Funktionelle neurologische Störungen: Psychogene nicht-epileptische Anfälle

PD Dr. Martin Hardmeier
Stv. Leiter Sprechstunde für Epilepsie und Schlaf
Leiter Langzeit-EEG-Video-Monitoring
Neurologie, USB

Fortbildung der Psychosomatik, USB
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Überblick

Definition und Epidemiologie

Erklärungsmodelle für funktionelle neurologische Störungen und PNES

Psychogene nicht-epileptische Anfälle
- Semiologie
- Ko-Morbiditäten
- Diagnostische Kriterien
- Anamnese und Conversation analysis
- EEG-Video-Langzeitmonitoring
- Behandlungsansätze

Zusammenfassung

Definition und Epidemiologie

Psychogene nicht-epileptische Anfälle (PNES) =
Involuntary, experiental or behavioural responses to internal or external triggers

Incidence: 5/100,000   Prevalence: 33/100,000
- Manifestation mainly in early adulthood (range: children as young as five to older adults)
- About 20% presenting to a seizure clinic is diagnosed with PNES

PNES fulfils in most cases DSM-5 criteria of a **Functional Neurological Symptom Disorder (FND)**

The diagnostic entity "PNES" has primarily developed because patients with these seizures present to medical settings that are also used by patients with epilepsy, and because experts charged with making diagnoses have tended to attribute these phenomena to "psychological" causes without wanting to commit themselves to a particular mechanism or to identifying a specific psychiatric disorder.

The comparator model for neural control of action and agency

- Action begins with an intention or desired goal state
- an inverse model computes the motor command and generates the motor command
- a forward model uses an efference copy to predict the probable sensory consequences
- Prediction is compared with sensory feedback signals
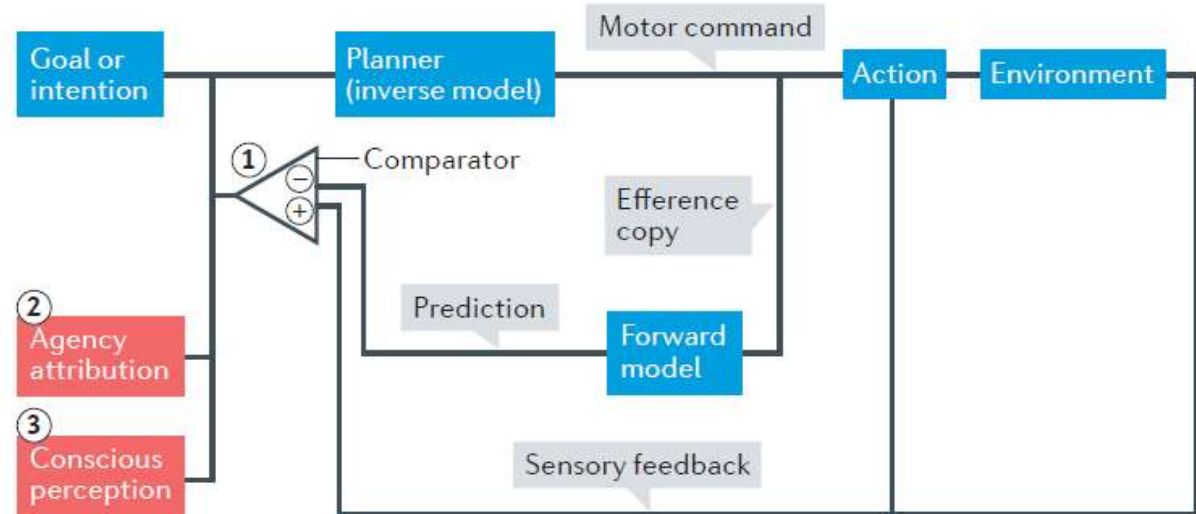
Result of the comparison are used
- to adjust the current motor command (**1**)
- to attribute agency for actions (**2**)
- to attenuate predictable, self-produced sensations (**3**)

Sense of agency in the human brain; Haggard P, Nat Rev Neuroscience 2017

Neural mechanisms of functional neurological disorder

Brain regions of the comparator model in the case of functional movement disorders
- Intention: DLPFC
- Planning/Preparation: SMA
- Movement generation: M1
- Integration: rTPJ

Predictive coding is additionally based on the brain's model of the body and world

