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Review

A systematic review of suggestive seizure induction for the diagnosis of psychogenic nonepileptic seizures

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ABSTRACT

Suggestive seizure induction is a widely used method for diagnosing psychogenic nonepileptic seizures (PNES). Despite seven decades of multidisciplinary research, however, there is still no unified protocol, no definitive agreement on the ethical framework and no consensus on diagnostic utility. This systematic review surveys the evidence at hand and addresses clinically relevant aspects of suggestive seizure induction. In addition to its use for facilitating the diagnostic process, its mechanism of action and utility in elucidating the psychopathology of PNES will be discussed.

1. Introduction

In 1945, within the inaugural decade of clinical electroencephalography (EEG), Herbert Kupper reported the first instance of a seizure induced by hypnotic suggestion while his patient was hooked up to an electroencephalograph [1]. While Kupper's conclusions about the convergence of epileptic and emotional seizure triggers were fallacious, his method inspired Schwarz et al. [2] to test the utility of seizure induction via hypnotic suggestion during EEG to distinguish psychogenic from epileptic events. In 16 patients with "convulsive disorder and concomitant electroencephalographic findings" hypnotic suggestion failed to induce a typical fit; however, it did provoke the habitual attacks in ten other patients with presumed epileptic seizures [2]. The EEG showed no ictal abnormalities and, thus, these ten patients were the first ever to be diagnosed with psychogenic nonepileptic seizures (PNES) using suggestive seizure induction (SSI).

Nowadays, video documentation of a typical event during simultaneous EEG co-registration is required for the definitive diagnosis of PNES [3]. The commonly recommended method for achieving this is telemetric long-term video-EEG-monitoring (VEEG) [4,5]. When long-term VEEG is unavailable, inconclusive or fails to record a spontaneous event, induction techniques are recommended to facilitate diagnosis [3,6].

The era of evidence-based medicine has seen the validation and standardization of most diagnostic procedures in clinical practice, yet there have been relatively few attempts at unifying and systematically evaluating SSI [7,8]. Despite its widespread utilization [6,9,10], there is currently no established protocol, no universal consensus on the ethical framework, and only a limited selection of studies on diagnostic yield. This review aims to systematically survey the available literature and draw applicable conclusions for the ethically permissible and diagnostically efficient use of SSI in epileptology practice.

2. Methods

Studies on the clinical application of SSI were identified by searching PubMed (NCBI), ISI Web of Science (Thomson Reuters) and Google Scholar. Combinations of search terms associated with PNES and seizure provocation were used (see Appendix A for a complete list). All articles were assessed based on title and abstract, and, if eligible, were retrieved in full and re-assessed. Additionally, the reference lists of all selected articles were scanned for related citations. Only studies in English were

Abbreviations: EMU, epilepsy monitoring unit; ES, epileptic seizures; HV, hyperventilation; IQ, intelligence quotient; Mo, months; N/a, not applicable or (data/information) not available; PNES, psychogenic nonepileptic seizures; PS, photic stimulation; SSI, suggestive seizure induction; VEEG, video-EEG-monitoring; Y, years.

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considered. Studies that focussed exclusively on pediatric population were excluded. Non-peer-reviewed articles and published abstracts, as well as case reports and small case series ($n < 10$) were also excluded. Appendix B summarizes relevant studies that were excluded from the systematic review.

Next, to assess the quality and strength of each study, its methodological characteristics were identified based on the recommendations of the American Academy of Neurolgy (AAN) [11]. Specifically, the following characteristics of each study were extracted and assessed: purpose of study, cohort enrollment, setting, independent reference standard, comparison group, follow-up, formal psychiatric assessment, inclusion criteria, sample size, age, percentage of women, SSI technique, standardized protocol, timing of SSI, blinded evaluation, patient information, excerpt referring to patient information, degree of deception, yield, study conclusion, class of evidence, ethical committee approval.

Classes of evidence were assigned using Clinical Practice Guideline Process Manual of the AAN [11]. One study was classified using the criteria for prognostic accuracy; all other studies were evaluated based on one of two matrices available diagnostic procedures: diagnostic accuracy and population screening. For diagnostic accuracy, class III or higher requires an independent reference (“gold”) standard in terms of sensitivity [11,12]. Although long-term VEEG is frequently referred to as the “gold standard”, it is such only in terms of diagnostic *confidence* when positive, just as SSI is [3]. A “gold standard” in terms of perfect (near 100%) *sensitivity* does not exist for PNES, since even long-term VEEG often remains inconclusive or negative in cases of suspected or confirmed PNES [13–15]. Despite these and other methodological considerations [12,16,17] for the purpose of this review long-term VEEG was considered an adequate independent reference standard. Many systematic studies on SSI evaluated the diagnostic yield which is more appropriately reflected in the evidence classification criteria for population screening. The diagnostic yield, or calculated sensitivity of a diagnostic test, will depend on the pre-test selection criteria (i.e. disease prevalence) [18]. Although formal classifications of evidence favour population-based sampling with a broad spectrum of patients [11], for the practicing clinicians studies that reflect their own setting and patient sampling (i.e. tertiary referral center, suspected PNES) are most useful [18].

