = 4.76$, $p = 0.093$). Frequency of events was not independent of gold-standard diagnosis ($\chi^2(6) = 54.5$, $p < 0.001$), with PNES patients being over-represented and syncope under-represented in the high-frequency group, as displayed in Table 4.1.9.

| | Number of events in past year | | | |
|---|---|---|---|---|
| | **None** | **Up to 5** | **5 to 50** | **More than 50** |
| **Correct (N)** | 33 | 61 | 83 | 42 |
| **Incorrect (N)** | 3 | 0 | 6 | 19 |
| **Accuracy (%)** | 91.6 | 100 | 93.2 | 68.9 |

*Table 4.1.8. Classifier performance by number of events in past year.*

| **Diagnosis** | Number of events in past year | | | |
|---|---|---|---|---|
| | **None** | **Up to 5** | **5 to 50** | **More than 50** |
| **Epilepsy (N)** | 13 | 18 | 28 | 25 |
| **PNES (N)** | 6 | 7 | 38 | 33 |
| **Syncope (N)** | 17 | 36 | 23 | 3 |

*Table 4.1.9. Frequency of events in last year by diagnosis.*

### Time since onset of blackouts

We asked subjects to report their age at their first blackout and current age, and from this information determined how long they had been experiencing blackouts. 235/249 (94.4%) of respondents gave complete and coherent answers (i.e. both current age and age at onset given, with age at onset not greater than current age). We used binary logistic regression to evaluate whether time since onset predicted classification success. We summarise the regression model in Table 4.1.10. Time since onset of blackouts did not significantly predict classification success ($\chi^2(1) = 1.808$, $p = 0.179$, Nagelkerke $R^2 = 0.022$).

| | *B* | $e^B$ (95% CI) | *p* |
|---|---|---|---|
| **Constant** | -2.403 | 0.090 | 0.000 |
| **Time since onset** | -0.031 | 0.97 (0.92-1.02) | 0.221 |

*Table 4.1.10. Summary of binary logistic regression model for effect of time since onset of blackouts on classification success.*

#### *4.1.7.3. Misclassification by witness-patient and patient-only RFs*

The majority (75%) of cases misclassified by the patient-only RF were classified correctly by the witness/patient RF; the converse is also true, 67% of cases misclassified by the witness/patient RF being correctly classified by the patient-only RF.

# 4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

## 4.2.1. Introduction

### *4.2.1.1. Background and importance*

Transient loss of consciousness (TLOC) – spontaneous disruption of consciousness not due to head trauma, with complete recovery[1] – is one of the commonest neurological complaints in primary/emergency care.[2] Over 90% is due to syncope, epilepsy or functional/dissociative seizures (FDS; 'Psychogenic Nonepileptic Seizures').[3,4] Rapid, accurate diagnosis is vital for appropriate further management. However, 20-30% of patients are misdiagnosed or mismanaged.[5,6] Patients who could be reassured that they experienced uncomplicated vasovagal syncope are told they cannot work or drive until expert assessment. Patients who should be investigated by cardiologists are referred to neurologists and vice versa. Investigations to identify life-threatening pathologies are delayed.[2,3,5,7–9] Misdiagnosis is particularly common in patients with FDS. Mean interval from first presentation to diagnosis of FDS is four to seven years,[3] causing prolonged disability and risking potentially fatal mistreatment.[10,11]

Diagnosis is complicated by the lack of unique distinguishing single clinical features[2,3] and because inter-ictal investigations are non-contributory in most cases.[9,12] The optimal extraction of historical information from the patient and any witnesses remains the cornerstone of diagnosis. Previous research suggests that clusters of features can distinguish between causes of TLOC better than individual features.[3,13–15]

At present, taking and interpreting the history requires time and specialist expertise, which may not be available in emergency or primary care settings. However, studies based on clinical data such as peri-ictal symptoms suggest that systematic questionnaires may support diagnosis.[3,16]

In previous research, we have shown the diagnostic potential of systematic symptom reporting questionnaires (captured in the Paroxysmal Event Profile [PEP]), and of witness reporting (the Paroxysmal Event Observer [PEO]) to support differential diagnosis of TLOC.[3,17] We used machine learning to reduce these extensive questionnaires to the much shorter initial PEP (iPEP). This 36-item iPEP was used to train a machine learning-based diagnostic classifier (the 'iPEP classifier') to discriminate between diagnoses in a cohort of patients with established gold-standard diagnoses. In a separate validation sample this classifier accurately diagnosed 74/86 (86.0%) of patients correctly (100% syncope, 85.7% epilepsy, 75.0% FDS).[18]

However, such a tool would be of maximal clinical utility at the point of first presentation; and the validity of using a training sample of patients with long-standing, established diagnoses to support diagnoses in a target population of patients newly presenting with TLOC is uncertain.

### *4.2.1.2. Goal of this investigation*

The object of this study was to develop and validate a patient-completed questionnaire-based machine learning classifier within the target population (patients first presenting with TLOC), with questionnaires incorporating new items of potential diagnostic utility identified since development of the PEP/PEO.[13]

4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

## 4.2.2. Methods

### *4.2.2.1. Setting*

We performed this study in a single large teaching hospital in the United Kingdom, with a large adult Emergency Department (ED) and tertiary Neurology and Cardiology services.

### *4.2.2.2. Recruitment and participants*

Prospective recruitment took place from 10th February 2022 to 9th January 2023. One team member (DH) screened all admissions to the ED and Acute Medical Unit (AMU) for presentations with transient loss of consciousness, and all new referrals to Neurology and Cardiology departments for transient loss of consciousness, according to the following criteria:

- Inclusion criteria
    - Patients first presenting with TLOC
    - Referred to secondary care for diagnostic evaluation OR given firm diagnosis of syncope in accordance with European Society of Cardiology (ESC) guidelines for syncope presentations not requiring further investigation
    - Adult over the age of 16 years
    - Able to complete questionnaire independently
    - Sufficient English language ability to complete questionnaire without support
- Exclusion criteria
    - Unable to give informed consent to participation in research
    - Unable to complete questionnaire independently
    - Previous specialist (neurological or cardiological) assessment of TLOC
    - Secondary cause of TLOC identified

We invited participants either in person (during their ED or AMU attendance) or prior to specialist assessment, sending participant information sheets about the study to all individuals identified as eligible.

We asked participants to identify a witness to their TLOC, and to share with them a separate information sheet regarding the study. We sought independent consent from witnesses to participate.

### *4.2.2.3. Sample size*

#### Development

There are no simple rules for calculating sample sizes for machine learning with random forest (RF) classifiers. Although the RF approach is optimised for classification problems in low-n high-p settings,[19] performance improves with increased sample size.[20,21] We previously demonstrated robust performance of an RF classifier for this problem in a training set of 163 participants.[18] Simulating classification performance using our previous study data demonstrated that classifier accuracy increased progressively with a sigmoidal distribution flattening out at 40-50 participants. To ensure that we captured enough participants with a sufficiently certain diagnosis to allow inclusion in the analysis, we aimed to recruit 100 participants for the training stage of this study.

#### Validation

We consider the primary clinical problem to be one of separating 'cardiological' (syncope) presentations from 'neurological' (epilepsy or FDS). In our pilot study, the iPEP classifier had

sensitivity for syncope of 100% (95% confidence interval [CI] 86.7-100%). Therefore (assuming target sensitivity of 97.5%) demonstrating sensitivity for syncope within the previously-determined 95% CI (>86.7%) then, for one-tailed $\alpha = 0.05$ and $\beta = 0.9$, this requires 42 participants with syncope in our validation sample.[22] Previous studies suggest prevalence of syncope in our target population of approximately 50%.[23] This gives a total validation sample size of 84. A study of ED attendances with suspected seizures in our target population found 14.3% could not be given a firm diagnosis of a primary TLOC cause (1.1% unknown diagnosis, 9.9% acute symptomatic seizure, 3.3% missing data).[24] We therefore adjusted our target to 98 participants to ensure recruitment sufficient numbers with clear diagnoses. Adjusting for loss to follow-up (estimated 6%[25]) provides final validation sample size 105 participants.

#### *4.2.2.4. Study instruments*

##### PESQ and PEWQ

We used two brief questionnaires derived from previous development work[18] and subsequently-published reviews[13,26]: one for patients themselves, one for witnesses if available. A 52-item patient questionnaire (the 'Paroxysmal Event Symptoms Questionnaire' [PESQ]) comprises 3 demographic questions (age, gender, years of formal education), 14 questions regarding past medical history, and 35 peri-ictal symptoms. An 18-item witness questionnaire ('Paroxysmal Event Witness Questionnaire' [PEWQ]) comprises 18 questions regarding ictal semiology. Participants/witnesses could complete the PESQ/PEWQ either online (via a dedicated interface, hosted on a secure university server) or on paper.

We provide PESQ and PEWQ in Appendix §4.2.7.

##### Diagnostic reference standard

As we sought to recruit an unselected first-presentation TLOC cohort, we were unable to use gold-standard diagnoses as reference; the majority of people with epilepsy or FDS do not have sufficiently frequent seizures to capture ictal EEG recordings,[6] while ESC guidance supports making clinical diagnosis without further investigation of uncomplicated vasovagal syncope.[27] However, consensus clinical diagnosis of TLOC-causing disorders by multiple experts is highly reliable.[28,29] We therefore use as reference standard the consensus diagnosis reached by two independent TLOC experts (MR and SJH), blinded to PESQ and PEWQ data (questionnaire responses and classifier predictions), from notes review at least 6 months after enrolment.

Participants for whom no firm clinical diagnosis could be reached at the end of follow-up, or who had multiple diagnoses, were excluded from further analysis. A previous study of patients with suspected seizures in this population found that only 1.1% of patients could not be given a single aetiological diagnosis, so we anticipated a low diagnostic failure rate.[24]

#### *4.2.2.5. Analysis*

##### Development

We employed an iterative feature-selection algorithm to identify most highly-discriminatory features from the PESQ data provided by the first 100 participants. The details of this stage of the analysis are the same as that used in our previous initial development research.[18] An RF trained using the CART algorithm on all development data (5000 iterations, sampling $\sqrt{p}$ predictor variables [where $p$ = number of predictors] at each iteration) ranked the relative prediction importance of each predictor variable; progressively smaller RFs are then trained by removing the least important 20% of predictors, and calculating out-of-bag prediction error (OOBE; average of the prediction error of each tree in the ensemble for data not sampled in its

training, an estimate of generalisation error equivalent to cross-validation methods[30]) of the resulting RF. The final set of predictor variables and RF used is that which minimises OOBE; we previously found that more parsimonious feature selection resulted in significant impairment in performance.[31] The final prediction model was an RF trained on all development data using the selected set of predictor variables. We selected hyperparameters on the basis of optimisation in our pilot study, combined with evidence that classifier performance is robust to variations in these hyperparameter settings.[32]

To compare a non-linear machine learning-based classifier against more traditional regression approaches, we also trained a penalised maximum likelihood (LASSO) classifier, choosing the model complexity/regularisation parameter $\lambda$ that minimised the cross-validated mean-squared error.

#### Validation

We validated prediction models against an independent validation dataset. Both RF and regression models classified participants into likely diagnoses of epilepsy, syncope, or FDS, evaluating performance in terms of overall classification accuracy, as well as sensitivity, specificity, positive (PPV) and negative (NPV) predictive values.