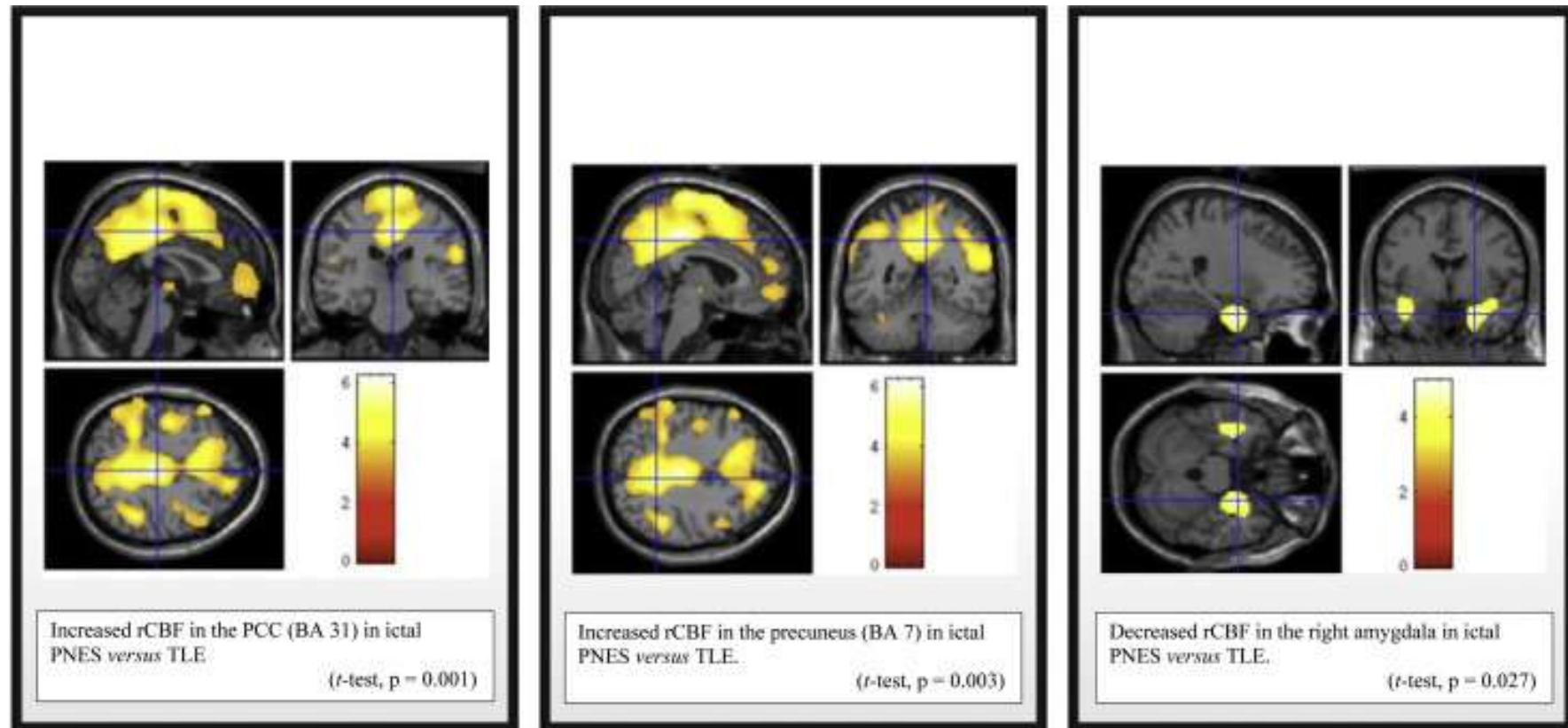Emotional and attentional systems modify feedback signal