To assess the degree of deception involved in informing patients about SSI we classified the reported communication strategies into three categories: “explicitely deceptive”, when a statement is made that is untruthful (e.g. “a seizure will be produced [...] by placing a vibrating tuning fork on the forehead and sending ‘electric vibrations’ through the brain”, [19]); “truthful but omissive”, when the information is technically truthful, but an exclusively organic process is still implied (e.g. “we will inject an IV drug that will perhaps help in inducing the usual spell [...] We did not say the words ‘epileptic seizure’ in order to avoid lying to the patient”, [15]); and “explicitely open”, when the information provided is technically correct and a psychological process is explicitely introduced as a possiblity before SSI (“The possible occurrence of both epileptic and psychogenic seizures during hyperventilation and photic stimulation was stressed”, [20]).

3. Overview of studies on SSI

Using the aforementioned search strategies and selection criteria 32 studies that examine the utility of SSI for the diagnosis of PNES were identified. Table 1 offers a summary; an expanded version of this table with all study characteristics listed in the “Methods” section is available as Supplementary Marterial. Overall, there was a marked methodological heterogeneity and low level of evidence. Only one study was considered Class II, 16 Class III and 15 Class IV. Common reasons for these relatively low classifications were that most studies were performed in specialized tertiary referral centers, few had control groups and in no study was SSI performed by an examiner blinded to pre-test conditions. These limitations, however, reflect the pre-selected population and clinical setting of most clinicians that are likely to routinely perform SSI.

The majority of studies (82%) that reported gender distribution had a female predominance in their cohorts. Of the five studies with a higher proportion of men, four recruited from veteran populations. The reported mean age was between 21 and 47 years, with an age range spanning at least four decades in most cases (13 of 17 studies with available information). Overall, the demographic data of all studies combined reflects the patient characteristics known for PNES patients [21] and implies a sufficient level of generalizability for epileptology practice.

Almost all studies were performed at tertiary referral centers. Eight studies (25%) offered follow-up data. Seven studies (22%) reported some form of formal psychiatric and/or psychological assessment, which would help identify closely related psychiatric disorders (such as panic disorder, post-traumatic stress disorder and others). The most commonly examined SSI technique was intravenous saline infusion alone or in combination with other techniques (16 studies, 50%); ten studies (31%) examined hyperventilation and photostimulation.

In light of these observations, the following aspects of SSI that are of interest to clinicians are discussed below: ethical considerations; techniques of SSI; role in diagnostic workup; risks and side effects; psychobiological mechanisms; predictive factors; therapeutic effect.

4. Ethical considerations

The debate around the ethical justification of SSI has been addressed comprehensively on many occasions in the past [6,22–29]. Nonetheless, a reappraisal of ethical aspects is called for as new data becomes available.

A common point of criticism is the danger of undermining the physician-patient relationship by performing SSI [28]. Few studies have tested this assumption. Chen and colleagues report that “none of the 51 enrolled patients reported feeling deceived following the induction attempt” [30]. In line with this, when Goyal and colleagues asked 50 PNES patients (who had undergone a considerable battery of various induction methods) to characterize the experience via a questionnaire, 47/50 patients found SSI “patient friendly and satisfactory” and 44/50 indicated they would undergo SSI again in the future if needed [31].

Opinions converge that abstaining from outright lies is a crucial step towards preserving patients’ continuing trust [6,28]. Furthermore, introducing the possibility of psychological factors before SSI facilitates an open and easy debriefing [20,32]. Out of the 32 studies at hand, 24 report the strategies of patient information. Using the categorization described above, in the twelve studies published before 2000, the majority was catgorized as “explicitely deceptive”. In the twelve studies published after 2000, on the other hand, only one was categorized as “explicitely deceptive”, seven as “truthful but omissive” and four as “explicitely open” (see Fig. 1). A tendency towards more honest communication over the years becomes evident. Moreover, two recent studies show that honestly informing patients beforehand about the possibility of PNES does not impair the efficiency of SSI [20,32].

One of the chief arguments in support of the ethical license of SSI lies in the trade-off between the degree of deception involved and the efficacy of this procedure to establish a diagnosis and

Table 1
Summary of studies on suggestive seizure induction.