Given that syncope due to structural or arrhythmic cause is the condition with highest short-term morbidity/mortality, we determined sensitivity for syncope to be our primary outcome. We compared sensitivity for syncope of the new RF to that found in our initial research,[18] ($\chi^2$ test, one-tailed $\alpha = 0.05$ for target sensitivity 97.5%). We also tested the hypothesis that classification accuracy of the RF is significantly greater than the regression model (McNemar's test, $\alpha = 0.1$).

Furthermore, we performed a post-hoc analysis simulating performance of the classifier as a clinical decision aid (CDA) augmenting the initial assessing clinician's evaluation. For this, classifier diagnosis was used as 'tie-break' for occasions when initial assessing clinician gave no working diagnosis, otherwise the initial diagnosis was used; these diagnoses were compared to our reference standard.

#### *4.2.2.6. Standard protocol approvals, registrations, and patient consent*

We pre-registered the study protocol on clinicaltrials.gov (ID: NCT05367999). Ethical approval came from NHS Health Research Authority Edgbaston Research Ethics Committee (IRAS: 304114). All patients and witnesses confirmed their consent to participate prior to completing the PESQ/PEWQ and were able to withdraw at any time.

#### *4.2.2.7. Data availability*

Deidentified dataset, data dictionary and analytic code for are available upon request from the authors.

### 4.2.3. Results

#### *4.2.3.1. Descriptive results*

#### Screening and recruitment

Of 2,811 patients screened for recruitment, 1,181 were approached to participate. Of these, 186 (15.7%) gave consent and completed the PESQ. Seven participants either withdrew or were deemed ineligible at end of follow-up. One participant was excluded as no final diagnosis could be reached. Therefore we included 178 participants in further analyses; the first 100

participants constituted the development dataset, the remaining 78 validation. Of 178 included participants, 46 identified a witness who completed the PEWQ. Figure 4.2.1summarises participant flow through the study. Patients were deemed ineligible at screening most commonly due to not experiencing TLOC (592, 36.3%), having prior specialist care for a TLOC-causing disorder (352, 21.6%), or having a secondary cause for their TLOC (285, 17.5%). Only 59 (3.6%) were ineligible for inability to complete the PESQ due to language or other barriers.

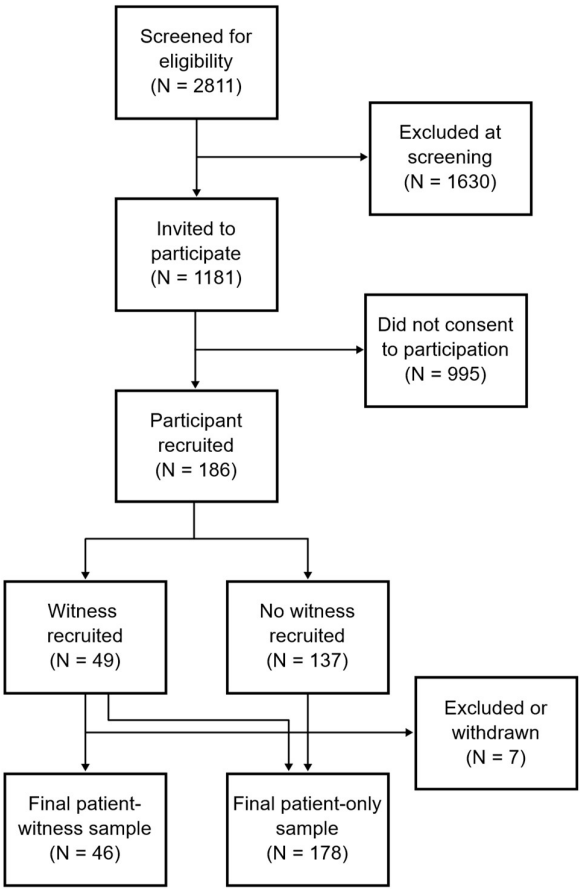


*Figure 4.2.1. Participant flow diagram.*

## Demographics and diagnoses

Syncope was the most common final diagnosis (134 participants; 75.3%), followed by epileptic seizure (32 participants, 18.0%). Table 4.2.1 summarises participant demographics.

| Diagnosis | *N* (% total) | Median age (range) | N (%) female | N (%) providing witness |
|---|---|---|---|---|
| **Syncope** | 134 (75.3) | 64 (17-94) | 75 (56.0) | 34 (25.4) |
| **ES** | 32 (18.0) | 47.5 (16-86) | 14 (43.8) | 11 (34.4) |
| **FDS** | 12 (6.7) | 31 (16-57) | 9 (75.0) | 1 (8.3) |

*Table 4.2.1. Summary of participant demographics. ES = epileptic seizure. FDS = functional/dissociative seizure.*

4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

Expert raters agreed on diagnosis in 144/178 (80.1%) cases. For the remainder, consensus diagnoses were reached by discussion. One participant was excluded due to persistent uncertainty regarding diagnosis.

Expert raters agreed with initial clinician diagnosis in 120/178 (67.4%) cases.

### Patient questionnaire

Most-frequently endorsed PESQ items across all participants were 'I want to know what has happened when I black out' (140 participants), a history of light-headed spells (88 participants), and 'I feel hot or cold in my attacks'; (80 participants). Least-frequently endorsed items were 'The sight of blood or needles triggers my attacks', 'During my attacks I have memories of a past bad experience which I cannot stop', and a history of brain tumour (each 4 participants).

Figure 4.2.2 summarises relative proportions of participants endorsing each PESQ item by final diagnosis, with hierarchical clustering of questionnaire items.

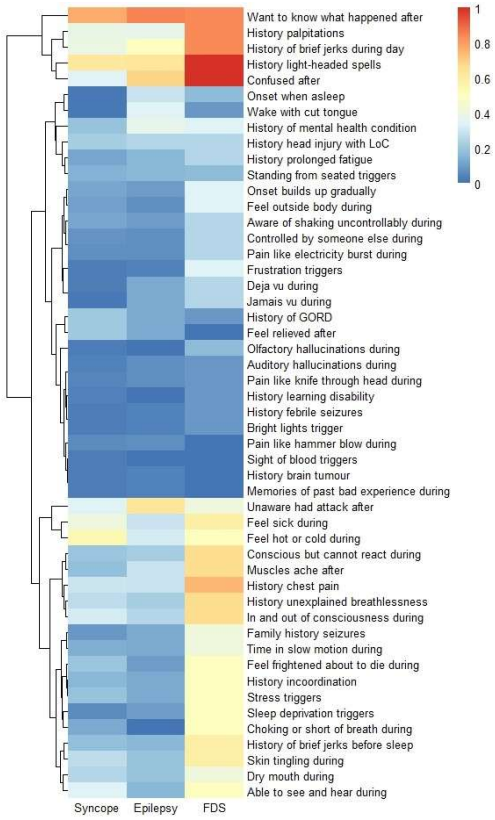


*Figure 4.2.2. Heatmap of relative frequency of patient-reported symptoms by diagnosis. Colour depicts proportion of respondents with each diagnosis endorsing each item. FDS = functional/dissociative seizures. Dendrogram on the left-hand side demonstrates hierarchical clustering of questionnaire items (items that are most likely to co-occur are clustered, then item-clusters most likely to co-occur clustered on higher levels)*

### Witness questionnaire

46 witnesses completed the PEWQ. Of these, only one was for a participant with FDS. Most frequently endorsed items were 'The skin or lips looked pale during the attack' (33 witnesses), 'During the attack, arms and legs are limp' (31 witnesses), and 'Breathing was shallow or quiet after the attack' (28 witnesses). Least frequently endorsed were 'The attacks involve violent thrusting of the hips' (2 witnesses), 'The attacks involve chewing, smacking, or licking

movements of the mouth and lips' (4 witnesses), and 'The attacks involve scratching or bicycling movements of the legs' (4 witnesses).

Figure 4.2.3 summarises relative proportions of witnesses endorsing each PEWQ item by diagnosis; since only one participant with FDS identified a witness, results are shown for syncope and epileptic seizures only.

Hierarchical clustering of PEWQ items (displayed in the dendrogram in Figure 4.2.3) identifies two high-level clusters of 'syncopal' features (shallow breathing, flaccidity, pallor) and 'other' features. The 'other' features sub-cluster into a group highly reported in epileptic seizures (post-ictal stertor, violent shaking, rigidity, and prolonged shaking), and a group of less-frequently reported symptoms.

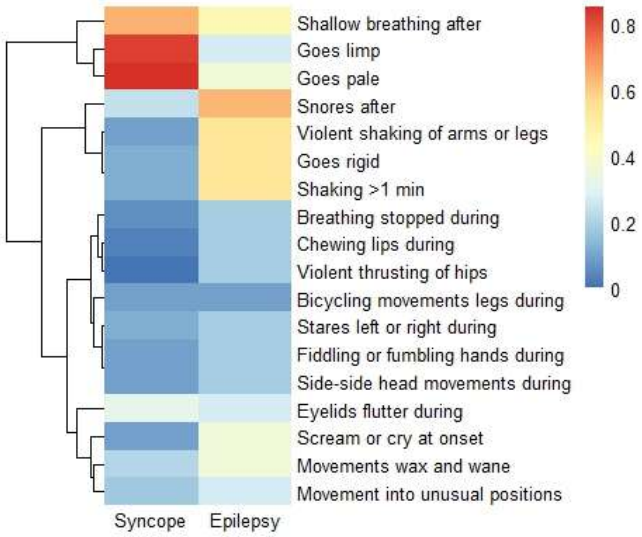


*Figure 4.2.3. Relative frequency by diagnosis of witness reports. Colour depicts proportion of witnesses for respondents with each diagnosis endorsing each item. Dendrogram to the left depicts hierarchical clustering of questionnaire items (items that are most likely to co-occur are clustered, then clusters of items most likely to co-occur clustered on higher levels). FDS not shown as only a single PEWQ was completed for participant with this diagnosis.*

### *4.2.3.2. Sensitivity and specificity of individual questionnaire items*

No item was more than 80% sensitive and specific for any diagnosis. Three PESQ items had individual sensitivity and specificity >0.5 for either syncope or epileptic seizures. More met this criterion for FDS, but given low FDS prevalence, PPV/NPV did not exceed 0.2.

Seven PEWQ items had individual sensitivity and specificity >0.5 for either syncope or epileptic seizures.

The most sensitive individual question for syncope with adequate specificity was 'The skin or lips looked pale during the attack' (sensitivity=85.3%); most specific with adequate sensitivity was 'During the attack, arms and legs are limp' (specificity=72.7%). For epilepsy, the most sensitive item was from the PESQ, 'After my attacks I feel very confused' (68.8%), while the most specific was 'The attacks involve violent shaking of the arms or legs' (91.2%) from the PEWQ.

