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Seizure self-prediction; myth or missed opportunity?

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Abstract

Purpose

Many patients report being able to predict their own seizures, and yet most seizures appear to strike out of the blue. This inherent contradiction makes the topic of seizure self-prediction controversial as well as difficult to study. Here we review the evidence for whether this ability exists, how many patients are capable of self-prediction and the nature of this capability, and whether this could provide a target for intervention.

Methods

Systematic searches of bibliographic databases including MEDLINE, EMBASE and PsycINFO through OVID were performed to identify relevant papers which were then screened by the study authors for inclusion in the study. 18 papers were selected for inclusion as the focus of this review.

Results

On the basis of two studies, between 17% and 41% of patients demonstrate a significantly greater than chance ability to predict an upcoming seizure in the following 12-hour time window. This risk is correlated with self-reported anxiety, stress, sleep deprivation, mood and certain prodromal symptoms. However, there is no evidence for any subjective experience which directly heralds an imminent seizure. Thus, while patients may be aware of seizure risk, and have some ability to predict seizure occurrence over a wide time window, they are unable to subjectively recognise seizure onset in advance.

Conclusion

Utilising subjectively acquired knowledge of seizure risk may provide a widely implementable tool for targeted intervention. The risk fluctuates over a time course appropriate for pharmacotherapy which may improve seizure control and the side-effect profile of anti-epileptic medication.

Key Words

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Introduction

For most people with epilepsy seizures appear out of the blue with little or no warning. It is this inherent unpredictability that leads to much of the associated morbidity and social impact. However, it has long been recognised that some patients experience warning symptoms minutes or even hours before a seizure[1]. This is of huge potential benefit as it would allow patients to intervene to prevent the seizure occurring or to mitigate its consequences by taking avoiding action or additional medication. An ability to predict generalised tonic-clonic seizures may help mitigate the risk of

SUDEP (Sudden Unexpected Death in Epilepsy). Further study of how patients self-predict seizures could also help understand the underlying neurobiology.

The topic is difficult to study. The majority of studies are based on questionnaires or interviews with patients. These are highly subjective, and produce evidence which is retrospective and largely anecdotal. They give an insight into patient beliefs about their seizures and premonitory symptoms, but little hard evidence to support them. Collecting data on the temporal relationship between symptoms and the occurrence of seizures is even more difficult. Paper diaries of seizures are often poorly maintained and unreliable, and patient recognition and recall of seizures is imprecise[2]. They are also prone to retrospective entry and manipulation. Electronic diaries allow timestamping of data entry, but do not necessarily improve patient compliance and accuracy[3].

The patient population itself is extremely heterogeneous with over 30 different epileptic syndromes and complicated by mimics such as dissociative seizures. Without very large numbers of subjects, subgroup analysis is difficult and patients with different types of epilepsy end up being analysed within the same cohort. Furthermore, the terminology used to describe subjective experiences preceding a seizure, such as prodrome, aura, premonitory symptoms and precipitating factors do not have clear definitions and are often used interchangeably. This has led to very different criteria for categorising premonitory symptoms between studies. For example, some studies simply ask patients about any symptoms noticed prior to a seizure, while other require symptoms to occur at least 30 minutes prior to a seizure and be semiologically distinct from any usual aura.

Given the lack of consensus and the potential benefit to patients we performed a review of the published literature seeking to answer the following questions: Can patients truly predict their seizures? If so, what proportion of patients are capable of doing so, on the basis of what information, and could this be used for interventional therapies?

Methods

Our search strategy is detailed in table 1. Concept one and three terms are searched as keywords, while concept 2 terms are searched as subject headings. Concept four and five are used to narrow down results to exclude papers using EEG for seizure prediction, and look for papers studying human seizure prediction since 1980.

Searches were run on the MEDLINE, EMBASE and PsycINFO databases through OVID in December 2014 by EG. We used all five concepts in all searches, and subject headings were used without subheadings. The search of the MEDLINE database used focussed subject headings and returned 233 results. The searches of EMBASE and PsycINFO used unfocussed subject headings and returned 523 and 180 results respectively, giving a total of 936 papers. Removal of duplicate results returned 661 papers for screening. Review author HM screened the titles and abstracts of all identified studies for inclusion resulting in the retrieval of 17 full-text papers. Full-text study reports were then independently screened by review authors MM and HM for inclusion and all papers were considered suitable for inclusion. Reference lists of primary studies and review articles were checked for additional references resulting in one further paper considered suitable for inclusion. A total of 18 papers comprised the focus of this review.