Study	Purpose of study	Enrollment	Setting	Inclusion criteria	*n*	SSI Technique	Patient information	Yield[a]	Class of evidence
Schwarz et al., 1955 [2]	use of hypnosis for SSI	retrospective	inpatient	suspected epilepsy	26	hypnosis	n/a	n/a	IV
Cohen et al., 1982 [46]	use of saline infusion as SSI	retrospective	inpatient	atypical or intractable seizures	57	saline i.v.	"explicitely deceptive"	89%	IV
Guberman et al., 1982 [19]	descriptiv study of PNES	retrospective	inpatient	suspected PNES	12	tuning fork to the forehad	"explicitely deceptive"	100%	IV
Luther et al., 1982 [52]	evaluate SSI	retrospective	inpatient EMU	confirmed PNES	30	saline i.v., HV, PS, others	n/a	80%	IV
Lesser et al., 1983 [51]	evaluate frequency of PNES-ES-comorbidity; evaluate effect of AED-withdrawal in PNES-patients	retrospective	inpatient EMU	suspected, confirmed PNES	79	saline i.v.	n/a	n/a	IV
Drake, 1985 [50]	evaluate utility of SSI	prospective	inpatient EMU	atypical or intractable seizures	20	saline i.v.	"explicitely deceptive"	40%	IV
Rowan et al., 1987 [53]	evaluate ambulatory VEEG with or without SSI	retrospective	outpatient EMU	all consecutive patients	124	saline i.v., alcohol pad	n/a	n/a	III
Cohen et al., 1992 [98]	evaluate psychiatric interview as SSI-technique	retrospective	inpatient EMU	psychiatric consultation for suspected PENS	32	psychiatric interview	"explicitely open"	59%	IV
Grubb et al., 1992 [99]	evaluate utility of tilt-table testing for SSI	retrospective	inpatient cardiology unit	recurrent idiopathic seizure-like episodes ($n=10$)	10[b]	tilt testing	n/a	30%[b]	IV
Buchanan et al., 1993 [49]	evaluate management and outcome of PNES	retrospective	inpatient EMU	confirmed PNES; follow-up information available	50	saline i.v., cold stimulus to the wrist	"truthful but omissive"	n/a	IV
Bazil et al., 1994 [47]	evaluate frequency of PNES and sensitivity of SSI	prospective	inpatient EMU	all patientins in EMU except those with progressive mass lesions or significant medical conditions; age ≥ 18	52	saline i.v.	"explicitely deceptive"	37%	III
Lancman et al., 1994 [13]	evaluate diagnostic accuracy of SSI	retrospective	inpatient EMU	confirmed PNES; no signs of additional epilepsy	93	alcohol patch	"explicitely deceptive"	77%	III
Walczak et al., 1994 [55]	evaluate the utility of SSI to diagnose PNES	prospctive	inpatient EMU	all patientins in EMU except those with intracranial electrodes	76	saline i.v.	"truthful but omissive"	77% in VEEG-confirmed PNES	III
Slater et al., 1995 [54]	evaluate the validity of SSI to discriminate between PNES and ES	prospective	inpatient EMU	presumed refractory epilepsy; age ≥ 18	101	saline i.v.	"explicitely deceptive"	91%	III
Bhatia et al., 1997 [48]	evaluate utility of outpatient short-term VEEG with SSI	prospective	outpatient EMU	suspected and confirmed PNES	50	saline i.v.	"explicitely deceptive"	46%	III
Dericioğlu et al., 1999 [57]	evaluate utility of outpatient SSI	retrospective	outpatient EMU	suspected PNES	72	verbal only, saline i.v.	"truthful but omissive"	72%	III
Zaidi et al., 1999 [100]	evaluate utility of tilt-table testing for SSI	prospective	outpatient autonomic research laboratory	attack disorder; no signs of additional epilepsy	21	tilt testing	"truthful but omissive"	81%	IV
Barry et al., 2000 [38]	evaluate the validity of hypnotic SSI to discriminate between PNES and ES	retrospective	inpatient EMU	psychiatric referrals for differential diagnosis of attack disorder	69	hypnosis	"explicitely open"	77%	IV

Table 1 (*Continued*)