Table 4.2.2 summarises diagnostic performance of most highly-discriminating individual items from the PESQ and PEWQ; supplementary worksheet 1[b] provides complete data for all items.

| FINAL DIAGNOSIS | | Item | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| **SYNCOPE** | **Patient** | Hot or cold during | 0.537 | 0.636 | 0.818 | 0.689 |
| | **Witness** | Limp during | 0.824 | 0.727 | 0.903 | 0.571 |
| | | Pale during | 0.853 | 0.636 | 0.878 | 0.583 |
| | | Shallow breathing after | 0.647 | 0.545 | 0.814 | 0.333 |
| **EPILEPSY** | **Patient** | Confused after | 0.688 | 0.603 | 0.275 | 0.102 |
| | | Unaware had attack | 0.625 | 0.658 | 0.286 | 0.111 |
| | **Witness** | Violent shaking of arms or legs | 0.545 | 0.912 | 0.667 | 0.861 |
| | | Arms and legs rigid | 0.545 | 0.882 | 0.600 | 0.857 |
| | | Shaking > 1 minute | 0.545 | 0.882 | 0.600 | 0.857 |
| | | Snoring after | 0.636 | 0.736 | 0.438 | 0.862 |

*Table 4.2.2. Predictive performance of most highly discriminating individual PESQ and PEWQ items. PPV = positive predictive value; NPV = negative predictive value.*

### *4.2.3.3. Model development*

#### PESQ only

As PESQ and PEWQ were available for only 46 participants, we performed model development using PESQ responses only. Supplementary Figure 4.2.5 (Appendix 2, §4.2.8.1) demonstrates relative predictor importance of PESQ responses. Some items contributed heavily to classifier performance (e.g. 'My attacks come on when I am asleep'; 'I wake from my attacks with a cut tongue'), while others decreased performance (e.g. 'I want to know what has happened when I black out'; 'History of light-headed spells'). Historical variables showed generally lower predictor importance than peri-ictal symptoms.

Feature selection identified a 9-variable RF as optimal: it used one demographic variable (age in years); and eight symptoms. Figure 4.2.4 shows these symptoms and relative reporting proportions by diagnosis. Hierarchical clustering demonstrates two high-level clusters within these items - a 'seizure' cluster (onset from sleep, waking with cut tongue, déja vu, sleep deprivation trigger); and a 'polysymptomatic' cluster, highly reported in FDS.

The optimal RF had OOBE=0.21 (79% accuracy).

[b] Due to the amount of data, Supplementary Worksheet 1 is not included within the thesis copy of this paper.

4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

Penalised regression (LASSO) identified 7 predictors with non-zero coefficients: one demographic (age in years); one historical (brief jerks during the day); and five symptoms ('My attacks come on when I am asleep'; 'I wake from my attacks with a cut tongue'; 'I feel hot or cold in my attacks'; 'After my attacks I feel very confused'; and 'During my attacks I smell things that are not really there'). Table 4.2.7 (§4.2.8.2) provides model coefficients.

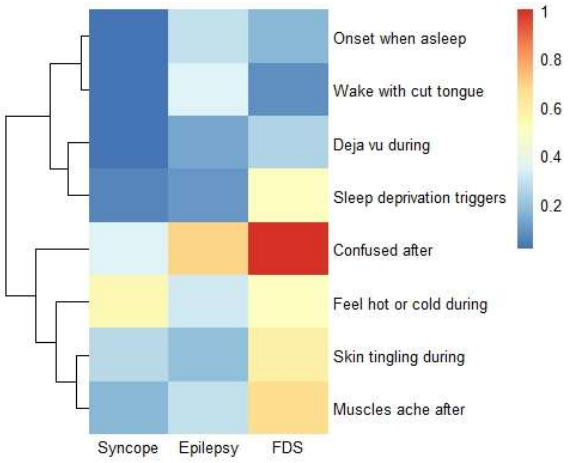


*Figure 4.2.4. Relative reporting proportions of predictors included in PESQ classifier. FDS = functional/dissociative seizures.*

### PESQ-PEWQ

Given the small PESQ-PEWQ dataset, we used all available data for model development. As only one participant in this dataset had FDS, they were excluded from analysis and a binary classifier for distinguishing syncope from epileptic seizures developed. Supplementary Figure 4.2.6 demonstrates predictor importance for the combined PESQ-PEWQ classifier. Again, symptom and witness reports were the most important predictors, with the latter disproportionately represented amongst the most important predictors.

The optimal model used 3 predictor variables: two symptom reports from the PESQ ('My attacks come on when I am asleep', and 'I wake from my attacks with a cut tongue'); and one from the PEWQ ('During the attack, arms and legs are limp').

#### *4.2.3.4. Model validation*

### PESQ-only

To avoid overfitting, we performed external validation using a separate holdout dataset comprising the last 78 recruited participants. The PESQ classifier correctly identified 63/78 (80.8%; 95% CI 70.0-88.5) of diagnoses. Sensitivity for syncope was 96.6% (87.0–99.4). Table 4.2.3 summarises the diagnostic performance for each diagnosis. Supplementary Table 4.2.4 gives the confusion matrix.

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **Syncope** | 0.966 (0.870-0.994) | 0.400 (0.200-0.636) | 0.824 (0.708-0.902) | 0.800 (0.442-0.965) |
| **Epilepsy** | 0.429 (0.188-0.704) | 0.969 (0.882-0.995) | 0.750 (0.356-0.956) | 0.886 (0.782-0.946) |
| **FDS** | 0.167 (0.009-0.635) | 0.986 (0.915-0.999) | 0.500 (0.095-0.905) | 0.934 (0.847-0.976) |

*Table 4.2.3. Diagnostic test statistics for the PESQ classifier. Values in brackets represent 95% confidence intervals. Syncope sensitivity denotes the proportion of those diagnosed with syncope after 6-month follow-up that were*

*classed as syncope based on the initial questionnaire at first presentation and the PESQ classifier. Syncope specificity denotes, out of those participants those who (after 6 months) were given a non-syncope diagnosis, were also give a non-syncope diagnosis using the PESQ classifier at first presentation. Syncope PPV = Positive predictive value, the proportion of those classified as syncope who received a syncope diagnosis at follow-up. Syncope NPV = negative predictive value, the proportion of those classified as non-syncope who received a non-syncope diagnosis at follow-up. The same applies mutatis mutandis for epilepsy and FDS.*

The classifier did not differ significantly from our pre-specified target sensitivity for syncope of 97.5% ($p$ = 0.644). We also performed a post-hoc analysis comparing classifier diagnosis to the initial assessing clinician's diagnosis, and referral or discharge diagnosis. The classifier accuracy was numerically, but not statistically significantly, superior to initial diagnosis (accuracy 70.5%; $p$ = 0.192) and referrer diagnosis (accuracy 75.6%; $p$ = 0.561).

We hypothesised that machine learning classifiers like RFs would outperform regression modelling, since they allow for items to have different contributions to differential diagnosis depending on co-occurrence with other items. We therefore compared performance of the PESQ classifier with a linear model (penalised regression model). The latter classified 58/78 (74.4% [63.0-83.3]) of diagnoses correctly. The performance was therefore worse than the PESQ classifier, but this difference was not statistically significant ($p$ = 0.499). We provide the confusion matrix and diagnostic statistics for this model in the supplementary materials.

To assess whether the RF classifier development described in our prespecified protocol could be improved upon using other machine-learning methods and models, we describe elsewhere a post-hoc analysis using ensemble comparison of multiple machine learning approaches using $H_2O$ AutoML. However, this did not produce a model that outperformed our RF classifier.[33]

### PESQ-PEWQ

There was no separate validation dataset for the PESQ-PEWQ classifier. Evaluating model performance using training data will overestimate model performance due to overfitting; we therefore use OOBE (equivalent to cross-validation methods.[30])

OOBE was 11.1%, equivalent to classification accuracy of 88.9%. Supplementary Table 4.2.5 displays the confusion matrix for this classifier, Table 4.2.6 diagnostic test statistics.

### Pilot iPEP classifiers

The patient-only and patient-witness iPEP classifiers from our pilot study performed worse than the new models in this external validation dataset, classifying 75.8% (68.8 – 81.8) and 78.3% (63.2 – 88.5) of diagnoses correctly. We provide full details in supplementary appendix §4.2.8.3.

### PESQ-augmented clinician performance

Using PESQ classification to adjudicate in cases where the initial assessing clinician gave no diagnosis, or one unlikely to cause TLOC (e.g. TIA), then classifier-augmented clinical decision agreed with experts on 66/78 patients (accuracy = 84.6% [95% CI 74.3-91.5]).

When comparing classifier performance to that of the initial clinician, the initial clinician made the correct diagnosis in 8 cases in which the classifier was incorrect; 6 of these were epileptic seizures, 2 syncope. In 16 cases in which the initial clinician misdiagnosed the patient or made no diagnosis, the classifier was correct; 15 of these were syncopal, 1 FDS.

## 4.2.4. Discussion

This study provides evidence that a machine-learning based classifier solely using patients' own responses to a brief patient-completed questionnaire can identify common causes of TLOC

with an accuracy greater than 80%. In this study, only 67.4% were correctly diagnosed in emergency or primary care at the point of presentation or received no probable diagnosis on initial assessment, and 76.4% after further non-specialist assessment. While overall performance is insufficient to recommend its routine clinical use, comparison with the present standard of care does suggest that such a tool may helpfully augment present unstructured clinical assessment; and an illustrative post-hoc analysis suggests that classifier-augmentation could improve the diagnostic accuracy of initial clinical diagnoses to 84.6%.

There is increasing recognition that artificial intelligence and machine learning can be used to augment (rather than replace) clinicians' decisions in this fashion.[34] With estimated annual (direct and indirect) costs of epilepsy misdiagnosis in England and Wales running to £138 million,[35] this represents potential for significant cost savings as well as patient benefit.

The PESQ classifier is unusual in providing three-way classification including all of the common primary causes of TLOC. Candidate clinical decision rules for discriminating between syncope and bilateral tonic clonic seizures,[15,36] or epilepsy and FDS,[16,26,37] focus on the mathematically simpler problem of binary classification. Our classification problem more accurately reflects the challenge facing the primary/emergency care clinician.

Our results underscore the importance of holistically evaluating clusters of clinical features in the differential diagnosis of TLOC, rather than treating individual features in isolation as pathognomonic. No single PESQ or PEWQ item proved both sensitive and specific for any diagnosis; furthermore, a classifier that evaluated combinations of features non-linearly performed better than a linear model in identifying the correct diagnosis (though this did not reach statistical significance).

Our results also underscore the utility of systematic interrogation of ictal experience. Peri-ictal symptoms were more discriminating than participants' medical histories, highlighting the importance of thoroughly exploring TLOC experiences. Prior work suggests combining open questions with systematic, prompted questioning about ictal experience (e.g. through questionnaires like the PESQ) identifies more ictal symptoms than open questions alone;[38,39] the effect of prompting may differ between diagnoses.[26,40]

#### *4.2.4.1. Limitations*

A major limitation of this study is the low witness recruitment. Just 46/178 participants (25.8%) identified a witness able to complete the PEWQ. We could therefore not both develop and independently validate a classifier based on both PESQ and PEWQ. This reflects a common difficulty: while professional guidance stresses the importance of obtaining a witness report for patients with TLOC,[41] in practice clinicians may struggle to achieve this. Further work should identify means of supporting witness identification and questioning to aid TLOC differential diagnosis. In our previous study involving patients with long-standing TLOC disorders, witness information was available from 83% of participants;[17] initial presentations may be less likely to be observed (or observed by those close to the patient). Given the low number of witnesses recruited, and our consequent inability to provide independent validation of the combined PESQ-PEWQ classifier, the results for this classifier should be considered exploratory only.

Only 15.7% of eligible presentations were recruited to our study. If there were systematic differences in recruitment by diagnosis (or e.g. patient demographics), this would bias the external validity of our results. Further work should address barriers to recruitment in such

studies (which in principle place minimal burden on participants, and evidence from our qualitative work suggests the interventions were highly acceptable to participants).