Functional neurological disorders
- overweighting of feedforward message
- past expectations overrule feedback
- reduced attention to objective body signals
- abnormal increased attention to the symptom
- abnormal sense of agency
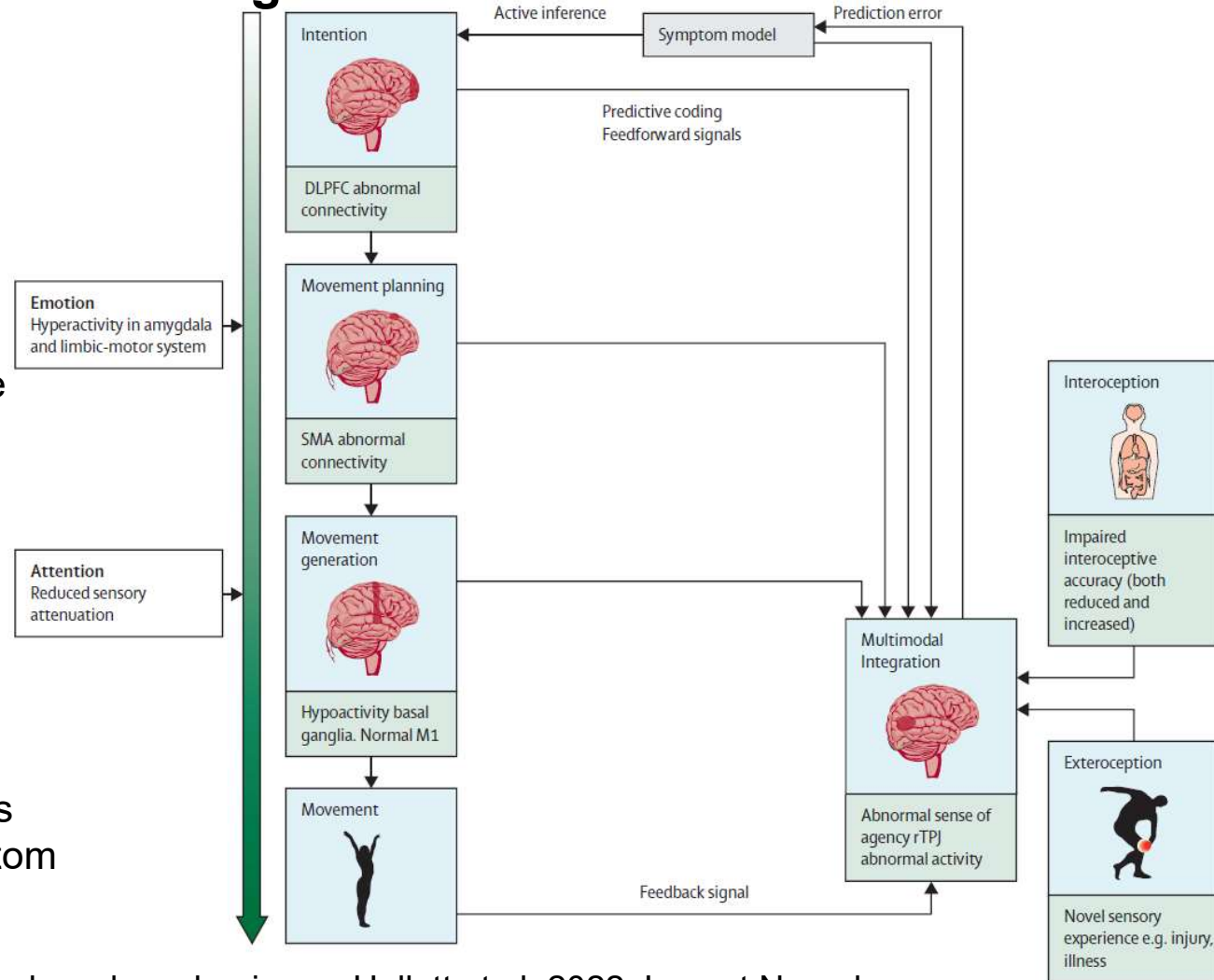
Functional neurological disorder: new subtypes and shared mechanisms ; Hallett et al. 2022, Lancet Neurology

Ictal SPECT in Psychogenic Nonepileptic and Epileptic Seizures

Increased rCBF in the PCC (BA 31) in ictal PNES *versus* TLE
(*t*-test, p = 0.001)

Increased rCBF in the precuneus (BA 7) in ictal PNES *versus* TLE.
(*t*-test, p = 0.003)

Decreased rCBF in the right amygdala in ictal PNES *versus* TLE.
(*t*-test, p = 0.027)

Gallucci-Neto et al. 2021

The Integrative Cognitive Model for PNES

- PNES results from the automatic execution of a learnt mental representation of seizures (the "seizure scaffold") in the context of high level inhibitory dysfunction

Seizure scaffold:
- sequence of perceptions and motor activities
- formed by experiences or/and by personal knowledge or modelling
- triggered by sensory inputs
- generated by pre-existing expectations
- sequence of perceptions and actions is relatively stable (conditioned reflex)
- disrupts the individual's (full) awareness of distressing material
- experienced as non-volitional