Study	Purpose of study	Enrollment	Setting	Inclusion criteria	*n*	SSI Technique	Patient information	Yield[a]	Class of evidence
Benbadis et al., 2000 [23]	evaluate the diagnostic value of SSI	prospective	inpatient EMU	suspected PNES	21	HV and PS	"truthful but omissive"	84%	III
McGonigal et al., 2002 [62]	evaluate the yield of outpatient VEEG and SSI	prospective	outpatient EMU	suspected PNES; no signs of additional epilepsy; age > 16	30	HV and PS	"truthful but omissive"	67%	III
Wassmer et al., 2003 [8]	evaluate the utility of SSI	retrospective	inpatient EMU	suspected PNES; no signs of additional epilepsy	66	saline i.v.	"truthful but omissive"	62%	III
Benbadis et al., 2004 [60]	evaluate the yield of short-term VEEG with SSI	retrospective	outpatient EMU	suspected PNES; age ≥ 18	74	HV and PS	"truthful but omissive"	64%	III
McGonigal et al., 2004 [63]	evaluate the usefulness of short VEEG and SSI	retrospective	outpatient EMU	attack disorder	143	HV and PS	"truthful but omissive"	36%	III
Ribaï et al., 2006 [15]	evaluate usefulness of long-term VEEG and SSI for the diagnosis of PNES	retrospective	inpatient EMU	attack disorder, suspected PNES or confirmed PNES	28	saline i.v.	"truthful but omissive"	68%	III
Varela et al., 2007 [64]	evaluate the yield of short-term outpatient VEEG with SSI for the diagnosis of PNES in a V.A. population	retrospective	outpatient EMU	suspected PNES	52	HV and PS	"truthful but omissive"	69%	III
Khan et al., 2009 [40]	evaluate use of hypnotic SSI in differentiating PNES from ES	prospective	inpatient EMU	medically refractory attack disorder; age ≥ 18	47	hypnosis	n/a	35%	IV
Chen et al., 2011 [30]	evaluate influence of clinical characteristics on success of SSI	prospective	inpatient EMU	suspected PNES; no signs of additional epilepsy; no spontaeous PNES in 48h VEEG	51	saline i.v., HV, PS	n/a	82%	III
Hakak et al., 2013 [61]	evaluate role of VEEG and SSI in diagnosis of PNES	retrospective	inpatient EMU	confirmed PNES; no signs of additional epilepsy	33	HV and PS	n/a	n/a	IV
Hoepner et al., 2013 [32]	evaluate effect of patient information on SSI	retrospective	inpatient EMU	confirmed PNES	144	HV and PS	"explicitely open"	38%	III
Gambini et al., 2014 [66]	evaluate longterm outcome of PNES	retrospective	inpatient EMU	confirmed PNES; 18–60 years, normal IQ, no or mild intellectual disabilities	27	alcohol patch	"explicitely deceptive"	n/a	II
Goyal et al., 2014 [31]	compare diagnostic accuracy and discomfort of various SSI techiques	prospective	inpatient EMU	suspected PNES; age ≥ 8	140	Various[c]	"explicitely open"	41–66%	IV
Popkirov et al., 2015 [20]	evaluate utility of multimodal SSI	retrospective	inpatient EMU	confirmed PNES	52	HV, PS, saline i.v.	"explicitely open"	74%	IV

[a] Yield is defined as ratio of positive SSI out of all performed SSI.
[b] Additional 42 patients with recurrent syncope of unknown origin, yield refers to patients with presumed ES only.
[c] Compression of temple region, verbal suggestion, tuning fork application, moist swab application, torch light stimulation and saline injection.

prevent years of inappropriate treatment [6]. While the significance of finding a definitive diagnosis early on is laid out convincingly elsewhere [3,33], the efficacy of SSI will be adressed in the next section.

5. Techniques of SSI

Even before the seminal study by Schwartz and colleagues in 1955 [2], hypnosis had been used to differentiate between

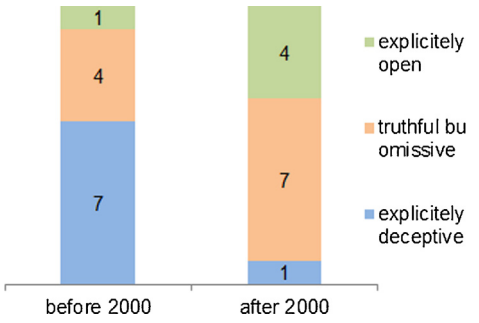

Fig. 1. Strategies for patient information in SSI.

epileptic and psychogenic seizures through hypnotic recall of events during seizures [34,35]. This method has later been revisited and its effectiveness confirmed [36,37]. Hypnosis as a method of seizure provocation has been examined in several case series and two larger studies since [2,38–42]. In 36 patients with PNES, 22 with epilepsy and 11 with both, Barry and colleagues established significantly higher hypnotizability in patients with PNES alone or dual pathology than those with epilepsy alone [38]. In patients with PNES (with or without concomitant epilepsy) 77% had typical seizures induced during hypnosis. Among other advantages, the authors stress its potential to function as a "conduit for long-term treatment", referring to the therapeutic potential of hypnosis [43]. Khan and colleagues conducted a prospective study of 47 patients who underwent VEEG and SSI: 24 had spontaneous events under VEEG and, of those, 11 also had events under hypnotic suggestion (2009). This relatively low diagnostic yield of 46%, and the fact that none of the patients with inconclusive VEEG had inducible seizures led the authors to conclude, that alternative methods of SSI ought to be explored [40]. Overall, hypnosis has established important characteristics of PNES aetiology and psychopathology [44] but cannot be recommended for routine application outside the hands of experienced hypnotists within scientific studies.