Our reference standard diagnosis does not represent the gold standard for any of our target conditions. This places an obvious caveat to our estimations of classifier performance, since the reference is a 'best possible' diagnosis rather than a clinically definite one. This is underlined by the fact that our expert raters either initially disagreed on or needed discussion to arrive at a consensus diagnosis for 34/178 (19.1%) of participants. However, this was a necessary compromise to ensure the ecological validity of our sample; the vast majority of people presenting with TLOC will not achieve a gold-standard diagnosis – for example, their attacks will be too infrequent (or even one-off) to be witnessed by an expert or captured on video-EEG or cardiac monitoring. We intend to follow up clinical outcomes for our participants to evaluate the stability of 'best possible' diagnoses over the longer term and the impact this may have on validity of our results.

We did not achieve our target validation sample size; since prevalence of syncope was higher than expected, the study was nonetheless adequately powered for our primary outcome. However, the sample was smaller than that recommended in simulation studies that estimate empirical sample size requirements for external validation of multivariable prognostic models.[42] The high prevalence of syncope in our sample is striking, differing from estimates reported elsewhere.[23,43] This may reflect the true incidence of the respective diagnoses;[2,12,44] however it may be that people with epilepsy and FDS - still stigmatised conditions[45,46] - were less willing to participate. It is a strength of this study that recruitment included not only patients referred to specialist clinics, but that we were also able to recruit 39 participants diagnosed with reflex syncope (the single most common cause of TLOC[23]) who were directly discharged directly from ED or AMU with no further assessment. This population would not have been captured in specialist clinics.

#### *4.2.4.2. Further work*

We demonstrate that a simple, patient-completed questionnaire can provide relevant information to differential diagnosis of TLOC, but cannot replace clinician assessments. Rather than automated assessment, such tools may best have a role in augmenting clinician evaluation, as CDAs.[34] This would allow the clinician to combine outputs with their own holistic assessment to determine a working diagnosis.

Patient-completed tools to reduce clinician workload are not frequently employed, despite demonstrated feasibility of patient application of CDAs for their own care.[47,48] Given that around 9 in 10 patients attending EDs in England in 2018-19 spent over an hour in the department,[49] ED attendances provide ample opportunity for self-administration. Implementation within now-commonplace smartphone or browser-based applications could ensure user-friendliness. Combining machine learning predictions with tools like locally-intelligible model-agnostic explanations (LIME)[50] in order to render them more explainable to patients and clinicians may help clinicians to feel their use more defensible, overcoming objections to their otherwise 'black-box' nature.[33] Together these considerations should address the main factors affecting ED clinicians' willingness to employ CDAs in their clinical practice.[51] Patient-completed tools need not be restricted to simple questionnaires as we have used; in other work we have also demonstrated feasibility of automated capture and analysis of patients' spoken accounts;[52] these two approaches could be combined. Further research on clinician experience of interacting with such a CDA could support wider use.

Misdiagnosis leads to ineffective, potentially dangerous, treatment.[8,10] Diagnoses like epilepsy also have psychological and social implications, such as for employment and driving.[35] Methods to support accurate, prompt, diagnosis with efficient use of medical resources – both human (e.g. referral to the appropriate specialist team), and investigative (reducing requesting of inappropriate low-yield investigations such as chest or brain imaging for syncope)[12] – are needed to ensure efficient and effective management of this common and disruptive presentation. There is also a need for work clarifying the human and economic costs of missed or delayed diagnoses to support economic modelling of benefits of implementation of CDAs.

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### 4.2.7. Supplementary appendix 1: PESQ and PEWQ

# PESQ

**Personal background**

1. What is your age in years?
2. For how many years were you in formal education?
3. How would you describe your gender? (Man/woman/other gender)

**Medical history**

Which of the following conditions do you have or have you had?

1. Febrile seizures in childhood
2. Episodes of chest pain or tightness
3. Breathlessness unrelated to exercise
4. Palpitations
5. Brain tumour
6. Head injury with loss of consciousness
7. Lightheaded spells
8. Brief jerks of the arms or legs
9. Poor coordination
10. Chronic fatigue
11. Gastro-oesophageal reflux disease (GORD)
12. Learning disability
13. Family history of seizures
14. Any mental health condition (diagnosed by a healthcare professional)

**Symptoms**

Which of the following do you experience in your blackouts?

1. My attacks come on when I am asleep
2. The sight of blood or needles triggers my attacks
3. May attacks are associated with sitting or standing for a long time
4. My attacks are associated with emotional stress
5. My attacks are triggered by sleep deprivation
6. My attacks are triggered by exposure to bright lights
7. My attacks are triggered by frustration
8. My attacks build up gradually
9. In my attacks I seem to be controlled by someone outside me
10. In my attacks I have a sense or feeling as if I have seen something before when I know I have not
11. In my attacks I have a sense of feeling as if I've never seen something before when I know I have
12. In my attacks I feel sick
13. I feel hot or cold in my attacks
14. In my attacks I experience tingling or numbness of my skin
15. During my attacks I hear things that are not really there
16. During my attacks I smell things that are not really there

17. In my attacks my mouth goes very dry
18. During my attacks I can see or hear the people around me
19. In my attacks I am conscious but cannot react to things
20. In my attacks I drift in and out of consciousness
21. I am aware of shaking uncontrollably during an attack
22. During my attacks I feel as if I am outside my body
23. My attacks make time go in slow motion
24. In my attacks I feel like I am choking or very short of breath
25. During my attacks I have memories of a past bad experience which I cannot stop
26. During my attacks I am frightened I am going to die
27. My attacks are like a burst of electricity in my brain
28. My attacks are painful like a hammer blow
29. My attacks feel like a knife through the head
30. I wake from my attacks with a cut tongue
31. After my attacks my muscles ache
32. After my attacks I feel very confused
33. I want to know what has happened when I black out
34. After my attacks I feel relieved
35. Afterward I have no idea that I have had an attack

## PEWQ

1. The attacks involve chewing, smacking, or licking movements of the mouth and lips
2. The attacks involve fiddling, picking, or fumbling movements of the hands
3. The attacks involve scratching or bicycling movements of the legs
4. In the attacks the head moves rapidly from side to side
5. The attacks involve violent shaking of the arms and legs
6. The attacks involve movements that are not rhythmic, or wax and wane
7. The attacks involve violent thrusting of the hips
8. During the attack, arms and legs are limp
9. During the attack, arms and legs are rigid
10. During the attack, the person stares to the left or right
11. During the attack, the eyelids flutter
12. Shaking of the arms and legs goes on for over 1 minute
13. The attacks involve movement into unusual positions
14. The skin or lips looked pale during the attack
15. The attack started with an unusual scream or cry
16. Breathing stopped during the attack
17. Breathing was shallow or quiet after the attack
18. Breathing was like snoring after the attack

## 4.2.8. Supplementary appendix 2

### *4.2.8.1. PESQ/PEWQ classifiers*

#### PESQ only predictor importance

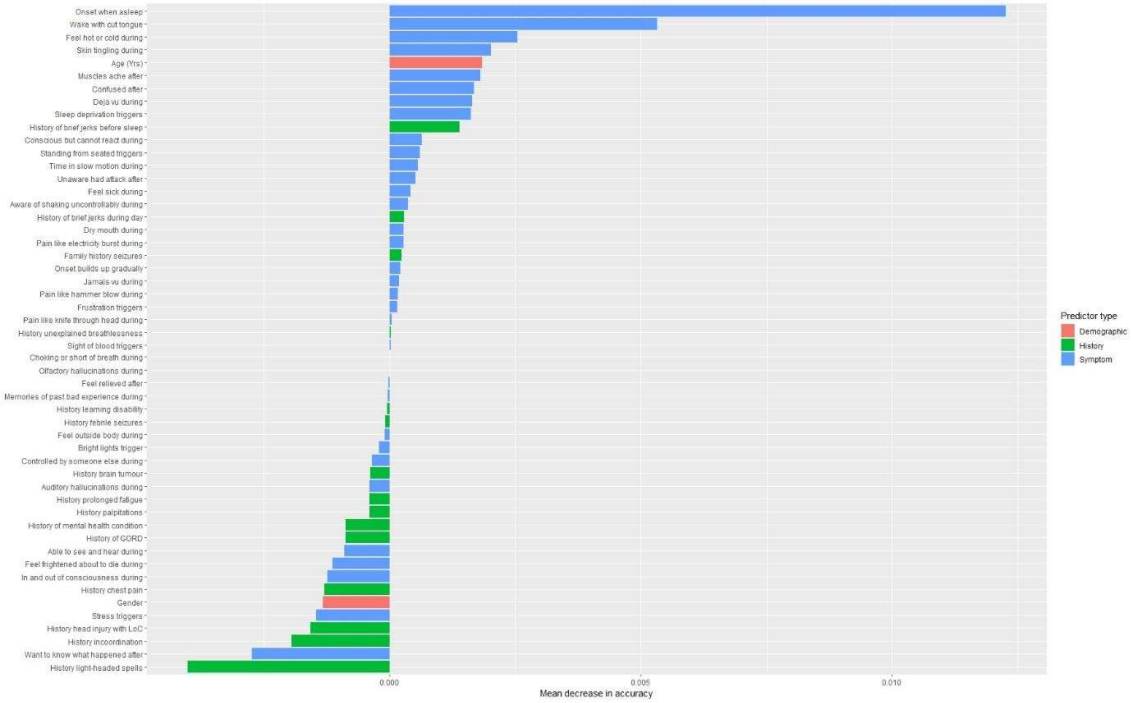


*Figure 4.2.5. Predictor importance for diagnostic classification using PESQ only. This plots the mean decrease in prediction accuracy if the information for any specific question was not available, i.e., the decrease in prediction accuracy had that question not been asked. The key questions are likely to be those which, when dropped, show a substantial decrease in prediction accuracy. These lie at the top of the plot.*

4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

### PESQ-PEWQ predictor importance

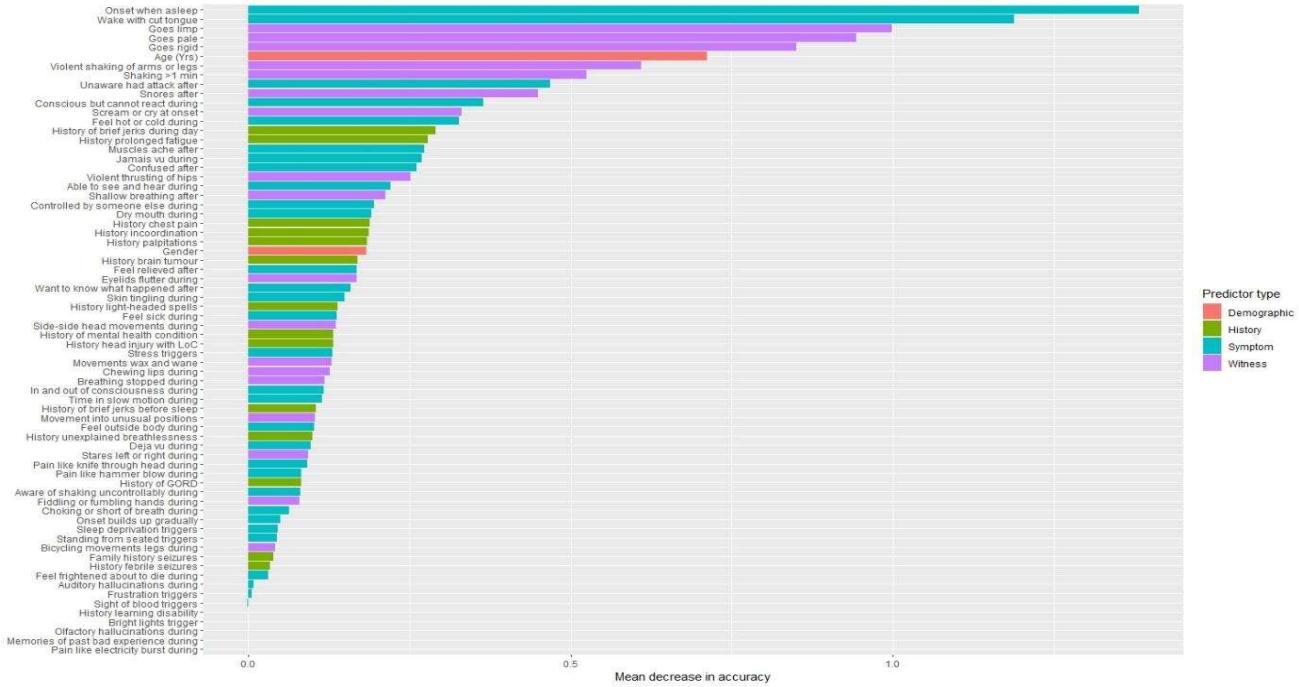


*Figure 4.2.6. Predictor importance for combined PESQ-PEWQ classifier.*

### Validation model performance

| | | PREDICTED DIAGNOSIS | | |
|---|---|---|---|---|
| | | **Syncope** | **Epilepsy** | **FDS** |
| **FINAL DIAGNOSIS** | **Syncope** | 56 | 1 | 1 |
| | **Epilepsy** | 8 | 6 | 0 |
| | **FDS** | 4 | 1 | 1 |