We have excluded reflex epilepsies from this review, as these epilepsies are defined by the reliable triggering of seizures by a known stimulant. Therefore the central question of this review; whether patients are able to predict their own seizures, is redundant in these populations. Additionally, consideration of this population of patients does not contribute anything to the analysis of seizure self-prediction by the general epilepsy population, and would indeed confound the results.

Within the appraised literature the terminology used was somewhat inconsistent; however most authors regarded prodromes as symptoms which may occur hours to minutes before a seizure. They were considered to be non-ictal, but their cause is unknown. Triggers, or precipitating factors, were external factors which exposure to, or experience of, may precipitate a seizure. Premonitory symptoms referred to any prodromal symptoms or precipitating factors which the patient believed had, or which could be shown to have, predictive ability for seizure risk. Due to the heterogeneity in study design, definitions and outcomes, a meta-analysis of data was not considered possible. However, in most studies there was a clear distinction made between precipitating factors and prodromes, albeit with slightly differing definitions in terms of temporal relationship to an ensuing seizure, and hence we divided the analysis into these two broad categories.

Precipitating factors and seizure risk

It has been suggested that truly unprovoked seizures may be rare, and that seizures predominantly occur in the presence of precipitating factors[4]. Seizure triggers are widely reported in the general epilepsy population, with up to 90% of patients reporting having at least one seizure precipitant and the majority of patients reporting multiple precipitants[4-14]. In addition to those studies in table 2, numerous other studies have qualitatively investigated seizure precipitants[15-17]. The most commonly described precipitants were stress, anxiety, mood disturbances, and sleep deprivation, as well as missing or changing medications. The study by Pirikahana and Dono also collected data from 78 carers of patients with epilepsy (PWE) of whom 88.5% reported being able to recognise at least one trigger factor[13]. They also noted that amongst PWE, younger patients were significantly more likely to report trigger factors than older patients, particularly tiredness, stress and medication changes[11].

As the study by Dahl noted, 84% of interviewed patients reported being able to recognise seizure onset through particular situations in which seizures tended to occur[5]. If seizures are truly precipitated by these factors, then their presence would provide predictive information. Dubois *et al.* performed a prospective seizure prediction study during inpatient admission for video EEG monitoring, asking patients each day if they predicted a seizure would occur in the next 24 hours. When patients made a negative prediction the chances of a seizure in the next 24 hours was 0.151. When patients made a positive prediction this doubled to 0.320; a significant increase[2]. The study however did not attempt to elucidate on what basis subjects were making these predictions.

Studies by Haut *et al.* explored this effect in greater detail using prospective seizure diaries given to adult outpatients with focal epilepsy[9]. In the first study participants were required to keep a paper diary of seizures, and in addition to answer the question; *"Do you think you will have a seizure in the next 24 hours: very likely, likely, unlikely or very unlikely?"*, each day. 71 patients returned at least 30 days of seizure diary and were included in the study. The standout finding was that a small subset of patients (12 of 71) contribute lots of successful predictions. For this subgroup of predictors, the sensitivity was 37%, and the specificity was 90%. Crucially the positive predictive value of a response of "*very likely*" was around 40%, while the negative predictive value of the response "*very unlikely*"

was around 90%. The odds ratio for a positive prediction was 3.14. The subgroup of the remaining 59 participants was not as able to predict their seizures, however the overall OR for this group remained significant at 1.38 (1.06 to 1.80). Predictors were younger than non-predictors and had higher seizure frequency, but there was no association with seizure localisation.

As part of the above study, patients had also been asked to record medication compliance, hours of sleep, stress and anxiety on 10-point scales, alcohol intake and menstruation on a daily basis[10]. Using a multivariate regression model including known or suspected seizure precipitants they found that unit changes in hours of sleep, anxiety score or stress score were significant predictive factors of a seizure in the following 24 hours with odds ratios of 0.91 (0.82 to 0.99), 1.07 (1.02 to 1.12) and 1.06 (1.01 to 1.12) respectively. In a second model in which seizure self-prediction was included, positive self-prediction was highly significant with an OR of 3.7 (1.8 to 7.2). High levels of stress, anxiety and lack of sleep were associated with greater likelihood of a subject's positive self-prediction. As a result, in this second model stress and anxiety scores were now non-significant predictive factors, while sleep remained significant. This suggests that patients are using either conscious or unconscious knowledge of potential precipitating factors to make predictions, and that these factors do indeed correlate with seizure occurrence.

This is reinforced in a later paper which found in addition that both general mood and changes in mood were correlated with the risk of an upcoming seizure[7]. They also looked at patient reporting of 18 premonitory symptoms and found that 10 of these symptoms were strongly correlated with increased seizure risk in the following 12 hours, among them; blurred vision, light sensitivity, dizziness and feeling emotional. However patient self-prediction outperforms a combination of all the measured factors suggesting that patients are using additional sources of information to make superior predictions.