In 1979, Remick and Wada first used intravenous agents during VEEG to provoke a seizure in a patient with presumed refractory epilepsy. A typical attack without any epileptiform EEG changes was induced and categorized as psychogenic [45]. This led Cohen and Suter [46] to test intravenous application of saline for SSI in 57 patients with poorly controlled or atypical seizures: while 3 had spontaneous PNES, 48 of the remaining 54 (89%) had induced PNES. Saline injection has since become the best documented method of SSI [8,15,20,30,47–56]. Depending on the patient sample (i.e. the pre-test probability) i.v.-saline-based SSI can achieve a diagnostic yield of up to 89–91% in eventually confirmed PNES [15,46,54] and 29–37% in rather unselected samples [47,54]. Overall, the majority of studies utilizing saline injection for SSI alone or in combination report a yield of over 70% (see Table 1).

Two disadvantages of saline injection are the higher levels of reported discomfort [31] and the explicit deception involved with placebo administration [23]. However, saline injection provides a significant additional yield in protocols that begin with hyperventilation and photic stimulation and use saline only when necessary [20,52].

Openly discussing possible psychological factors beforehand and refraining from false statements can help (see previous section). A protocol incorporating both non-invasive and invasive techniques might help limit the use of placebo-based SSI to the necessary minimum, without striking it out of the epileptologist's armamentarium altogether [20,49,52,57].

Since the crucial element of PNES induction is suggestion, in theory, any intervention from presenting fragrances [58] to applying additional EEG-electrodes [59] could induce a psychogenic seizure as long as its effects are explained or implied convincingly [31]. Commonly reported techniques, in addition to saline injection, are hyperventilation and photic stimulation [20,23,30,32,52,60–64] as well as placing a soaked pad on the patient's neck [13,31,65,66] or a vibrating tuning fork on the forehead [19,31].

An advantage of hyperventilation and photic stimulation is that both can be presented truthfully as methods that can potentially precipitate epileptic seizures [32,67]. This is an elegant bypass of the ethical dilemma of implied misinformation posed by placebo injections [23,32]. These methods have been tested repeatedly in an outpatient setting with diagnostic yields of 64–69% in suspected PNES [60,62,64] and 36% in all "attack disorders" [63].

6. Role in diagnostic workup

There have been many attempts at providing guidelines for the optimal diagnostic workup of patients with suspected PNES [3,7,33,68–70].

A patient with seizures of unknown or disputed aetiology will usually be monitored in an epilepsy monitoring unit for a few days before SSI is performed [3]. This diagnostic sequence has the advantage of increasing the sensitivity regarding epileptiform abnormalities in interictal EEG in cases of epilepsy or dual pathology [71]. Also, a spontaneous seizure during VEEG obviates the perceived ethical issues of SSI [28].

There are no universal guidelines on how many days of VEEG one should wait for a spontaneous habitual event before opting for SSI. In several retrospective analyses the majority (75–96%) of PNES occurred within the first 48 h of VEEG [4,72–74]. This establishes a reasonable minimum of VEEG, but uncertainty remains about a sensible upper limit. While in one study all psychogenic events occurred within 58 h [73], in another spontaneous PNES manifested as late as 207 h after the start of VEEG [74]. Importantly, the reported numbers do not reflect the yield of all examined patients, but only the latency of events that were eventually recorded. In the study by Ribaï and colleagues the average VEEG duration was 4.6 days, and still 32% of PNES patients had inconclusive VEEG but positive SSI [15]. One recent study specifically investigated the utility of long-term VEEG in the diagnosis of 150 patients with suspected PNES [14]. The authors calculated a cut-off at 5.5 days of VEEG, after which the length of stay was associated with an increased risk of being inconclusive; no such cut-off was seen in 333 patients with epilepsy [14]. In the study by Chen and colleagues, none of the patients who had an unsuccessful SSI (9/51, 18%) had a spontaneous event afterwards during VEEG of 3.5 days on average [30].