*Table 4.2.4. Validation confusion matrix for the PESQ classifier.*

| | | PREDICTED DIAGNOSIS | |
|---|---|---|---|
| | | Syncope | Epilepsy |
| **TRUE DIAGNOSIS** | Syncope | 34 | 0 |
| | Epilepsy | 5 | 6 |

*Table 4.2.5. Cross-validation confusion matrix for the PESQ-PEWQ classifier.*

| | **SENSITIVITY** | **SPECIFICITY** | **PPV** | **NPV** |
|---|---|---|---|---|
| **SYNCOPE** | 1.00 (0.87-1.00) | 0.55 (0.25-0.82) | 0.87 (0.72-0.95) | 1.00 (0.52-1.00) |
| **EPILEPSY** | 0.55 (0.25-0.82) | 1.00 (0.87-1.00) | 1.00 (0.52-1.00) | 0.87 (0.72-0.95) |

*Table 4.2.6. Diagnostic test statistics for the PESQ-PEWQ classifier. Values in brackets represent 95% confidence intervals.*

### Comparison of PESQ and PESQ-PEWQ classifier

While this provisional analysis should be treated only as illustrative and exploratory (since it involves validation on the training data), the PESQ-only classifier correctly identified 40/45 diagnoses in the patient-witness dataset (accuracy = 88.9% [75.2-95.8]), while the PESQ-PEWQ classifier identified 41/45 (accuracy = 91.1% [77.9-97.1]). OOBE for the PESQ-only classifier

was 0.21 (equivalent to 79% accuracy), while it was 0.11 for the PESQ-PEWQ classifier (89% accuracy).

#### *4.2.8.2. Patient-only penalised regression model*

##### Cross-validation to determine optimal λ

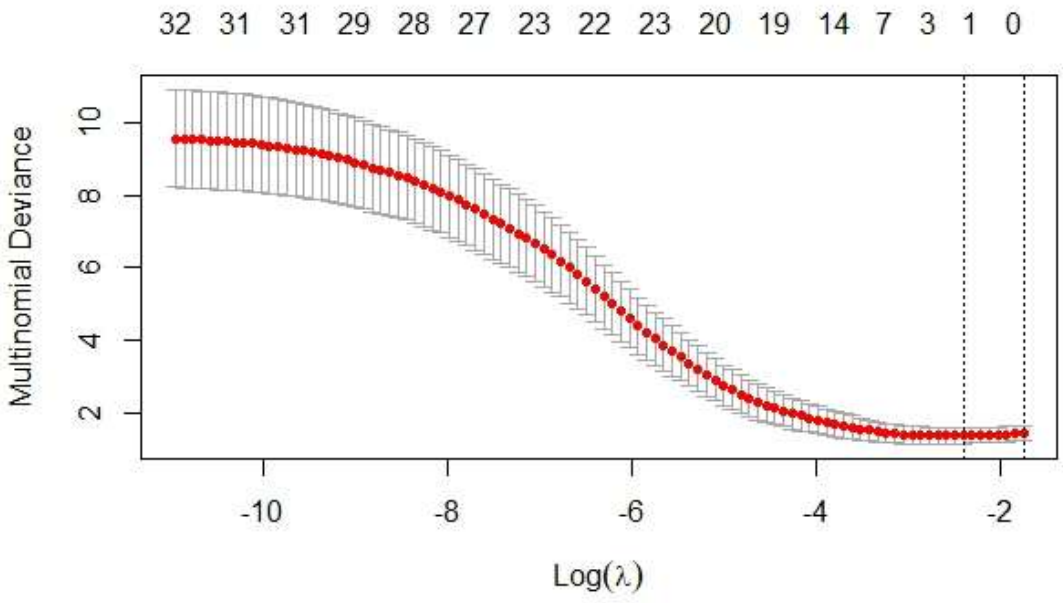


*Figure 4.2.7. Determination of optimal value of hyperparameter λ for LASSO regression model.*

##### Model summary

The optimal LASSO model was selected with hyperparameter λ = 0.083, and explained 14.4% of null deviance. Model parameters are as listed in the table below:

| DIAGNOSIS | PREDICTOR | β |
|---|---|---|
| **Syncope** | Intercept | 1.323 |
| | Age | 0.005 |
| | History of brief jerks during day | -0.140 |
| | Onset from sleep | -1.420 |
| | Feel hot or cold during | 0.319 |
| | Confused after | -0.223 |
| **Epileptic seizures** | Intercept | -0.142 |
| | Wake with cut tongue | 0.563 |
| **FDS** | Intercept | -1.188 |
| | Olfactory hallucinations during | 1.100 |

*Table 4.2.7. LASSO model coefficients.*

##### Confusion matrix

| | | PREDICTED DIAGNOSIS | | |
|---|---|---|---|---|
| | | Syncope | Epilepsy | FDS |
| **TRUE DIAGNOSIS** | Syncope | 56 | 1 | 1 |
| | Epilepsy | 12 | 2 | 0 |
| | FDS | 5 | 1 | 0 |

*Table 4.2.8. Confusion matrix for LASSO model validation.*

### Diagnostic test statistics

Overall classifier accuracy: 0.744 (0.630-0.833)

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **Syncope** | 0.965 (0.874-0.990) | 0.150 (0.040-0.389) | 0.767 (0.651-0.855) | 0.600 (0.170-0.927) |
| **Epilepsy** | 0.143 (0.025-0.438) | 0.969 (0.882-0.995) | 0.500 (0.150-0.850) | 0.838 (0.730-0.910) |
| **FDS** | 0.00 (0-0.483) | 0.986 (0.915-0.999) | 0 (0-0.945) | 0.922 (0.832-0.968) |

*Table 4.2.9. Diagnostic statistics for LASSO classifier by diagnosis.*

### *4.2.8.3. Pilot iPEP classifier performance*

### Patient iPEP only

We also evaluated performance of the pilot iPEP classifiers trained on a cohort of patients with gold-standard diagnoses of syncope, epilepsy, or FDS. The original iPEP classifier from our pilot study used 34 patient-reported items to classify participants into diagnoses of syncope, epilepsy, or FDS. In the pilot validation sample it did so with overall classification accuracy 78.3% (95% confidence interval [CI] 68.4-86.2%).[183] This classifier did not perform significantly worse in this validation sample, identifying 135/178 diagnoses accurately (75.8% [68.8 – 81.8]).

*Confusion matrix*

| | | PREDICTED DIAGNOSIS | | |
|---|---|---|---|---|
| | | Syncope | Epilepsy | FDS |
| **TRUE DIAGNOSIS** | Syncope | 115 | 1 | 18 |
| | Epilepsy | 16 | 12 | 4 |
| | FDS | 3 | 1 | 8 |

*Table 4.2.10. Pilot iPEP patient-only classifier confusion matrix.*

*Diagnostic test statistics*

Overall classifier accuracy: 0.758 (0.688 – 0.818)

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **Syncope** | 0.858 (0.785-0.910) | 0.568 (0.411-0.713) | 0.858 (0.785-0.910) | 0.568 (0.411-0.713) |
| **Epilepsy** | 0.375 (0.217-0.563) | 0.986 (0.946-0.998) | 0.857 (0.562-0.975) | 0.878 (0.815-0.922) |
| **FDS** | 0.667 (0.354-0.887) | 0.867 (0.804-0.913) | 0.267 (0.130-0.461) | 0.972 (0.928-0.991) |

*Table 4.2.11. Diagnostic test statistics for pilot iPEP patient-only classifier.*

### Patient and witness iPEP

The pilot patient-witness iPEP classifier used 36 patient- and witness-reported items to classify participants into diagnoses of syncope, epilepsy, or FDS. In the pilot validation sample it did so with overall classification accuracy 86.0% (95% confidence interval [CI] 76.9-92.6%).[183] This classifier did not perform significantly worse in this sample, identifying 36/45 diagnoses accurately (78.3% [63.2 – 88.5]).

*Confusion matrix*

| | | PREDICTED DIAGNOSIS |
|---|---|---|

| | | Syncope | Epilepsy | FDS |
|---|---|---|---|---|
| **TRUE DIAGNOSIS** | Syncope | 30 | 4 | 0 |
| | Epilepsy | 3 | 6 | 2 |
| | FDS | 0 | 1 | 0 |

*Table 4.2.12. Confusion matrix for pilot iPEP patient-witness classifier.*

*Diagnostic test statistics (95% CIs)*

Overall classifier accuracy: 0.783 (0.632-0.885)

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **Syncope** | 0.882 (0.716-0.962) | 0.750 (0.428-0.933) | 0.909 (0.745-0.976) | 0.692 (0.389-0.896) |
| **Epilepsy** | 0.545 (0.246-0.818) | 0.857 (0.690-0.946) | 0.545 (0.246-0.819) | 0.857 (0.690-0.946) |
| **FDS** | 0.000 (0.000-0.945) | 0.956 (0.836-0.992) | 0.000 (0.000-0.802) | 0.977 (0.865-0.999) |

*Table 4.2.13. Diagnostic test statistics for pilot iPEP patient-witness classifier.*

### *4.2.8.4. Further descriptive statistics*

#### Certainty of reference diagnoses

Reference standard diagnoses for this study were determined by 2-expert rate evaluation of all available clinical evidence (except PESQ and PEWQ questionnaires or classifiers, to which they were blinded). Through the course of their clinical assessment, participants underwent routine standard of care investigations for duration of follow-up. This allowed us to classify the degree of investigative evidential support for the reference standard diagnoses.

For syncope, we define 'confirmed' syncope as patients for whom a typical attack was captured with explanatory physiological changes on either tilt table testing, lying-standing blood pressure monitoring, or ECG monitoring. 'Supported' diagnoses are those where a typical attack was not captured during monitoring but physiological evidence supports the syncopal diagnosis – either in the form of an ECG with high-risk (as per ESC guidelines[3]) features for arrhythmic syncope, or a documented clinically significant postural drop on lying/standing blood pressure measurements (>20mmHg systolic or >10mmHg diastolic).