In a further study Haut *et al*. refined this protocol using an e-diary on a Personal Digital Assistant (PDA) as opposed to a paper diary[8]. Patients were asked to make a prediction twice daily 12 hours apart, and the times at which they did so were logged. 19 patients were included in this study of which 9 could predict their seizures to a statistically significant degree. For these 9 predictive factors, the mean sensitivity was 34% and mean specificity was 92%. By logging the times of self-prediction as well as of seizures it is possible to look at the timeframe for seizure occurrence following self-prediction. For the population as a whole, the odds ratio for a seizure following a positive self-prediction was 4.02 ($p<0.001$) at 0-4h post-prediction, peaking at 6.72 ($p<0.001$) at 4-6h, then 2.81 ($p<0.001$) at 6-12h and falling to non-significance >12h after prediction.

Given this apparent predictive ability it is perhaps unsurprising that significant numbers of patients claim they can prevent a seizure from happening, with studies giving proportions of between 25% and 50%[6; 11-14; 18]. The most common methods which patients employed to prevent seizures were relaxing (deep breathing, closing eyes, being quiet), concentration (reading, praying) or taking extra anti-epileptic medication. However, it is telling that in the study by Pirikahana and Dono, while 26.7% PWE reported being able to stop a seizure occurring only 15.4% of carers felt their patients could stop a seizure. Additionally 62.2% of PWE admitted to being unable to stop seizures occurring while 75.6% of carers stated that their patient was unable to do so[12].

Prodromes and the pre-ictal state

One reason patients may struggle to stop seizures is that the seizure predictability demonstrated so far seems to relate to a heightened risk of seizure occurrence over a wide time window, as opposed to direct warning of an imminent seizure. The ability to detect some physiological change which reliably heralds the onset of a seizure is a topic of intense research, as it would provide a powerful tool for informing interventions aimed at preventing seizure generation.

Evidence that a pre-ictal state does exist, and has a neurophysiological origin, comes from several sources. Increases in brain perfusion have been detected prior to seizures using fMRI[19-21] and near-infrared spectroscopy[22; 23]. Cortical hyperexcitability has also been shown to precede seizures using transcranial magnetic stimulation[24; 25] and cortico-cortical evoked potentials[26; 27]. In addition, much work has been done looking for changes in the patient's EEG heralding an upcoming seizure. For example a study by Li *et al.* looking at the EEGs of 14 patients with mediobasal temporal lobe epilepsy[28]. Comparing 61 interictal epochs with 44 pre-ictal epochs an hour in duration, they found a measurable change in the EEG signal occurring around 35 minutes prior to seizure onset and lasting until seizure start.

A possible subjective manifestation of the pre-ictal state is the epileptic prodrome. A prodrome is best described as a set of symptoms experienced by a patient, over a timeframe of minutes to hours prior to a seizure, which is perceived to herald an imminent seizure but is semiologically distinct from an aura. Prodromal symptoms are widely reported anecdotally, but studies which questioned patients whether they experienced prodromes report the proportion of patients who experience prodromes as anywhere from 7% to 87%[11-13; 18; 29-31]. Much of this variability can be put down to the methodology of the studies; namely how subjects were asked about prodromal symptoms, and how a prodrome was defined. For example, the study by Pirikahana and Dono simply asked, *"Have you experienced/noticed any of the following symptoms just before a seizure?"*, followed by a list of 16 possible symptoms. There was no control for timing relative to seizure onset, or whether these symptoms constituted the patients semiology, and as such they found 86.9% of patients reported experiencing at least one of the listed symptoms prior to a seizure[12].

In contrast the study by Hughes *et al.* required that a prodrome must precede a seizure by at least 30 minutes and found that only 29% of patients reported having such symptoms[29]. Schulze-Bonhage *et al.* also excluded prodromal symptoms if they ever occurred within this 30-minute cut-off, and required that the semiology of a prodrome must be distinguishable from their habitual seizures. They found that only 7% (35/500) of patients met these criteria for defining a prodrome. Of these, 25 could give a temporal relationship; 9/25 estimated the prodrome occurred 30-60mins prior to a seizure, 10/25 estimated 1-3 hours, and 6/25 estimated greater than 3 hours[31]. Other studies have reported prodromal symptoms occurring up to 24 hours in advance of seizures, further blurring the distinction between prodromes and precipitating factors[7]. Rajna *et al.* also looked in more detail at the timing of prodromal symptoms. Of the 562 patients recruited, 262 (46.6%) had experienced prodromes, and 233 could give more precise information on how far in advance these symptoms preceded their seizures. Of these 13.7% had symptoms which preceded the seizure by 0-10 seconds, 44.6% by 10-300s and 41.6% by >300 seconds[18], again calling the definition of 'prodrome' into doubt.