It seems reasonable to recommend a VEEG-duration of 48–72 h before opting for SSI when PNES are suspected.

7. Risks and side effects

Although the induction techniques discussed so far are themselves reasonably innocuous in healthy subjects, there are certain risks and side effects reported for SSI. One commonly described effect is the induction of non-habitual events [47,55,60,63,64]. Using hyperventilation and photic stimulation non-habitual events are reported in 3–13% of cases [60,63,64]; in saline-based SSI studies it is 10% and 23% respectively [47,55]. This difference might be an indicator of a higher suggestive potency of placebo injections. The possibility of inducing non-habitual events makes it imperative to always confirm the genuineness of recorded events by showing them to patients or their relatives.

On rare occasions, *epileptic* seizures can occur during SSI [40,55]. In such cases, careful examination of EEG and semiology should allow the distinction between pure coincidence (especially in patients with high seizure frequency), reflex seizures or

stress-induced seizures [55]. However, most studies that performed SSI in control subjects with confirmed epilepsy reported no induced epileptic seizures at all [13,31,47,54].

The possible complications of induced PNES themselves should also be considered [75]. The most common emergency complication of PNES is the so-called status pseudoepilepticus or pseudostatus [76], which can be induced by SSI [77]. Even though this complication has only been reported once so far [77] and is not specified in any of the SSI studies cited, it dictates caution in cases when patient history reveals prolonged or refractory (psychogenic) seizures.

A recent prospective study has challenged the common assumption that PNES, as opposed to epileptic seizures, seldom lead to ictal injuries [78,79]. In fact, as many as 31% of PNES patients report minor injuries, like lacerations or bruises, and even major ones, like dental injury or burns [78]. However, subjective reports might be skewed towards aggravation [75]. Although the studies on SSI reviewed above do not specifically report on ictal injuries in induced PNES, one should arrange for appropriate precautions during SSI (e.g. a mattress for patients with ictal falls).

8. Psychobiological mechanisms

The presumed psychopathology of PNES is a matter of continuing research and debate, and has been reviewed elsewhere [21,80]. Assumptions about the mechanisms of SSI have to be formulated carefully in light of this uncertainty. Considering the wide variety of induction methods, both psychological and physiological effects have to be accounted for.

On a cognitive level, general suggestion and hypnotic induction offer certain insights. Studies have demonstrated convincing neurophysiological parallels between symptoms of dissociation induced by hypnosis and those inherent in disorders formerly classified as "hysteria" [81]. For example, fMRI studies have shown parallels between paralysis in conversion disorder and hypnotically induced paralysis [82,83]. Similarly, dissociative amnesia and hypnosis-induced amnesia both involve decreased temporal lobe activation on fMRI [81,84]. Several studies have demonstrated higher hypnotisability in PNES patients [36,38,40]. Others, however, have failed to replicate these results [44,85]. These discrepancies call for future studies using standardized measures of hypnotisability and uniform protocols of induction.

On a physiological level, stress induction appears to be a key factor in SSI. An abnormal reaction to emotional or psychosocial stress has been identified as a pivotal factor in the pathogenesis and maintenance of PNES [21]. Empirical data reflect both the psychological aspects of such maladaptation [86,87] and the dysregulation in stress neurocircuitry and autonomic response systems [88,89]. In one study, anxiety and stress situations were identified as precipitating factors in 22 out of 37 of recorded PNES (73%) [52]. In several studies, an "escalation" of induction methods (from neutral to more unpleasant stimuli) has increased the yield of SSI [20,49,52,57]. Whether unpleasant methods are more "potent" due to a stronger stress reaction or a more convincing suggestion remains unclear. A closer examination of the physiological effects of SSI might elucidate crucial questions about the relationship between stress and PNES. It is unlikely that generic stress is solely responsible for induction, since it has only mild effects on physiological stress markers such as cortisol levels and heart rate variability in PNES patients compared to healthy controls [90].

Stone and Carson offer a model of PNES induction that incorporates (patho-)physiological stress response and dissociation [91]. In a small cohort, they identified eleven patients, who reported unpleasant auras (reminiscent of incipient panic attacks) preceding their seizures and a desire for them to "hurry up" in order to be relieved of those unbearable prodromal symptoms. This "wilful submission" can be interpreted as a conversion reaction in terms of the classical theory of hysteria: somatic manifestation of stress and anxiety [92,93] are deflected in the form of dissociation, i.e. a PNES [81,91].