Understanding psychogenic nonepileptic seizures—Phenomenology, semiology and the Integrative Cognitive Model; Reuber & Brown, Seizure 2016
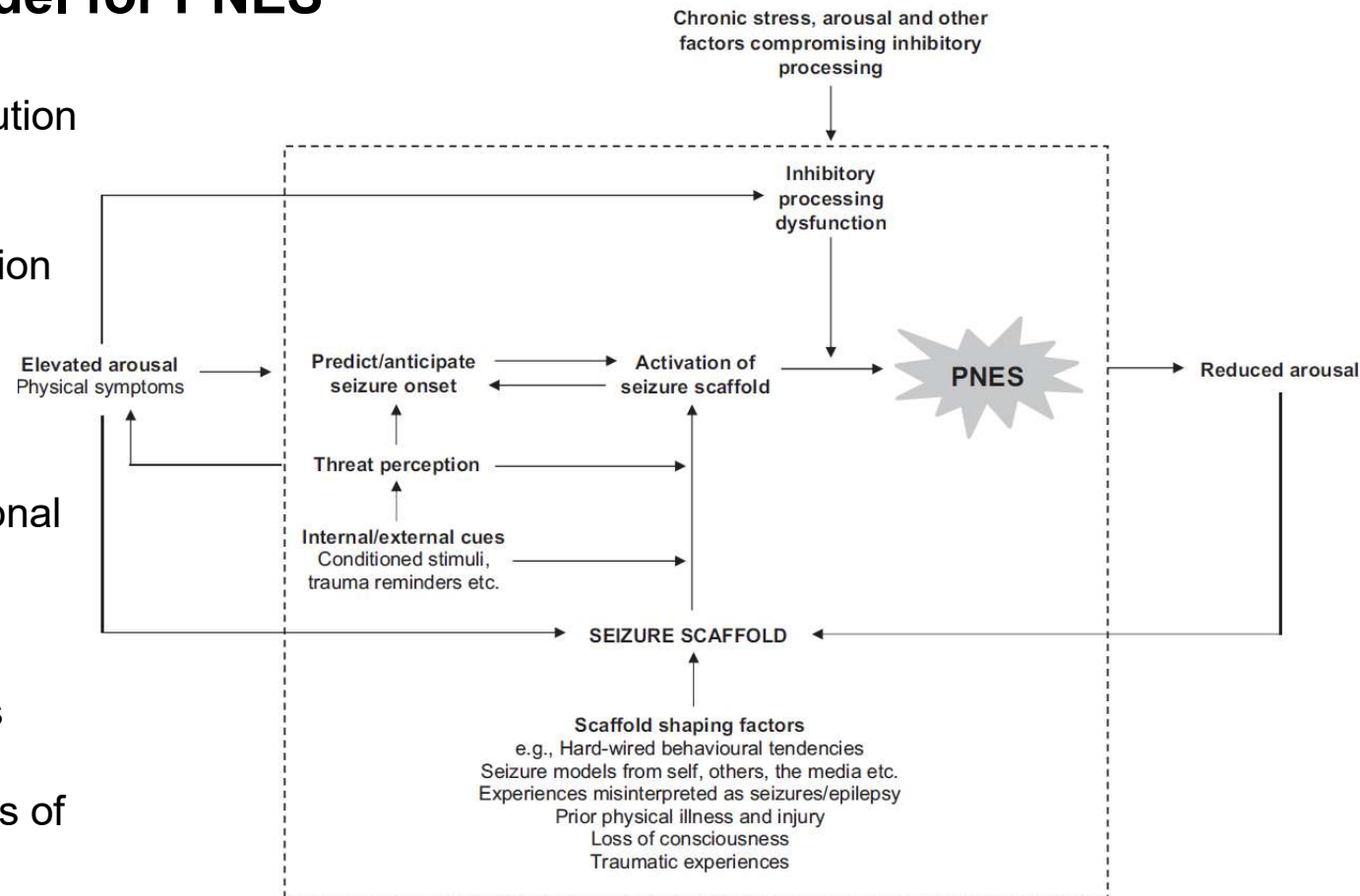
Semiological signs suggestive of psychogenic nonepileptic seizures (PNES)

Suggestions and observations	PNES sign	Number of studies	Sensitivity (%)	Specificity (%)
During seizure				
Measure time	>2 minutes	8	65	93
Observe				
Ictal course	Waxing and waning	3	36–90	96–100
Synchrony of the limbs	Asynchronous	5	43–96	82–100
Pelvic movements	Pelvic thrusting	8	8–60	88–100
Body posture	Arc de cercle	2	6–33	98–100
Head movement	Side-to-side movements	4	25–70	92–100
Eyes	Eyes closed	4		98–100
	Eyelid fluttering	5	0–19	88–100
Vocalizations	Ictal crying or weeping	7	7–32	98–100
Attempt to open the eyes	Forced closure	1		100
Provide an item to be remembered	Recall is satisfactory	3	50–88	94–100
Test for responsiveness	Eye response or other people can alleviate seizure or preserved awareness	4	0–83	77–100
After seizure				
Observe the return of cognitive functions	Rapid recovery; no confusion	4	15–73	38–85
Observe breathing	No stertorous breathing	2		
	Shallow breathing	1	3	98
	Long duration of breathing (>94 seconds)	1		
Test plantar reflex	No Babinski reflex			
Check for urine loss	No urinary incontinence	4		
Check the mouth and oral	No oral ulceration	1		

Clinical classification of psychogenic non-epileptic seizures based on video-EEG analysis and automatic clustering

Analysis of 22 clinical signs of 145 PNES in 52 patients

PNES types: Non-discriminatory elements
- side-to-side head shaking (20 %)
- moans and tears (19%)
- normal postictal state (74%)
- closed eyes (61%)