For epilepsy, 'confirmed' diagnoses would require capture of a typical attack during simultaneous video- and EEG monitoring, with concordant ictal EEG changes demonstrated. We define 'supported' diagnoses as those with either epileptiform discharges on inter-ictal EEG, or specific features with high risk of epileptogenesis identified on neuroimaging (following the classification of Hakami et al.[184]).

For functional/dissociative seizures (FDS), 'confirmed' diagnosis required capture of a typical attack on video-EEG with no epileptiform activity before, during, or after the attack on EEG, and semiology supportive of FDS (i.e. 'documented' FDS, by the ILAE Task Force classification of LaFrance et al.[185]). 'Supported' diagnosis required clinician review of a video recording showing typical semiology (i.e. 'probable' FDS on the ILAE classification).

| DIAGNOSIS | N (%) CONFIRMED | N (%) SUPPORTED | N (%) CLINICAL |
|---|---|---|---|
| **Syncope** | 5 (3.7) | 37 (27.6) | 92 (68.7) |
| **Epilepsy** | 0 (0.0) | 2 (6.3) | 30 (93.7) |
| **FDS** | 1 (8.3) | 1 (8.3) | 10 (83.3) |

*Table 4.2.14. Degree of certainty of reference diagnoses. Confirmed, supported, and clinical diagnoses are documented in the text. FDS = functional/dissociative seizure.*

4.2. Validation of a machine learning clinical decision aid for the differential diagnosis of transient loss of consciousness

### Comparison of expert diagnoses to initial clinician diagnosis

*Initial assessing clinician*

| | | INITIAL DIAGNOSIS | | | |
|---|---|---|---|---|---|
| | | **Syncope** | **Epilepsy** | **FDS** | **Other** |
| **FINAL DIAGNOSIS** | **Syncope** | 94 | 10 | 0 | 30 |
| | **Epilepsy** | 2 | 25 | 0 | 5 |
| | **FDS** | 4 | 6 | 1 | 1 |

*Table 4.2.15. Confusion matrix for initial assessing clinician (Emergency or Primary care) diagnosis against reference standard diagnosis. 'Other' includes: non-TLOC diagnosis; or no diagnosis given.*

*Discharge diagnosis*

| | | DISCHARGE DIAGNOSIS | | | |
|---|---|---|---|---|---|
| | | **Syncope** | **Epilepsy** | **FDS** | **Other** |
| **FINAL DIAGNOSIS** | **Syncope** | 107 | 11 | 1 | 15 |
| | **Epilepsy** | 3 | 27 | 0 | 2 |
| | **FDS** | 2 | 7 | 2 | 1 |

*Table 4.2.16. Confusion matrix for diagnosis at time of discharge (where patients admitted after first presentation) against reference standard diagnosis. 'Other' includes: non-TLOC diagnosis; or no diagnosis given.*

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# 4.3. Acceptability and utility of an online patient-completed clinical decision aid for the differential diagnosis of transient loss of consciousness: a qualitative interview study

## 4.3.1. Introduction

With rising demand for healthcare services and increasing resource pressures, new tools are needed to ensure more efficient and effective care delivery. Clinical decision aids (CDAs) are sets of instructions use accessible clinical data to provide clear guidance on appropriate next steps in patient management. Appropriately applied, they reduce inefficient resource use and patient risk in acute and emergency settings.[1]

One barrier to the application of CDAs is clinician time burden. This could be addressed through patient self-completion, prior to or following clinician assessment. Existing work demonstrates the feasibility of inviting patients to participate in application of CDAs for their own care.[2,3] Increasingly mobile health (mHealth) technologies such as tablet or smartphone applications are allowing for patient-led data collection and CDA deployment.[4] These have largely been used in outpatient and elective settings for care of patients with chronic health problems,[4–6] but there is evidence that such tools are feasible in the Emergency Department (ED) setting,[7–9] and no less acceptable than clinician-completed use of the same tool.[10] Given that around 9 in 10 patients attending Emergency Departments (EDs) in England in 2018-19 spent over an hour in the department,[11] ED attendances provide ample opportunity for self-administration.

However, in order for such complex interventions to become applicable to general clinical practice, it is important to understand acceptability to their target audience – patients. Guidelines on developing such interventions highlights the importance of acceptability assessment as part of the process.[12,13]

In this paper, we report the acceptability of a novel patient-completed self-assessment CDA to support differential diagnosis of transient loss of consciousness (TLOC) at first presentation – the Paroxysmal Event Symptoms Questionnaire (PESQ). TLOC is a common emergency presentation, but 20-30% are not accurately diagnosed or treated at presentation.[14–16] This has significant resource implications – in 2002, the annual direct medical costs of epilepsy misdiagnosis in England and Wales were estimated to be £29,000,000.[17]

However, the use of CDAs in the diagnosis and management of TLOC presentations has thus far been limited. There are no well-supported criteria for the distinction between all common causes of TLOC. While there are some candidate CDAs designed to discriminate between syncope and bilateral tonic clonic seizures,[18,19] or epilepsy and functional/dissociative seizures (FDS),[20,21] none covers all relevant presentations, nor has been prospectively validated in mixed TLOC populations. This lack of robust criteria is acknowledged in the UK National Institute of Clinical Excellence (NICE) guidance on TLOC assessment, which provides very limited suggestions of features that should lead doctors to “suspect epileptic seizures” based on low and very low quality evidence and expert opinion alone.[22]

In this paper, we use patient experiences of interacting with the PESQ to elucidate understanding of patient requirements of an online, patient-completed CDA. We performed a concurrent nested qualitative study within a larger quantitative research project developing and

validating the PESQ in a first-presentation TLOC population. We aimed to identify whether users found the tool acceptable for use, easy to use, and relevant to their clinical presentation.

## 4.3.2. Methods

The data reported in this paper come from interviews conducted as the qualitative arm of a mixed-method study developing and validating the PESQ for use in a first-presentation TLOC population (§4.2).[23] The design, setting, participants, interviews, and analysis are described fully elsewhere (§2.3).[24]

### *4.3.2.1. Setting and participants*

We conducted the study within a single large hospital Trust in the United Kingdom, screening all patients presenting to the ED with TLOC or referred to first seizure or syncope clinics, within the window of 10th February 2022 to 9th January 2023. All participants recruited to the quantitative study were also invited to interview; we approached those who consented to interview sequentially.

We had a provisional target of 30 participants, using empirical data showing 24 participants reliably achieves saturation, the narrow specification of subject matter, and the study team's expertise in the subject matter.[25]

### *4.3.2.2. Instruments*

All participants in the quantitative study completed the PESQ at or shortly after presentation to the Emergency Department or primary care with TLOC. The majority completed using a simple online platform. The PESQ comprises a brief (52-item) questionnaire comprising 4 demographic questions, 13 regarding patient medical history, and 35 peri-ictal symptoms. The online platform delivered these with sequential presentation of each question, with the option for binary yes/no responses (except for the demographic questions age and years of education, which allowed for any integer answer). Participants could skip questions, or navigate back and forth between them. A previous Appendix lists PESQ items (§4.2.7).[26] For this study, all PESQ data was stored in anonymised fashion on a University secure database.

### *4.3.2.3. Interviews*

Two researchers (AW and DH) conducted remote (video, via Microsoft Teams, or telephone) semi-structured interviews following a pre-defined interview schedule (§2.3.8).[27] Interviews lasted between 30 minutes and one hour. Interviewers noted initial reflections in contemporaneous logs, to support reflexive engagement with later analysis. An independent, non-clinical, professional transcription service transcribed all interviews for subsequent analysis.

### *4.3.2.4. Analysis*

We undertook thematic analysis[28] of transcribed interviews.[29] One researcher (LB; an experienced qualitative researcher with no clinical background or experience of TLOC) imported transcribed interviews into NVivo, and two researchers (LB and AW; a specialty registrar [senior resident] in Neurology, with prior experience as a core trainee [junior resident] in Cardiology and Emergency Medicine) developed and refined themes through iterative coding.

We assessed for saturation through interim analyses, stopping recruitment when saturation was reached.

#### *4.3.2.5. Ethics, review, pre-registration, and reporting.*

We pre-registered the study protocol on clinicaltrials.gov (ID: NCT05367999). Ethical approval came from NHS Health Research Authority Edgbaston Research Ethics Committee (IRAS: 304114). We report results in line with the Standards for Reporting Qualitative Research (SRQR);[30] a completed SRQR checklist is found in an appendix (§4.3.8).[31]

## 4.3.3. Results

#### *4.3.3.1. Participants and demographics*

Of 2811 potential participants screened for recruitment, 1181 were eligible. Of these, 186 responded to the invitation to participate, and 133 also consented to approach for interview. We approached 40 participants for interview, aiming diversity of age and gender. After 20 interviews, we achieved data saturation.

Of interview participants, 14 (70%) received final diagnoses of syncope, and 6 (30%) epilepsy. 12 participants (60%) were female. Median age was 69 years (range 17-90y). Interviews were held a median of 69 days (range 35-283) from initial presentation. Table 4.3.1 displays full participant demographics.

| ID | Age | Gender | Diagnosis |
|---|---|---|---|
| TL095 | 27 | F | Syncope |
| TL099 | 69 | F | Syncope |
| TL101 | 70 | M | Syncope |
| TL106 | 75 | M | Syncope |
| TL109 | 90 | F | Syncope |
| TL122 | 17 | F | Epilepsy |
| TL133 | 73 | M | Syncope |
| TL146 | 69 | F | Syncope |
| TL150 | 78 | F | Syncope |

| | | | |
|---|---|---|---|
| TL152 | 40 | M | Syncope |
| TL157 | 46 | M | Epilepsy |
| TL169 | 27 | F | Epilepsy |
| TL173 | 74 | F | Syncope |
| TL174 | 24 | F | Epilepsy |
| TL176 | 36 | F | Epilepsy |
| TL178 | 82 | M | Epilepsy |
| TL180 | 79 | F | Syncope |
| TL181 | 70 | F | Syncope |
| TL184 | 50 | M | Syncope |
| TL188 | 44 | M | Syncope |

*Table 4.3.1. Demographics and diagnoses of interview participants.*

### *4.3.3.2. Themes*

The semi-structured interview protocol included assessment of both participants' impressions of using the iPEP, and of their assessments of its utility and acceptability in clinical practice. We identified six themes addressing the former – three concerning the content of the questions, and three the design of the tool – and four themes addressing the latter. These are summarised in Table 4.3.3 (§4.3.9).

#### Content of questionnaire

*Appropriate questions*

Respondents were largely happy with the content and clarity of the questions asked and did not suggest significant changes. Several respondents (e.g. TL109; TL169) reported that the very act of being asked questions – and given the words with which to frame their experience – helped to remind them of the symptoms they had experienced and find the means with which to express them.

*Limiting structure*

Other respondents reported that the question structure – in particular, comprising binary yes/no questions – was limiting; they would value the opportunity to elaborate on some of their answers or provide more than yes/no responses. One felt that the questions were too simple and that the opportunity to gain better understanding or "go deeply" into their condition had been missed. More commonly, respondents found they were not always able to give a clear 'yes' or 'no' answer to some questions; "*I appreciate sometimes you wanna force people to make a yes or a no but I didn't [...] find that particularly helpful cos it wasn't really yes or no answers.*" (TL101).

*Questions not matching experience*

Some participants queried the content of the questions. These issues came in three broad forms: an assumption of multiple blackouts, when a person had only experienced one; including too many questions that bore little apparent relevance to their experience; or not including questions that were relevant to their experience.

The PESQ used in this study was derived from a questionnaire originally issued to people with long-standing disorders causing TLOC; as a consequence, many questions referred to "my attacks". Respondents who had only experienced a single episode found this phrasing confusing.