Accordingly, in order to record a habitual PNES, two conditions might be necessary: a stressor and a permissive setting. When the usual stressor is internal (e.g. stemming from childhood trauma) the spontaneous occurrence of a PNES in a permissive setting (i.e. epilepsy monitoring unit) can be expected. This could explain the short latency of habitual PNES during VEEG despite partly low seizure frequencies [73]. If, however, the stressor is exogenous (e.g. conflicts with a family member or mental overload at work), a spontaneous attack might fail to occur in the relatively stress-free epilepsy monitoring unit despite reportedly high seizure frequencies [14]. To facilitate diagnosis an exogenous stressor (SSI) combined with a permissive attitude suggested by the examiner ("it is safe to have an attack here") would be needed. Thus, SSI might not just be useful for economising a few days of VEEG, but could yield a diagnosis in patients that would otherwise remain inconclusive, as described previously [15,30]. It seems plausible that different subgroups of PNES (e.g. dissociative or conversion-related) [81,94] might respond to different elements of SSI (e.g. suggestion or stress-induction). One promising approach to elucidate the mechanisms of SSI and PNES psychopathology in general is to look for predictive factors for successful induction.

9. Predictive factors for SSI

Only two studies have specifically investigated whether clinical or sociodemographic factors could predict the success of SSI in patients with established PNES. Wassmer and colleagues compared patients with positive ($n = 41$) and those with negative SSI ($n = 25$) in terms of semiology and patient history [8]. Looking at 26 elements of seizure semiology and 17 sociodemographic characteristics, no significant between-group differences could be found [8]. A similar undertaking by Chen and colleagues also failed to find any difference in 11 sociodemographic factors between patients with successful SSI ($n = 42$) and those with unsuccessful SSI ($n = 9$) [30]. However, there were statistical differences in the results of some psychological instruments: a higher score on the Structured Inventory of Malingered Symptomatology predicted a positive SSI. One could surmise, that a tendency towards malingering manifests itself as the elusive, but crucial element of wilfulness of seizure initiation explored by Stone and Carson [91] (see previous section). Furthermore, higher scores in subscales of the brief COPE inventory showed significant differences, suggesting that patients whose PNES can be induced rely more on action-oriented coping strategies [30]. The implied proactive attitude and the desire to receive a diagnosis might increase the chances for SSI [30].

10. Therapeutic effect of SSI

The therapeutic effect of communicating a definitive diagnosis of PNES is well-established [95,96]. A potential role of SSI in long-term outcome, however, was first described by Wassmer and colleagues [8]. The ratio of attack-free PNES patients on follow-up 4–7 years after diagnosis was higher in the group with previously positive SSI than in the group with negative SSI, but the effect was not statistically significant (44% vs. 33%, $p = 0.82$). Gambini and colleagues analyzed the long-term outcome of 27 PNES patients 14–38 months after diagnosis: out of 11 clinical and sociodemographic characteristics, the only factor that statistically predicted a better outcome was positive SSI [66]. Even when controlling for psychological and psychiatric therapy (themselves not statistically significant factors), diagnosis via SSI remained a highly significant predictive factor for good outcome. One

explanation could be that positive SSI is an indicator for a certain subtype of PNES pathology that has a better outcome in terms of seizure frequency. On the other hand, it has been shown, that outcome hinges on understanding and accepting the diagnosis "psychogenic nonepileptic seizures" [97]. SSI might simply be a more coherent and convincing diagnostic test from the patient's point of view than several days of VEEG on an epilepsy monitoring unit. Whether the role of successful of SSI is merely predictive or in some way therapeutic remains to be addressed in future studies.

11. Conclusions

While the clinical significance, diagnostic pitfalls and therapeutic challenges of psychogenic nonepileptic seizures are widely recognized, there is still much uncertainty about psychopathology, staged diagnostic workup and optimal management. SSI is an accurate and effective tool that can facilitate and accelerate diagnosis, provide insights into disease mechanisms and even offer a promising therapeutic lever. The following conclusions can be gleaned from the research reviewed above:

- SSI is an essential diagnostic tool in the workup of suspected PNES, atypical seizures and paroxysmal attacks of unknown aetiology.
- Depending on pre-test selection of patients, it can have an excellent diagnostic yield.
- Various methods of SSI have been studied. There is strong evidence for the effectiveness of placebo-infusions, but also for suggestive hyperventilation and photic stimulation. A combination of two or three techniques is practicable and effective.
- Open patient information that avoids explicit deception will spare the therapeutic relationship and will not reduce the diagnostic yield.
- VEEG for 2–3(–5) days can be used to record spontaneous PNES, but should be supplemented by SSI when inconclusive.
- Patients and physicians should be aware of the potential risks and side effects of SSI, such as inducing non-habitual events or pseudostatus epilepticus.
- There are no known clinically relevant predictive factors of successful SSI in patients with PNES.
- There might be a therapeutic effect of diagnosis via SSI that demands further research.