Hierarchical cluster analysis
- dystonic attack with primitive gestural activity (32%)
- pauci-kinetic attack with preserved responsiveness (23%)
- pseudosyncope (17%)
- hyperkinetic prolonged attack with hyperventilation and auras (12%)
- axial dystonic prolonged attack (16%)

Hubsch et al, JNPP 2012

Table 1 Frequency of individual symptoms in the whole series

Clinical variable	Frequency (%)
Duration of seizure	
<1 min	31.7
1—5 min	43.1
>5 min	23.6
Auras ('I do not feel well, anxiety, feeling to choke, abdominal pain, swelling in the throat …')	27.5
Sudden onset or end	
Sudden onset	41.4
Sudden end	41.4
Responsiveness (verbal or motor responsiveness to the nurse or the doctor)	58.5
Dystonic movements	51.2
Tremor	43
Myoclonus	17.9
Hypermotor archaic gestural activity	8.1
Focal signs	
One limb, head	19.5
Halfbody	5.7
Two lower or upper limbs	13.8
Axial extension	15.4
Axial immobility	72.3
Closed eyes	60.9
Side-to-side head shaking	20.3
One-sided rotation of the head	21.1
Face asymmetry	8.9
Oro-alimentary movements	32.5
Vocalisation	18.6
Hyperventilation and vegetative signs (sweating, flush, pallor)	29.2
Sensory manifestations	12.1
Archaic gestural activity	19.3
Fluctuating intensity of signs	40.6
Postictal state (abnormal)	25.8

Psychiatric comorbidities in psychogenic nonepileptic seizures (PNES)

- Prevalence of psychiatric comorbidity is 53% to 100% in PNES
- Number (median) of psychiatric diagnoses: 3 in PNES vs. 1 in ES
- No significant difference for mood, psychotic and eating disorders
- PNES vs. ES with consistently higher prevalence rates for: Anxiety disorders, substance use disorders, posttraumatic stress disorder (PTSD), cluster A or B personality disorders
- PNES vs. other FND: trauma and borderline personality disorder more frequent in PNES

- PTSD: sensitivity of 58% and specificity of 87% (PPV : 85%) for PNES vs. ES
- personality disorders sensitivity of 71.4% and specificity of 74.3% for PNES vs. ES and healthy subjects
- psychiatric diagnosis other than depression is a predictor of PNES versus ES

- Screening of psychiatric comorbidities is a necessary step in all patients with suspected PNES
- Psychiatric comorbidities are also frequent in epilepsy
- PNES cannot be assumed solely based on the presence of PTSD or personality disorders.

Medical comorbidities in psychogenic nonepileptic seizures (PNES)

- PNES and ES:
  - no more than 10% of adults with PNES have concurrent ES
  - in people with intellectual disability concurrent ES is probably higher
  - Witnessed seizure in another person: 66% in PNES, 11% in ES
- PNES plus ES:
  - in 70% ES before PNES, in 28% simultaneous onset of ES and PNES

- Traumatic brain injury (TBI): in 24% to 83% of PNES (most frequently mild TBI)
- moderate / severe TBI: development of PNES in 1/3, development of ES in 2/3, also mixed PNES+ES!
- TBI is frequently labeled as the etiological factor for PNES by patients

- Syncope: PNES in 1% of patients referred for assessment of blackouts (1/2 with syncope and PNES)

- Obesity: more than double the number of PNES patients obese vs. ES
- Asthma and allergies: significant associations to PNES

- Medically unexplained symptoms (MUS) and other functional syndromes: in 57.4% to 70.8% of PNES
- Fibromyalgia, chronic pain, fatigue: common in PNES (Fibromyalgia: PPV=75%; pain: OR=2.25 for PNES)
- Having one disorder of interest: PPV of 75.5% for PNES

Psychological Traits in psychogenic nonepileptic seizures (PNES)

- Alexithymia and emotion dysregulation frequently described traits in PNES
- Comparisons between PNES and ES show mixed results

- Probably two subtypes in PNES:
    - Typ 1 with high levels of psychopathology, somatization, alexithymia and emotion dysregulation
    - Typ 2 with comparatively normal levels of alexithymia and emotion regulation
- PNES subtypes in regard to emotion regulation profiles:
    - underregulator subtype with emotional reactivity, poor arousal tolerance, difficulty controlling affect
    - overregulator subtype with emotional avoidance, excessively controlled behavior, somatization

- Regression model with somatization, dissociation and general psychopathology scores:
    somatization score strongest single differentiating factor, sensitivity=79.4%

- Neuropsychological testing: no significant differences between PNES and ES

Minimum requirements for the diagnosis of PNES

Possible PNES
- A nonclinical witness or the patient describes possible semiologic features typical of functional seizures
- EEG: Routine or sleep-deprived interictal EEG shows no epileptiform activity.

Probable PNES
- A clinician (who reviewed a video recording or observed the event in person) describes semiologic features typical of functional seizures
- EEG: Routine or sleep-deprived interictal EEG shows no epileptiform activity.