It is nevertheless clear that the premonitory symptoms reported by patients are occurring over a timeframe from seconds to hours in advance of a seizure. Over short time frames preceding a

seizure, this represents the blurred distinction between an aura and a prodrome, and the variation between studies depends upon how carefully a study has tried to separate the two. Over longer time frames prodromal symptoms which occur a significant time in advance of a seizure become harder for patients to causally link to that seizure. It can also be noted that the proportion of patients responding varies depending on whether they are asked open questions, or asked to pick symptoms from a list.

Despite the large variation in the proportion of patients reporting prodromal symptoms between studies, one aspect on which they are remarkably consistent is what those symptoms most commonly are. The most widely reported prodromes are mood disorders; symptoms such as irritability, anxiety, depression, fear, anger, excitability and reduced tolerance. Other common prodromes include a non-specific "funny feeling", headache, and cognitive disturbances; bradypsychia, speech disturbances and attentional deficits. The presence of mood and cognitive changes prior to a seizure is corroborated by carers of PWE[13].

Most studies do not report any difference in the patient demographics between the groups which do and do not experience prodromes. There is limited evidence that prodromes occur predominantly in focal epilepsies[18; 29], and that prodromes are more often followed by a generalised tonic-clonic seizure or complex partial seizure, as opposed to a simple partial seizure[18].

The weakness of all these studies lies in the relationship between premonitory symptoms and the seizure being accurately identified by the patient. Maiwald *et al.* sought to negate this problem using a PDA based e-diary of prodromal symptoms and seizures, allowing timestamping of data entry[32]. Of 500 patients interviewed, 31 claimed to have prodromal symptoms at least 30 minutes in advance of a seizure, and 11 took part in the study. Of these only 5 of the patients experienced any seizures over the 4-5 week period. In total, they experienced 29 seizures and 66 prodromes, with twelve of the seizures being preceded by a prodrome within 24 hours corresponding to a sensitivity of 44.1%. They calculated that the prodromes were no better at predicting a seizure in the following 24 hours than a random prediction.

Discussion

Any discussion about seizure self-prediction confronts two contradictory viewpoints. One the one hand, epilepsy is characterised by the spontaneous and seemingly random occurrence of seizures. Indeed, it is this aspect that causes such a profound effect on patients' quality of life and leads to many of the legal restrictions placed on patients. At the same time, as long as there has been epilepsy there has been the concept that seizures can be provoked or triggered, and that they may be preceded by warning signs or symptoms. The evidence presented herein supports the conclusion that some patients do indeed have a degree of awareness of their underlying seizure risk. The series of studies by Haut *et al.* show that a subgroup of patients is able to utilise information gained from self-recognition of factors such as anxiety and stress to inform the perceived risk of impending seizures. This predictive ability peaks at 4-6 hours prior to a seizure and is seen in 17-41% of patients[7-10].

The evidence for patient awareness of the precise timing of an upcoming seizure is limited to anecdotal reporting by patients. While studies looking at the timing of prodromes find mixed evidence as to whether they are related to seizures, they do not find any close temporal link, on the

order of minutes, or with high positive predictive value. The study by Maiwald *et al.* suggests that many patients may be identifying prodromal symptoms retrospectively. Studies by *Haut et al*. also asked patients about prodromal symptoms and found a number of these symptoms were related to increased seizure risk in the following epoch. Taken together the evidence suggests that what patients are reporting as prodromes are more appropriately interpreted as representing increased seizure risk, but are not heralding an imminent seizure.

There is significant overlap in the nature of the symptoms described as prodromes and those described as precipitating factors; particularly mood disruptions and cognitive changes. They are also functionally similar, both being prognostic for seizure risk, but neither heralding seizure onset. Factors such as stress, anxiety and tiredness may not be external precipitating factors, but may be internally generated by a neurological process common to that which increases seizure risk and generates prodromal symptoms. With this in mind we would like to rationalise the terminology used. A *precipitating factor* should refer to any *external* factor which increases the risk of an upcoming seizure. This could include sleep deprivation, alcohol, missed medication, or other drug use. A *prodrome* should refer to any set of symptoms experienced by the patient which do not have an obvious external source, are semiologically distinct from their habitual seizures and are perceived, or shown to be, related to seizure risk.