Others (e.g. TL184) noted that many of the questions referenced experiences or historical characteristics that did not appear relevant to them, and found the process of going through lots of questions to give them negative responses difficult; it was "*just a little bit frustrating to go through and go no I've not had that and, no I've not seen that, no this hasn't happened to me.*" The face validity of the questionnaire to respondents appeared to fall when this was the case.

Lastly, some felt that the questions did not sufficiently cover the aspects of their experience – or their general background – that they felt most important. This might be individual symptoms ("*I'd lost control of my bladder* [but] *there was nothing like that to say yes or no*" [TL173]), comorbidities e.g. coeliac disease (TL146), or the social milieu of their TLOC ("*the first one was actually different to the second one [...] if my wife hadn't [...] kinda like pushed me and shouted at me, I would have probably gone out*" [TL101]).

### Design of tool

*Ease of use*

In nearly all cases, respondents reported that the tool was easy to use and the interface easy to operate. A number of respondents (e.g. TL150) noted that the interface was accessible for people who were "*not a hundred percent au fait with the* [...] *computer*" (i.e. low self-evaluated digital literacy). There were no technical issues raised with the exception of one respondent (TL173) who had trouble with an outdated internet browser rather than with the tool itself. The simple format with few options and little text per page was highlighted as making navigation straightforward.

*Language used*

Respondents overwhelmingly felt that the questions they were answering made sense to them. Some struggled with individual items. This arose in some cases due to language use - either specific terms (e.g. 'febrile seizures' for TL101), or more generally language of a higher complexity that was not "*plain English*" (TL178).

*Going beyond the questionnaire*

Several participants made suggestions regarding how the tool could be extended beyond the original questionnaire and its intended applications. For some, this concerned other means in which users could narrate their experience than just the questionnaire, e.g. supplementing the yes/no questions with free-text description of ictal symptoms. Others felt that the tool could be adapted to support users' informational needs. This could be as simple as providing users with a record of their answers, for a reference description of ictal experience they could turn to later (TL099); others thought that after questionnaire completion would be a helpful time for users to be provided with further information about TLOC – either the model's predicted likely diagnosis for the user, with tailored information depending on cause (TL106), or general information regarding the TLOC assessment pathway; users wanted support in "*explaining [...] the process [...] what the next steps would be [...] cos I don't want to have to keep going to my GP or the A+E every time I experience these episodes.*" (TL169)

### Clinical utility and acceptability

*Expectation of benefit*

Many respondents did think that the tool would be helpful in an emergency setting. Those still in situations of diagnostic uncertainty (e.g. TL173) felt that it might streamline the assessment pathway or give them answers sooner. Some (e.g. TL095) saw the tool as licensing access to definitive investigations. Others (e.g. TL169) thought the existence of the questionnaire itself – independent of any diagnostic predictions it could generate – would improve the emergency assessment, by overcoming challenges related to the description of episodes – "*it's hard to put things into words yourself … there can be … a lot of confusion at appointments, trying to explain the … episodes*."

*Unable to gauge benefit*

Others felt they were unable to assess the potential for benefit in the emergency setting. For some (e.g. TL099) this related to the user-generated nature of the questionnaire outputs, which they saw as "*my interpretation*", contrasted with the "*objective method*" of medical assessment (TL099). For others, the difficulty rather came from the confusion or disorientation they experienced at the time of assessment, making this a difficult issue for them to adjudicate.

Many patients reported feeling confused and/or disorientated when asked to complete the questionnaire, even though this was done subsequently in their own home. In at least one case the respondent reported that they had difficulty remembering actually doing it. This in itself raises questions about whether the participants would have been able to complete the questionnaire in an emergency department shortly after their blackout occurred, and whether they would have required help from someone who had witnessed their blackout in order to answer the questions accurately.

*Unlikely to benefit*

Two respondents did not think there was any real prospect for the tool improving patient care; however, in both cases this was because they were entirely satisfied with the standard of care and felt nothing needed to be added to their assessment.

*A tool to benefit clinicians and researchers, not patients*

Two respondents challenged the question of benefit, by drawing a distinction between clinician (or researcher) benefit on the one hand, and patient benefit on the other. For these respondents, the questionnaire treated users as 'sources of information'[32] – passive objects to be 'read' for the clinician/researcher's epistemic gain – rather than 'informants' – peers in the creation and

exchange of knowledge. These respondents (e.g. TL106) felt that they would want to be able to use the outputs themselves – rather than them simply being passed to clinicians – to experience direct benefit. Information on the assessment pathway was again suggested as one means of realising patient benefit: "*to actually be able to say 'Look, you know, we're gonna investigate this and it's looking like you might have something like this going on so here's some reading'.*" (TL184)

## 4.3.4. Discussion

The experiences of our respondents provide general guidance for the development of patient-completed CDAs in the emergency setting, as well as for subsequent refinement of our specific tool. In general, respondents found a simple online questionnaire tool acceptable and understandable, though were divided on their assessment of likely clinical benefit. They highlighted some specific features of such tools that they found of particular value; other uses to which such a tool could be put, to support the patient navigation of their emergency assessment pathway; and identified important considerations in their design to maximise acceptability and potential benefit.

### *4.3.4.1. Value and limitations of structured history-taking*

Some respondents found that having a questionnaire as a prompt for ictal recall and description was itself of value. It could serve as an *aide-memoire* for particular ictal experiences ("*it … highlighted … some of the things that applied to me*;" TL109); or even could provide the conceptual resources for articulating experiences that are "*hard … to put into words yourself, not understanding it*" (TL169). Previous work comparing structured and open interviews to extract seizure histories has demonstrated the value of such systematic closed questioning to enhance the yield of ictal history-taking,[33,34] and support patients' self-understanding and interpretation of experience;[35] our respondents suggest similar benefits can be found when answers are elicited in a patient-administered, self-report format (more practical in resource-limited settings, with online capture easily facilitating computer-aided interpretation of results). This is consonant with previous work demonstrating that, in general, electronic data collection is more effective than paper-based administration of the same questionnaires.[6,36]

However, our participants also highlighted the limitations of this format. They described various ways in which a finite symptom-list, with binary yes/no answers, limited their ability to articulate their experience – whether from a surfeit of irrelevant questions, a lack of relevant ones, or feeling constrained by the insistence on the dichotomous presence or absence of a given experience, regarding which they might feel ambivalent or uncertain. Part of this issue may stem from a failure of the study team to articulate fully the purpose of the questionnaire – not to capture a complete description of the person's TLOC experience, but rather to use certain previously-identified highly-discriminating features to predict likely aetiology of the TLOC – but in part their concerns reflect those found more widely in the experiences of those completing symptom questionnaires. Exploring conditions as diverse as breathlessness and depression, patients completing symptom questionnaires describe ambivalent reactions to the depictions of their experience thus captured.[37,38] They may seek to reformulate questions, recontextualize them (as with TL101's avoiding of the present/absent dichotomy, or TL106's looking for follow-up exploration of symptoms), or reject their framing (as with TL184 concluding that the research was not directed toward their presentation).[38]

Beyond just highlighting this issue, our data suggests means to address it. Respondents were clear on the need for such a CDA to complement, not replace, in-person clinical assessment; and they suggested that a more nuanced description of their experience could be captured by

complementing the structured questions with free-text symptom reporting. The combination of questionnaires and AI-supported analysis of free speech seizure descriptions may address this potential deficiency of an approach based on closed questions alone.[39,40]

#### *4.3.4.2. Emergency Department implementation of patient-completed CDAs*

While much of the research on patient-completed CDAs has focussed on their role in management of chronic conditions,[4,41] there is increasing recognition of the opportunities they offer in acute and emergency care. In particular, several studies have explored the role of patient-completed symptom checkers in supporting triage at the ED front door.[8,9,42] While self-triage CDAs for unselected presentations have been found to perform inadequately,[42] quantitative assessments of acceptability and utility in this setting have generally shown patients are willing and able to interact with such tools.[8,9] Our study enriches this finding with qualitative data exploring patient preferences for interacting with such tools. As well as having a simple, navigable interface, they reported a preference for patient-facing outcomes to demonstrate benefit to them (explored more below).

It is important that such tools be able to be implemented in the ED setting, not only to allow swift and accurate triage, but because it maximises capture of reliable information. The richness of subjective symptom descriptions decrease with time from the event for many TLOC presentations, reducing utility of information captured.[43] Our respondents demonstrated this, with several unable to recall elements of their TLOC they reported in the CDA, or even using the CDA itself. Allowing patients to return to their answers to support recall for other clinical purposes would be one means of enhancing the patient utility of such tools. Allowing delayed access to review answers through an online platform would also provide patients with the opportunity to reflect on their responses, an option valued in other work on patient-completed CDAs.[41]

#### *4.3.4.3. Maximising patient benefit from patient-completed CDAs*

Respondents drew a distinction between clinical benefit – that which achieves the assessing clinician's aims (in particular, diagnosis) – and patient benefit – addressing the patient's immediate needs (prominently, information and management of uncertainty).[24] They proposed ways in which a CDA could be used for patient benefit. Access to answers after time of completion (e.g. through a print-out, or option to log-in and return to questionnaire answers) could help them as a reference point in later assessment and care. They also indicated that the time of questionnaire completion would be an ideal opportunity to address patients' informational needs. An online interface could easily provide patients as well as clinicians information about the results of the CDA and its implications for ongoing management, or links to explanations of assessment pathways and interim management while awaiting definitive diagnosis. As reported elsewhere,[24] these were predominant concerns of respondents after their first assessment for TLOC, and this represents a significant opportunity to add value to patient-completed CDAs.

Existing tools for supporting CDA development and implementation (such as the Theoretical Domains Framework[41,44] or GUIDES checklist[13]) provide high-level overviews of barriers and enablers of implementation; our data allow for more granular practical guidance. On the basis of our data, we offer a set of good practice points for development of patient-completed online CDAs, summarised in Table 4.3.2.

| | |
|---|---|
| **CONTENT** | • Language - consider reading age and educational background of your patient group. Pilot questions for intelligibility.<br>• Relevance - consider explaining relevance of different items so that patients do not disengage from questions not matching their experience. |
| **INTERFACE** | • Simplicity - keeping the CDA as simple as possible aids engagement for those not otherwise used to interacting with online or computer interfaces.<br>• Flexibility - Patients may value the opportunity to adapt their input e.g. through free-text supplements.<br>• Compatibility - If patients will complete the CDA on their own device, ensure cross-compatibility with different browsers and both smartphone and desktop access. |
| **OUTPUTS** | • Data storage - patients may want to be able to retrieve responses and outputs for their own use later. Consider how this can be achieved without increasing time demands or complexity of the interface (e.g. by accounts and logins).<br>• Direct patient benefit - Patients may have different priorities from clinicians in the use of a CDA. Consider what else might be important to patients using the CDA (e.g. information about the clinical problem and self-management or lifestyle advice) and how it can be addressed (e.g. with CDA outputs providing links to patient support groups or information and self-management guidance). |

*Table 4.3.2. Considerations to maximise utility and acceptability of a patient-completed online CDA. CDA = clinical decision aid.*

### *4.3.4.4. Limitations*

We note some important limitations. The inclusion criteria for the quantitative study necessarily left some groups under-represented, particularly those with insufficient English language proficiency to complete the questionnaire, or learning disability that would similarly make self-completion difficult. To an extent this is by design – since cross-language and cross-cultural validation would be necessary anyway after development of the English-language version of such a CDA prior to its employment in different languages. We did include within our sample a diverse age range, including older populations who may be less familiar with online tools – it is a strength of this study to note that even those who self-described as "*not a hundred percent au fait"* with computer use were able to use the tool without difficulty. Previous research has suggested that older adults are less likely to engage with tablet-based mHealth interventions,[4] but that when they do are no less likely to complete than younger patients, suggesting that perceptions of digital literacy may be lower amongst older patients than actual inability to engage with such tools. To remove such barriers, CDA design can emphasis aspects more likely to be acceptable in this demographic,[45] such as simple user interfaces, minimising numbers of clicks and scrolls, without intrusive features like pop-ups.