Clinically established PNES
- A clinician with experience in the diagnosis of seizure disorders (who reviewed a video recording or observed the event in person) describes semiologic features typical of functional seizures
- EEG: Routine or ambulatory ictal EEG with a typical seizure event shows no epileptiform activity.

Documented PNES
- A clinician with experience in the diagnosis of seizure disorders (who reviewed a video recording or observed the event in person) describes semiologic features typical of functional seizures.
- EEG: Ictal video EEG shows no epileptiform activity immediately before, during, or after the seizure event but shows semiologic features typical of functional seizures.

La France et al., Report from the International League Against Epilepsy Nonepileptic Seizures Task Force; Epilepsia, 2013

Eigen-Anamnese

Patienten berichten oft spontan nicht von allen Symptomen, sondern nur von den aufdringlichsten. Das zuerst genannte Symptom ist oft nicht das erste im Anfall, sondern das subjektiv eindrucksvollste.

- Was ist das erste Anzeichen eines Anfalls? (Frage wird nicht selten missverstanden und Patienten berichten über vermutete Anfallsauslöser)
- Was geht diesem evtl. voraus? (Auren werden subjektiv oft als Vorboten eingeordnet, die noch nicht zum Anfall gehören)
- Symptom-Sequenz? Auslösefaktoren (z. B. reflexepileptische Anfälle; Husten-, Schmerz- und Miktionssynkopen; affektiv ausgelöster kataplektischer Anfall; kinesigene paroxysmale Choreoathetose)?
- Abhängigkeit von Körperhaltungen (orthostatische Synkopen)?
- Erfahrungen mit Gegensteuern?
- Dauer des Anfalls?
- Tageszeitliche Bindung?

Wolf P in: Paroxysmale Störungen in der Neurologie; Schmitz B und Tettenborn B (Hrsg.); Springer 2005

Fremd-Anamnese

- Wodurch auf den Anfall aufmerksam geworden?
- Was war das erste beobachtete Symptom? Symptom-Sequenz?
- Bewegungen (mit Ausmaß, Geschwindigkeit und Richtung)?
- Zuckungen? Versteifungen (wo; einseitig oder beidseitig; Dauer)? Muskeltonus schlaff oder steif?
- Ausbreitung motorischer Symptome?
- Gezielte Frage nach Automatismen (werden oft nicht spontan berichtet, selbst wenn sie ausgeprägt sind)
- Sturz? Wie gestürzt (steif oder schlaff; Richtung)?
- Augen offen oder geschlossen? Verdreht? Gesichtsausdruck? Blick?
- Verfärbung? Speichelfluss? Zungenbiss (seitlich oder Spitze; immer, häufig oder gelegentlich)? Enuresis?
- Ansprechbarkeit? Beim Anfall gesprochen? Wie (Kauderwelsch; grammatikalisch richtig, aber zusammenhangslos; Paraphasien)?
- (Geschätzte) Dauer des Anfalls? (Beobachter haben Tendenz, postiktale Phase hinzuzurechnen)
- Beginn und Ende abrupt oder gleitend?
- Postiktale Symptome (Sprachstörung; Orientierungsstörung; Lähmung oder Schwäche; Abwehrverhalten)?
- Laufen alle Anfälle mehr oder weniger gleich ab?

Wolf P in: Paroxysmale Störungen in der Neurologie; Schmitz B und Tettenborn B (Hrsg.); Springer 2005

Listening to people with seizures: How can linguistic analysis help in the differential diagnosis of seizure disorders?

Summary of linguistic features found useful in the diagnosis of German speaking patients with epileptic and nonepileptic seizures

Feature	Focal Epileptic Seizure	Non-epileptic Seizure
Subjective seizure symptoms	Typically volunteered, discussed in detail	Avoided; discussed sparingly
Formulation work (eg formulation attempts).	Extensive, large amount of detail	Practically absent, very little detailing efforts
Seizures as a topic	Self-initiated	Initiated by interviewer
Focus on seizure description	Easy	Difficult or impossible ("focusing resistance")
Spontaneous reference to attempted seizure suppression	Usually made	Rarely made
Seizure description by negation	Rarely (negation is usually explained and contextualized)	Common and absolute ("no warning", "I feel nothing", "I do not know anything has happened")
Description of periods of reduced consciousness or self-control	Intensive formulation work.	"Holistic" description of unconsciousness" "I know nothing"
	Aiming at a precise, detailed description.	No self-initiated detailed description
	Attempts to fill gap in level of consciousness.	Naming of unconsciousness without differentiation or description.
	Precise placement of period of lost consciousness in the seizure process.	Pointing out inability to remember anything or take in anything.
	Display of willingness to know what precisely happened during periods of unconsciousness.	Presentation of gaps as most dominant element of the disorder.
	Degree of unconsciousness can be challenged interactively	Completeness of unconsciousness cannot be challenged.
Metaphors, conceptualization of seizures	Seizures presented as an external independent threatening entity.	No clear coherent concept – No definite external genesis
	Active struggle against seizure-threat, (metaphors describing a fight).	No description of active struggle against seizures