Conflict of interest

All authors declare, that they have no conflicts of interest.

Appendix A. List of search terms used in various combinations

psychogenic
non-epileptic
nonepileptic
pseudoepilep*
pseudoseizure*
dissociative
hysterical
hysteroepilepsy
conversion
seizure*
event*
attack*
induc*
provo*
suggestion
facilitat*

Appendix B. List of relevant articles that were excluded from the systematic review

Citation	Reason for exclusion
Cano-Plasencia R, Gómez-Marcos AM, Cano-Sánchez R. [Induction of pseudoseizures by placing inactive electrodes in the malar regions]. Rev Neurol. 2006 Dec 1-15;43(11):662–6.	Article in French
French JA, Kanner AM, Rosenbaum DH, Rowan AJ. Do techniques of suggestion aid the differential diagnosis of psychogenic versus epileptic seizures? Epilepsia 1987; 28:612–3.	Non-peer-reviewed abstract
French JA. Suggestion as a provocative test in the diagnosis of psychogenic nonepileptic seizures. In: Rowan AJ, Gates JR. Non-epileptic seizures. Boston, MA: Butterworth–Heinemann, 1993:101–109.	Non-peer-reviewed book chapter
Klingler D, Trägner H. Sleep deprivation as a provocation method in electroencephalography in patients with non-epileptic cerebral disorders. Neurol Psychiatr (Bucur). 1984 Jan-Mar;22(1):51–3.	Provocation of EEG-changes, not of seizures
Kupper HI. Psychic Concomitants in Wartime Injuries. Psychosom Med. 1945 Jan; 7:15.	Case report
Kuyk J, Jacobs LD, Aldenkamp AP, Meinardi H, Spinhoven P, van Dyck R. Pseudo-epileptic seizures: hypnosis as a diagnostic tool. Seizure. 1995 Jun; 4(2):123–8.	Hypnosis used for recall, not induction
LeVine WR, Ramirez C. Identifying pseudoseizures with anhydrous ammonia. Am J Psychiatry. 1980 Aug; 137(8):995.	2 cases; ammonia used to stop seizures, not induce them; no EEG
Martínez-Taboas A. The role of hypnosis in the detection of psychogenic seizures. Am J Clin Hypn. 2002 Jul; 45(1):11–20.	Small case series ($n = 8$)
Ney GC, Zimmerman C, Schaul N. Psychogenic status epilepticus induced by a provocative technique. Neurology. 1996 Feb;46(2):546–7.	Case report
Niedermeyer, E., Blummer, D., Holscher, E. and Walker, B.A. Classical hysterical seizures facilitated by anticonvulsant toxicity. Psychiatr Clin 1970; 3: 71–84.	3 cases; general facilitation, not specific induction
Olson DM, Howard N, Shaw RJ. Hypnosis-provoked nonepileptic events in children. Epilepsy Behav. 2008 Apr;12(3):456–9.	Pediatric population; small case series ($n = 9$)
Peterson DB, Sumner JW Jr, Jones GA. (1950) Role of hypnosis in differentiation of epileptic from convulsive-like seizures. Am J Psychiatry 107: 428–433.	Hypnosis used for recall, not induction
Remick RA, Wada JA. Complex partial and pseudoseizure disorders. Am J Psychiatry. 1979: 136:320–323.	Case report
Schmalbach K, Mueller E, Salazar-Munos M, Bushart W. [Syncope and other nonepileptic attacks. (The value and limitations of provocation measures)]. Dtsch Med Wochenschr. 1962 Oct 5;87:2027–30.	Article in German
Staudenmayer H, Kramer RE. Psychogenic chemical sensitivity: psychogenic pseudoseizures elicited by provocation challenges with fragrances. J Psychosom Res. 1999 Aug;47(2):185–90.	Case report
Sumner JW, Cameron RR, Peterson DB. Hypnosis in the d ifferentiationof epileptic from convulsive like seizures. 1952. Neurology. 1952; 27: 395–402.	Hypnosis used for recall, not induction
Wyllie E, Friedman D, Rothner AD, Luders H, Dinner D, Morris H 3rd, Cruse R, Erenberg G, Kotagal P. Psychogenic seizures in children and adolescents: outcome after diagnosis by ictal video and electroencephalographic recording. Pediatrics. 1990 Apr;85(4):480–4.	Pediatric population
Zalsman G, Dror S, Gadoth N. Hypnosis provoked pseudoseizures: a case report and literature review. Am J Clin Hypn. 2002 Jul;45(1):47–53.	Case report

Appendix C. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.plantsci.2004.08.011.

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