We also recruited only a small proportion of those eligible to participate. Anecdotally, the study team noted that recruitment rates appeared higher when potential participants were approached directly and contemporaneously with their assessment, rather than retrospectively by letter. Future research could assess differential recruitment rates and effects on sample representativeness of different recruitment pathways.

Additionally, as a measure of acceptability of such a CDA, we only describe qualitative findings; further work could complement this with quantitative data, both survey responses identifying users' evaluations of acceptability (along dimensions guided by the data presented in this study), and objective measures e.g. non-completion of the questionnaire.

## 4.3.5. Conclusions

In this study we find that an online, patient-completed questionnaire tool to support a CDA for the differential diagnosis of TLOC is generally acceptable to users, though opinions diverge on the likely utility of such a tool. Respondents highlighted the distinction between clinician and patient benefit – noting that while interests overlap, they are not coextensive – and offered means to improve the tool such that, in addition to supporting a CDA for clinical benefit, it could address the informational needs of patients at the time of their first assessment for TLOC.

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## 4.3.8. Appendix 1: SRQR checklist

| No. Topic | Item | Page |
|---|---|---|
| **Title and abstract** | | |
| S1 Title | Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended | 175 |
| S2 Abstract | Summary of key elements of the study using the abstract format of the intended publication; typically includes objective, methods, results, and conclusions | 131-2 |
| **Introduction** | | |
| S3 Problem formulation | Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement | 175 |
| S4 Purpose or research question | Purpose of the study and specific objectives or questions | 175-6 |
| **Methods** | | |
| S5 Qualitative approach and research paradigm | Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., positivist, constructivist/interpretivist) is also recommended | 176 |
| S6 Researcher characteristics and reflexivity | Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, or transferability | 176 |
| S7 Context | Setting/site and salient contextual factors; rationale[a] | 176 |
| S8 Sampling strategy | How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[a] | 176 |
| S9 Ethical issues pertaining to human subjects | Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues | 177 |
| S10 Data collection methods | Types of data collected; details of data collection procedures including (as appropriate) start and stop | 176 |

| | | |
|---|---|---|
| | dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[a] | |
| S11 Data collection instruments and technologies | Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study | Appendix 1 |
| S12 Units of study | Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results) | 177-8 |
| S13 Data processing | Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts | 176 |
| S14 Data analysis | Process by which inferences, themes, etc., were identified and developed, including researchers involved in data analysis; usually references a specific paradigm or approach; rationale[a] | 176 |
| S15 Techniques to enhance trustworthiness | Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[a] | 176 |
| **Results/Findings** | | |
| S16 Synthesis and interpretation | Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory | 178-81 |
| S17 Links to empirical data | Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings | 178-81 |
| **Discussion** | | |
| S18 Integration with prior work, implications, transferability, and contribution(s) to the field | Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field | 181-3 |
| S19 Limitations | Trustworthiness and limitations of findings | 183-4 |
| **Other** | | |
| S20 Conflicts of interest | Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed | 184 |
| S21 Funding | Sources of funding and other support; role of funders in data collection, interpretation, and reporting | 184 |

## 4.3.9. Appendix 2: Table of themes

| TOPIC | THEME | ILLUSTRATIVE QUOTATIONS |
|---|---|---|
| **1. Content of questionnaire** | 1.1. Appropriate questions | "*It was relevant and applicable.*" [TL095]<br><br>"*I'm not medical myself so I, I wouldn't know all the ins and outs but you could see that it was, there were some that were sort of leaning towards is it a heart issue or is it an epilepsy issue or is there, you know, other aspects of, of medical stuff going on. So yeah, you could see what it was aiming for.*" [TL184]<br><br>A: "*Well it just highlighted, you know, some of the things that applied to me.*" [TL109] |
| | 1.2. Limiting structure | "*I found it very narrow being yes and no [...] I appreciate sometimes you wanna force people to make a yes or a no but [...] it wasn't really yes or no answers.*" [TL101]<br><br>"*[A]t the end of a lot of questionnaires it's one, two, three and at the bottom 'other' if there'd have been an 'other' possibly, you know, a blank one, if there's anything that we've not covered could you please fill in sorta thing, if you get me drift?*" [TL146]<br><br>"*Generally yes; in fact probably the only feeling I've got about it was it was perhaps a little bit too simple and didn't go into things too deeply.*" [TL106] |
| | 1.3. Questions not matching experience | "*I mean they did, they were sort of appropriate but not, they seemed to be sorta more [...] generalised than [...] my specific case.*" [TL106]<br><br>"*[I]t was just a little bit frustrating to go through and go no I've not had that and, no I've not seen that, no this hasn't happened to me, and it seemed to be lots of nos [...] Iwas more sort of thinking [...] something's happened to me and there's obviously some research going on around this [...], and what's happened to me doesn't seem to fit with what the research is looking at.*" [TL184]<br><br>"*Obviously it's a generic one and [...] there are people that will have had other issues [...] I'm not saying that there's anything wrong with it but it [...] wasn't relevant to my experience*". [TL099] |
| **2. Design of tool** | 2.1. Ease of use | "*If I used it it must have been OK [...] because I'm not a hundred percent au fait with the [...] computer.*" [TL150] |

| | | |
|---|---|---|
| | | *"I think the content on the website is very, is very clear [...] easy to read, and the questions are worded very well..... I think it was like very easy to like navigate."* [TL169]<br><br>"*It was* ['a battle' to get on] *and then, as I say, the second time I tried to get on for my son to do it we just couldn't manage it."* [TL173] |
| | 2.2. Language used | *"You know, the way they were worded wasn't [...] plain English [...] wording was, you know, hospital speech, I would say [...] If it had been in plain English it'd have been easier to understand".* [TL178]<br><br>*"I mean even though I come from [a healthcare background], I don't know what febrile seizures means [...] for instance number five, my attacks are triggered by sleep deprivation; well it might have been better to have said associated cos [...] it depends what you're wanting to know, because I'd not been sleeping well for [...] quite a long time prior to these attacks and so I wouldn't say it's triggered, [...] but it could be associated with it."* [TL101] |
| | 2.3. Going beyond the questionnaire | *"[I]f I'd been sent a questionnaire in the post I would have probably have done it and posted it back and kept a record of it for myself as well. I, if I've done it online does that mean there is a record of it for me somewhere?"* [TL099]<br><br>*"[I]f I could get some further information on what was causing the blackouts or likely to in my particular circumstances, yeah, I, I think that's got to be a benefit."* [TL106]<br><br>*"I think as well maybe in [...] the questionnaire kind of explaining [...] the process maybe or like what the next steps would be, cos I think waiting in this kinda period of not knowing what it [...] is and not knowing when you're kind of gonna be seen it [...] makes it [...] a little bit difficult cos obviously I don't want to have to keep going to my GP or the A & E every time I experience these episodes."* [TL169] |
| **3. Clinical utility** | 3.1. Expectation of benefit | "*I think definitely one hundred percent, because it's hard to put things into words yourself, not understanding it; to be able to kind of have those questions can make you kind of look back and provide the answers for that question, whereas when I went to the GP it was so difficult to kind of explain exactly what it was.*" [TL169] |

| | | |
|---|---|---|
| | | *"Probably, because it might have then led to, more questions might have been asked which might have led to more investigations."* [TL095] |
| | 3.2. Unable to gauge benefit | *"I don't know [...] I suppose this is my [...] interpretation and A & E is an objective method, isn't it, of seeing what I, how I am."* [TL099]<br><br>*"To be honest, I can't remember, I can't remember doing it. I just remember, I remember doing the questionnaire but I don't remember getting out of it really."* [TL099]<br><br>"*I looked at it when you sent it through and I was thinking I don't really remember filling it out. I, I remember thinking I need to fill that out, but it, certainly in the week or two after the seizure lots of things were just coming and going."* [TL157] |
| | 3.3. Unlikely to benefit | "*"I, I don't think so. I think that on admission it was, you know, I was dealt with very, very well and everything they did was very thorough and the explanations they gave were, were really clear; so I, I knew what was going on and I knew that the right things were being investigated."* [TL184]<br><br>Q: "*So you think, don't think it would have added much to how things went and it would have gone more or less the same anyway?"*<br>A: "*I think so, yeah."* [TL181] |
| | 3.4. A tool for clinicians and researchers, not patients | "[I]*t's more sort of, if you like, helpful to you and your colleagues rather than myself doing the questionnaire because obviously I'm inputting the information to you rather than using the information meself, if you know what I'm saying?"* [TL106]<br><br>*"[I]f I'd come in with, you know, a classic heart issue or a classic epilepsy type issue or, you know, some of the other things that you might be able to almost screen for with a questionnaire, to actually be able to say "Look, you know, we're gonna investigate this and it's looking like you might have something like this going on so here's some reading" and, and to be able to give that sort of pre-warning almost to the medical team that it's looking like this is an issue, then I think that would be really helpful. It's just in, just in my case it, it probably wouldn't match whatever you had, so..."* [TL184] |

*Table 4.3.3. Summary of themes with illustrative quotations.*

# Section 5 Conclusion

## 5.1. Thesis summary

This thesis provides evidence of the ongoing need for more robust criteria to support generalist clinicians in prompt and accurate differential diagnosis of the transient loss of consciousness. It supplements existing data on the direct and indirect health and economic costs of TLOC misdiagnosis with qualitative evidence of the direct quality-of-life impact of experiencing a first TLOC, and receiving an inconclusive – or no – diagnosis at point of presentation, and how meeting patients' informational needs can help them navigate this 'No Man's Land'.

I also demonstrate the need for TLOC diagnosis research to take place in the setting where initial TLOC assessment takes place; patient cohorts recruited exclusively from secondary or tertiary care settings show a pronounced spectrum bias that can limit applicability of results to the first presentation. Well-validated diagnostic criteria in the first presentation setting are needed.

While the CDA for TLOC differential diagnosis developed and validated in this thesis did not statistically significantly (though did numerically) outperform the assessing clinician's diagnosis, this thesis does provide important further evidence to support development of a CDA for this setting. Post-hoc analysis demonstrated that using the CDA output to augment clinician assessment – rather than evaluating either clinician or CDA alone – could outperform both; this more accurately reflects how CDAs would be used in clinical practice, to support and not supplant decision-making. I demonstrate the feasibility of patient-completed, online CDAs in diagnostic triage. Patients generally found engaging with such a tool accessible and acceptable. Furthermore, they highlighted how such a tool could be used to meet their needs as well as the clinician's, by providing patient-facing information on TLOC assessment, diagnosis, and management.

Beyond demonstration of their clinical utility, patient-completed CDAs carve out a space in clinical assessment to ensure the patient's experience is not lost in the clinical assessment. The author and person with epilepsy Margiad Evans observed over 70 years ago that, in the assessment and management of TLOC, "the patient's half, that he can contribute to knowledge, is ignored." In this thesis I hope to go some way to rectifying this ignorance.

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