Schwabe et al. 2008 (basierend auf: Schöndienst 2000, 2001, Schöndienst/Gülich 1999; Wolf et al. 2000, Gülich 2005, Furchner 2002, Surmann 2002, 2005)

Seizure metaphors differ in patients' accounts of epileptic and psychogenic nonepileptic seizures
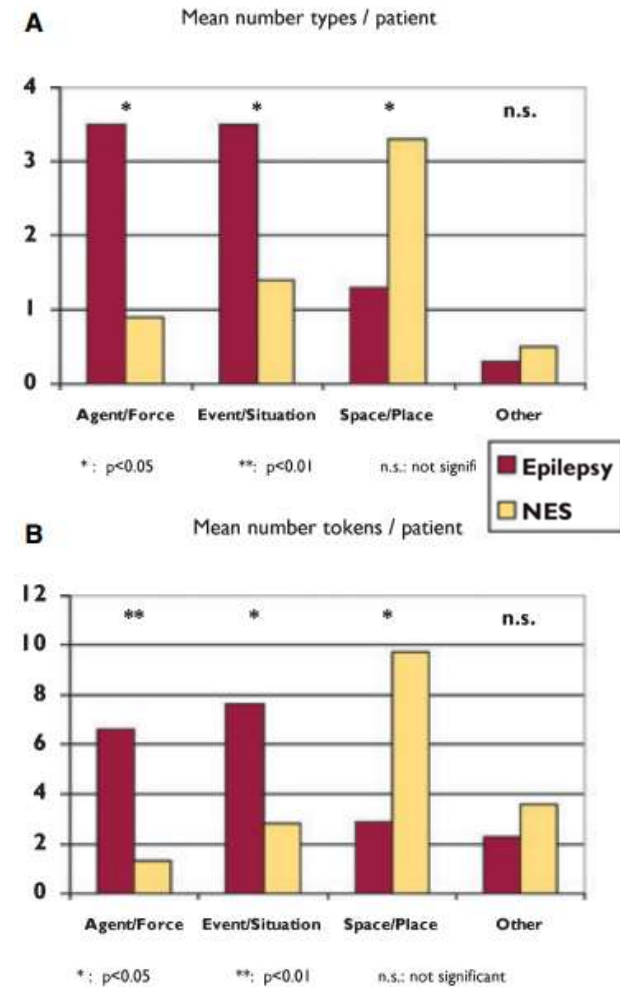
N=21 patients admitted with a diagnosis of epilepsy, 85% with ASM
Diagnosis after video-EEG: ES in 8, PNES in 13 patients

Table 2. Examples of metaphor types in the three most common conceptual categories

Category	Seizure as an agent/force	Seizure as an event/situation	Seizure as a space/place	Other
Grammatical subject	Seizure	Seizure	Patient	Variable
Semantic agency	With the seizure	Variable	With the patient	Variable
Examples	Seizures come, go, come in, come on, come up, creep up on you, get you, try to do things, set off, are sent in, are straight there, are fought, counteracted, contained, are let pass, wear off	Seizures happen, occur, take place, are due, start, finish, go on, carry on, develop, are experienced, witnessed, handled, controlled, stopped, avoided/put off, are brought on, run their course	Drifting off, being off, somewhere else, going, going off, being gone, coming back, coming round, coming to, going down, being down, not being there, being out into seizures, in seizures, out of seizures, within seizures, through seizures	Seizures are started up, are fixed, like an electrical charge, like the lights are on but nobody's at home, like something going off, like shutting a computer off, like cold or hot water on the top of your head, are as if your head carries on without you

Metaphor use:
- ES: 5 times more likely to use agent/force than the space/place category
- PNES 6 times more likely to use space/place than the agent/force category

Plug et al. 2009

A   Mean number types / patient

*: p<0.05   **: p<0.01   n.s.: not signifi

■ Epilepsy
□ NES

B   Mean number tokens / patient

*: p<0.05   **: p<0.01   n.s.: not significant

Conversation analysis can help to distinguish between epilepsy and non-epileptic seizure disorders

- Result strongly depend on the way the doctor conducts the conversation with the patient.
- Semi-standardized interview procedure: important to elicit the distinguishing linguistic features and for comparison of different patients' responses to the same communication challenges.
- Patient is allowed to develop his/her own communicative agenda
- Information given spontaneously has a different value compared to information as a response to a question
- The most significant differences from "traditional" history taking are that the doctor is encouraged not to interrupt the patient or introduce new topics into the consultation.