Regarding the distinction between seizure *prodrome* and *aura*, we believe the criteria used by Schulze-Bonhage *et al*[31] is most appropriate for distinguishing the two. An *aura* is part of the ictal event, is related to focal seizure activity in the corresponding brain region, and reliably precedes seizure progression. A *prodrome* should occur at least 30 minutes prior to seizure onset, and be semiologically distinct from a patient's habitual auras.

So, is it possible to intervene to prevent seizures? Patients certainly report behaviours aimed at preventing seizures after experiencing prodromes, such as resting and relaxing, or doing something which requires concentration, or taking additional medication[6; 14]. However, since most prodromes do not immediately precede a seizure, then short-term behavioural interventions are unlikely to be of any use. Few patients report these behaviours working, and carers suggest they are even less successful than patients think[13].

Patients however are able to appraise seizure risk, and this risk is one which rises to a peak 4-6 hours following prediction before reducing again. This provides an ideal timeframe for targeted pharmacotherapy. Any change in medication, or dose, takes on the order of hours to increase the steady-state blood concentration of the drug, and persists over a timeframe equivalent to that of increased seizure risk. An anti-epileptic drug regime which is responsive to seizure self-prediction may provide both better seizure control and an improved side effect profile. An alternative option would be the use of rescue medication during periods of increased seizure risk. This has been shown to have a positive benefit in patients both in terms of seizure control, prevention of GTCS and seizure clustering[33].

The studies by Haut *et al.* suggest that only a proportion of the population are good at seizure self-prediction, meaning much of the population who are unable to predict their seizure risk would not be amenable to this intervention. Can we make the rest of the population predictors? The same studies suggest that anxiety, mood, changes in mood and several prodromal symptoms are correlated with increased seizure risk over the following 12 hours. It may be that the predictors are

simply the patients most able to perform this self-analysis and predict seizure risk. In which case, it might be possible to create an instrument to collect this information from patients and calculate seizure risk with a view to guiding intervention or informing the patient. Alternatively, the true proportion of patients able to predict their seizures may not be apparent due to the limited duration of the studies. This is supported by the increased proportion of predictors in the longer studies, and the widespread perception of patients to have some predictive ability.

In conclusion, the ability of patients to predict seizure likelihood based on subjective experience is a real phenomenon based on the available evidence, and provides an easily implementable approach for improving seizure control through targeted pharmacotherapy.

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Concept 1: Sensation	**Concept 2: Disease**	**Concept 3: Species**	**Concept 4: EXCLUDE**	**Concept 5: INCLUDE**
Prodrom*	Epilepsy	Self*	EEG	human
Premonit*	Epileptic			1980-current
Predict*	Seizure			
Anticipat*	Ictus			
Warn*	Fit			
Pre-ictal	Episode			
Preictal	Event			
Pre-seizure	Paroxysm			
Preseizure	Convulsion			
Precipit*				
Impend*				
Presag*				
Aura*				
Trigger*				

Table 1: Search grid used to plan search strategy.

Study	n	% with seizure precipitants	Most common precipitants (%)	Sample
Pirikahana and Dono, 2009	225	89.8	Tiredness (65.3) Stress (64.0) Sleep deprivation (55.1)	Adults in Epilepsy foundation of Victoria's social research participant database
Spector *et al.*, 2000	100	91	Tense/anxious (66) Depressed (47) Tired (44)	Adult out patients
Dionisio and Tatum, 2010	112	74	Worry & stress (67) Sleep deprivation (58) Missed medication (54)	234 adult outpatients, subgroup analysis on 112 PWE with auras
Dahl, 1999	160	Not Reported	Drowsiness (84) Overactivity (83) Stress (78)	PWE aged 8-50 with frequency >3 seizures per week

Table 2: Summary of studies on seizure precipitants

Study	n	% with prodromal symptoms	Most common precipitants (%)	Sample
Rajna *et al.*, 1997	562	46.6	Headache Epigastric sensation "Funny Feeling"	adult outpatients with >6 month history of epilepsy
Hughes *et al.*, 1993	148	29.1	Emotional changes (50) Headache (13) "Funny Feeling" (8.3)	adult outpatients
Pirikahana and Dono, 2009	225	86.9	"Funny Feeling" (78.9) Confusion (60.0) Anxiety (52.8)	Adults in Epilepsy foundation of Victoria's social research participant database
Schulze-Bonhage *et al.*, 2006	500	7.0	Restlessness (28.6) Headache (17.1) Malaise (14.2)	adult outpatients
Scaramelli *et al.*, 2009	100	39.0	Behavioural Changes (33.3) Cognitive disturbances (28.2) Anxiety and mood disorders (23.1)	outpatients >14 years old

Table 3: Summary of studies on prodromal symptoms