Interview phase	Inquiries	Approximate duration
'Open' phase	What were your expectations when you came to hospital?	10 min
Elicited seizure episode accounts	Can you tell me about the first seizure you can remember?	10 min
	Can you tell me about the last seizure you can remember?	
	Can you tell me about the worst seizure you can remember?	
'Challenge' phase	Inquiry or inquiries challenging the patient's description	5 min
Doctor's instructions		
Avoid introducing new topics		
Tolerate silence		
Use continuers (*mmm*, *right*, etc.) to indicate continued attention		
Repeat what the patient has said to encourage elaboration		

Plug et al. 2009

Langzeit-EEG-Video-Monitoring

PNES is best confirmed by recording events simultaneously on video and EEG
- Event must be confirmed by an eyewitness as typical of those occurring in daily life
- Event must have PNES-consistent semiology
- Presence of normal awake EEG rhythms before, during, and after the event
- Typicality may be assessed on a scale of between 1 (totally atypical) and 10 (absolutely typical)
- If more than one event type, occurrence of each event type must be recorded.

Events that do not approximately correspond with known PNES semiology should be examined critically.
- simple partial ES and hypermotor FLE may not be accompanied by surface EEG changes

Ictal heart rate
- rapid ictal heart rate increase in ES
- heart rate commensurate with the physical activity in PNES

Duration of EEG-Monitoring and provocation
- Event within 24 hours in 77% and within 48 hours in 96%
- Provocation (hyperventilation, photic stimulation) provoke event in 10-30% of patients

Interictal abnormalities (2 studies)
- Abnormal EEG in 46% of PNES, epileptiform abnormalities in 9% (no spike wave complexes)
- nonspecific EEG changes in 50% of PNES, epileptiform changes in 8%

Treatment pitfalls in Functional Neurological Disorders

The clinician should

- Explain the diagnosis to the patient on the basis of positive clinical features of functional neurological disorder

- When possible, show the patient positive clinical signs supporting the diagnosis and explain signs to the patient's family and friends

- Check and consolidate the patient's understanding of the diagnosis, consider copying correspondence to patients and signpost patients to online information and support organisations (eg, neurosymptoms.org ↗, fndhope.org ↗, fndaction.org.uk ↗)

- Encourage early and active goal-directed rehabilitation and engage family and friends with that process

- Refer the patient for appropriate therapies (eg, physiotherapy, psychotherapy, speech-language therapy, or occupational therapy)

- Treat comorbidities (eg, depression, anxiety disorders [including post-traumatic stress disorder], or sleep disorders), and refer to psychiatry if necessary

- Review medication regimens; opiates, benzodiazepines, and other sedatives can worsen symptoms of functional neurological disorder

- Connect with, and train, other professionals to prevent the patient undergoing unnecessary and potentially harmful investigations or treatments

The clinician should not

- Make a diagnosis of functional neurological disorder on the basis of normal radiological or laboratory diagnostics

- Frame the patient's diagnosis as a medical mystery

- Highlight risk factors (eg, stress, psychological) when discussing possible causes

- Provide written information or signpost to online information without also providing treatment or referring the patient for further treatment

- Encourage unrealistic expectations; improvement is a gradual active process, and many patients do not improve

- Neglect to treat comorbid psychiatric disorders

- Withdraw medications suddenly or without explaining the reason

- Assume that any new symptoms are attributable to functional neurological disorder; the disorder could be comorbid with or precede other neurological disorders; new signs should be assessed on their own merits

Hallett et al, Lancet 2022

Zusammenfassung

PNES und funktionelle neurologische Störungen sind relevante Probleme

Integrative Erklärungsmodelle gehen von einer Fehlsteuerung multimodaler Assoziationsareale aus:
- Diskrepanz zwischen erwarteter und erlebter Realität löst eine «gelernte» Fehlreaktion aus
- Fehlreaktion verfestigt sich über die Zeit zu einem «konditionierten Reflex»
- Chronischer Stress, emotionale Dysregulation und symptombezogene Aufmerksamkeit tragen zur Chronifizierung bei

Goldstandard in der Diagnostik sind die exakte Erfassung der Symptome und die Korrelation eines patiententypischen Ereignisses mit Video-EEG-Daten

Diagnose basiert auf Positiv-Zeichen (keine Ausschlussdiagnose)

Therapieverfahren sind an individuelle Konstellation anzupassen
- Adäquate Kommunikation der Diagnose
- Psychiatrische Komorbiditäten müssen adressiert werden
- Psychotherapeutische, verhaltenstherapeutische, physio-/ergotherapeutische Therapieansätze möglich

Vielen Dank für Ihre Aufmerksamkeit!

Literatur

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